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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: **ASTRAZENECA AB** Dirección: S-151 85 Sodertalje, Suecia Nacionalidad o Domicilio: Suecia Lugar de Constitución: Suecia Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número 170.322 TP 1003
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10 ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $378.000
- [x] Comprobante de pago por reivindicación de prioridad. $106.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Fotocopia Autenticada Anexa
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud Internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud Internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [ ] Traducción del examen preliminar efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12x12.
- [ ] De ser el caso, Información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] Otros

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170.322 de Bogotá . T.P. 1003 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

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CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	30005-01-01 SOLICITUDES	115 PTC CAP-II EXAMEN DE PATENTIBILID	106,000.00
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SON: CIENTO SEIS MIL PESOS

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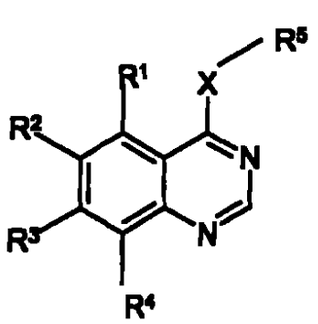
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(54) Title: SUBSTITUTED QUINAZOLINE DERIVATIVES AND THEIR USE AS INHIBITORS



(I)

(57) Abstract: The use of a compound of formula (I) or a salt, ester or amide thereof; where X is O, or S, S(O) or $S(O)_2$, or NR^6 where R^6 is hydrogen or C_{1-4}alkyl; R^5 is an optionally substituted 5-membered heteroaromatic ring. R^1, R^2, R^3, R^4 are independently selected from various specified moieties, in the preparation of a medicament for use in the inhibition of aurora 2 kinase. Certain compounds are novel and these, together with pharmaceutical compositions containing them are also described and claimed.

WO 02/00649 A1

SUBSTITUTED QUINAZOLINE DERIVATES AND THEIR USE AS INHIBITORS

The present invention relates to certain quinazoline derivatives for use in the treatment of certain diseases in particular to proliferative disease such as cancer and in the preparation of medicaments for use in the treatment of proliferative disease, to novel quinazoline compounds and to processes for their preparation, as well as pharmaceutical compositions containing them as active ingredient.

Cancer (and other hyperproliferative disease) is characterised by uncontrolled cellular proliferation. This loss of the normal regulation of cell proliferation often appears to occur as the result of genetic damage to cellular pathways that control progress through the cell cycle.

In eukaryotes, the cell cycle is largely controlled by an ordered cascade of protein phosphorylation. Several families of protein kinases that play critical roles in this cascade have now been identified. The activity of many of these kinases is increased in human tumours when compared to normal tissue. This can occur by either increased levels of expression of the protein (as a result of gene amplification for example), or by changes in expression of co activators or inhibitory proteins.

The first identified, and most widely studied of these cell cycle regulators have been the cyclin dependent kinases (or CDKs). Activity of specific CDKs at specific times is essential for both initiation and coordinated progress through the cell cycle For example, the CDK4 protein appears to control entry into the cell cycle (the G0-G1-S transition) by phosphorylating the retinoblastoma gene product pRb. This stimulates the release of the transcription factor E2F from pRb, which then acts to increase the transcription of genes necessary for entry into S phase . The catalytic activity of CDK4 is stimulated by binding to a partner protein, Cyclin D. One of the first demonstrations of a direct link between cancer and the cell cycle was made with the observation that the Cyclin D1 gene was amplified and cyclin D protein levels increased (and hence the activity of CDK4 increased) in many human tumours (Reviewed in Sherr, 1996, Science 274: 1672-1677; Pines, 1995, Seminars in Cancer Biology 6: 63-72). Other studies (Loda et al., 1997, Nature Medicine 3(2): 231-234; Gemma et al., 1996, International Journal of Cancer 68(5): 605-11; Elledge et al. 1996, Trends in Cell Biology 6; 388-392) have shown that negative regulators of CDK function are frequently down regulated or deleted in human tumours again leading to inappropriate activation of these kinases.

More recently, protein kinases that are structurally distinct from the CDK family have been identified which play critical roles in regulating the cell cycle and which also appear to be important in oncogenesis. These include the newly identified human homologues of the *Drosophila* aurora and *S.cerevisiae* Ipl1 proteins. *Drosophila* aurora and *S.cerevisiae* Ipl1, which are highly homologous at the amino acid sequence level, encode serine/threonine protein kinases. Both aurora and Ipl1 are known to be involved in controlling the transition from the G2 phase of the cell cycle through mitosis, centrosome function, formation of a mitotic spindle and proper chromosome separation / segregation into daughter cells. The two human homologues of these genes, termed aurora1 and aurora2, encode cell cycle regulated protein kinases. These show a peak of expression and kinase activity at the G2/M boundary (aurora2) and in mitosis itself (aurora1). Several observations implicate the involvement of human aurora proteins , and particularly aurora2 in cancer. The aurora2 gene maps to chromosome 20q13, a region that is frequently amplified in human tumours including both breast and colon tumours. Aurora2 may be the major target gene of this amplicon, since aurora2 DNA is amplified and aurora2 mRNA overexpressed in greater than 50% of primary human colorectal cancers. In these tumours aurora2 protein levels appear greatly elevated compared to adjacent normal tissue. In addition, transfection of rodent fibroblasts with human aurora2 leads to transformation, conferring the ability to grow in soft agar and form tumours in nude mice (Bischoff et al., 1998, The EMBO Journal. 17(11): 3052-3065). Other work (Zhou et al., 1998, Nature Genetics. 20(2): 189-93) has shown that artificial overexpression of aurora2 leads to an increase in centrosome number and an increase in aneuploidy.

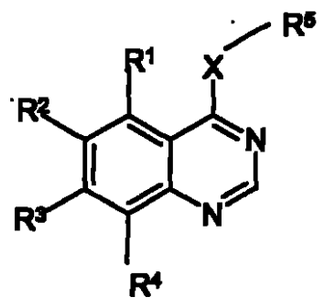
Importantly, it has also been demonstrated that abrogation of aurora2 expression and function by antisense oligonucleotide treatment of human tumour cell lines (WO 97/22702 and WO 99/37788) eads to cell cycle arrest in the G2 phase of the cell cycle and exerts an antiproliferative effect in these tumour cell lines. This indicates that inhibition of the function of aurora2 will have an antiproliferative effect that may be useful in the treatment of human tumours and other hyperproliferative diseases.

A number of quinazoline derivatives have been proposed hitherto for use in the inhibition of various kinases. Examples of such proposals are included in WO 92/20642 and EP-B-584222 which relates to bicyclic compounds which inhibit epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) receptor tyrosine kinase, WO 95/15758 which describes the use of bis ring systems for the selective inhibition of CSF-1R tyrosine

kinase activity, and WO 99/09016, WO 97/03069 and US 570158 which describe the use of certain quinazoline compounds as tyrosine kinase inhibitors in other contexts.

The applicants have found a series of compounds which inhibit the effect of the aurora2 kinase and which are thus of use in the treatment of proliferative disease such as cancer, in particular in such diseases such as colorectal or breast cancer where aurora 2 kinase is known to be active.

The present invention provides the use of a compound of formula (I)



(I)

or a salt, ester or amide thereof;

where X is O, or S, S(O) or $S(O)_2$, or NR^6 where R^6 is hydrogen or C_{1-6}alkyl,;

R^5 is an optionally substituted 5-membered heteroaromatic ring,

R^1, R^2, R^3, R^4 are independently selected from, halo, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, -NR^7R^8 (wherein R^7 and R^8, which may be the same or different, each represents hydrogen or C_{1-3}alkyl), or -X^1R^9 (wherein X^1 represents a direct bond, -O-, -CH_2-, -OCO-, carbonyl, -S-, -SO-, -SO_2-, -$NR^{10}CO$-, -$CONR^{11}$-, -SO_2NR^{12}-, -$NR^{13}SO_2$- or -NR^{14}- (wherein R^{10}, R^{11}, R^{12}, R^{13} and R^{14} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), and R^9 is selected from one of the following groups:

1) hydrogen or C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro or amino,

2) C_{1-5}alkylX^2COR^{15} (wherein X^2 represents -O- or -NR^{16}- (in which R^{15} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{16} represents C_{1-3}alkyl, -$NR^{17}R^{18}$ or -OR^{19} (wherein R^{17}, R^{18} and R^{19} which may be the same or different each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkylX^3R^{20} (wherein X^3 represents -O-, -S-, -SO-, -SO_2-, -OCO-, -NR^{21}CO-, -$CONR^{22}$-, -SO_2NR^{23}-, -$NR^{24}SO_2$- or -NR^{25}- (wherein R^{21}, R^{22}, R^{23}, R^{24} and R^{25} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{20} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

4) C_{1-5}alkylX^4C_{1-5}alkylX^5R^{26} (wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO-, -SO_2-, -NR^{27}CO-, -$CONR^{28}$-, -SO_2NR^{29}-, -$NR^{30}SO_2$- or -NR^{31}- (wherein R^{27}, R^{28}, R^{29}, R^{30} and R^{31} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{26} represents hydrogen or C_{1-3}alkyl);

5) R^{32} (wherein R^{32} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkylsulphonylC_{1-4}alkyl);

6) C_{1-5}alkylR^{32} (wherein R^{32} is as defined hereinbefore);

7) C_{2-5}alkenylR^{32} (wherein R^{32} is as defined hereinbefore);

8) C_{2-5}alkynylR^{32} (wherein R^{32} is as defined hereinbefore);

9) R^{33} (wherein R^{33} represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents on an available carbon atom selected from hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -$CONR^{34}R^{35}$ and -$NR^{36}COR^{37}$ (wherein R^{34}, R^{35}, R^{36} and R^{37}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

10) C_{1-5}alkylR^{33} (wherein R^{33} is as defined hereinbefore);

11) C_{2-5}alkenylR^{33} (wherein R^{33} is as defined hereinbefore);

12) C_{2-5}alkynylR^{33} (wherein R^{33} is as defined hereinbefore);

13) C_{1-5}alkylX^6R^{33} (wherein X^6 represents -O-, -S-, -SO-, -SO_2-, -NR^{38}CO-, -$CONR^{39}$-, -SO_2NR^{40}-, -$NR^{41}SO_2$- or -NR^{42}- (wherein R^{38}, R^{39}, R^{40}, R^{41} and R^{42} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore);

14) C_{2-5}alkenylX^{7}R^{33} (wherein X^7 represents -O-, -S-, -SO-, -SO_2-, -NR^{43}CO-, -CONR^{44}-, -SO_2NR^{45}-, -NR^{46}SO_2- or -NR^{47}- (wherein R^{43}, R^{44}, R^{45}, R^{46} and R^{47} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore);

15) C_{2-5}alkynylX^{8}R^{33} (wherein X^8 represents -O-, -S-, -SO-, -SO_2-, -NR^{48}CO-, -CONR^{49}-, -SO_2NR^{50}-, -NR^{51}SO_2- or -NR^{52}- (wherein R^{48}, R^{49}, R^{50}, R^{51} and R^{52} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore);

16) C_{1-3}alkylX^9C_{1-3}alkylR^{33} (wherein X^9 represents -O-, -S-, -SO-, -SO_2-, -NR^{53}CO-, -CONR^{54}-, -SO_2NR^{55}-, -NR^{56}SO_2- or -NR^{57}- (wherein R^{53}, R^{54}, R^{55}, R^{56} and R^{57} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore); and

17) C_{1-3}alkylX^9C_{1-3}alkylR^{32} (wherein X^9 and R^{28} are as defined hereinbefore):

in the preparation of a medicament for use in the inhibtion of aurora 2 kinase. In particular, such medicaments are useful in the treatment of proliferative disease such as cancer, and in particular cancers where aurora 2 is upregulated such as colon or breast cancers.

In this specification the term 'alkyl' when used either alone or as a suffix includes straight chained, branched structures. Unless otherwise stated, these groups may contain up to 10, preferably up to 6 and more preferably up to 4 carbon atoms. Similarly the terms "alkenyl" and "alkynyl" refer to unsaturated straight or branched structures containing for example from 2 to 10, preferably from 2 to 6 carbon atoms. Cyclic moieties such as cycloalkyl, cycloalkenyl and cycloalkynyl are similar in nature but have at least 3 carbon atoms. Terms such as "alkoxy" comprise alkyl groups as is understood in the art.

The term "halo" includes fluoro, chloro, bromo and iodo. References to aryl groups include aromatic carbocylic groups such as phenyl and naphthyl. The term "heterocyclyl" includes aromatic or non-aromatic rings, for example containing from 4 to 20, suitably from 5 to 8 ring atoms, at least one of which is a heteroatom such as oxygen, sulphur or nitrogen. Examples of such groups include furyl, thienyl, pyrrolyl, pyrrolidinyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, benzothiazolyl, benzoxazolyl, benzothienyl or benzofuryl.

"Heteroaryl" refers to those groups described above which have an aromatic character. The term "aralkyl" refers to aryl substituted alkyl groups such as benzyl.

Other expressions used in the specification include "hydrocarbyl" which refers to any structure comprising carbon and hydrogen atoms. For example, these may be alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl.

The term "functional group" refers to reactive substituents such as nitro, cyano, halo, oxo, $=CR^{78}R^{79}$, $C(O)_xR^{77}$, OR^{77}, $S(O)_yR^{77}$, $NR^{78}R^{79}$, $C(O)NR^{78}R^{79}$, $OC(O)NR^{78}R^{79}$, $=NOR^{77}$, $-NR^{77}C(O)_xR^{78}$, $-NR^{77}CONR^{78}R^{79}$, $-N=CR^{78}R^{79}$, $S(O)_yNR^{78}R^{79}$ or $-NR^{77}S(O)_yR^{78}$ where R^{77}, R^{78} and R^{79} are independently selected from hydrogen or optionally substituted hydrocarbyl, or R^{78} and R^{79} together form an optionally substituted ring which optionally contains further heteroatoms such as $S(O)_y$ oxygen and nitrogen, x is an integer of 1 or 2, y is 0 or an integer of 1-3.

Suitable optional substituents for hydrocarbyl groups R^{77}, R^{78} and R^{79} include halo, perhaloalkyl such as trifluoromethyl, mercapto, hydroxy, carboxy, alkoxy, aryl, heteroaryl, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyalkoxy, aryloxy (where the aryl group may be substituted by halo, nitro, or hydroxy), cyano, nitro, amino, mono- or di-alkyl amino, oximino or $S(O)_y$ where y is as defined above.

Preferably R^4 is hydrogen.

Suitably R^1 is hydrogen or a group set out for R^2 or R^3 below. Frequently, R^1 is hydrogen.

In a preferred embodiment, at least one group R^1, R^2 or R^3, preferably R^3, comprises a chain of at least 3 and preferably at least 4 optionally substituted carbon atoms or heteroatoms such as oxygen, nitrogen or sulphur. Most preferably the chain is substituted by a polar group which assists in solubility.

Suitably R^3 is a group X^1R9. Preferably in this case, X^1 is oxygen and R^9 is selected from a group of formula (1) or (10) above. Particular groups R^9 are those in group (1) above, especially alkyl such as methyl or halo substituted alkyl, or those in group (10) above. In one preferred embodiment, at least one of R^2 or R^3 is a group $-OC_{1-3}alkylR^{33}$ and R^{33} is a heterocyclic ring such as an N-linked morpholine ring such as 3-morpholinopropoxy.

Suitably R^2 is selected from, halo, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, $-NR^9R^{10}$ (wherein R^9 and R^{10}, which may be the same or different, each represents hydrogen or C_{1-3}alkyl), or a group $-X^1R^{11}$. Preferred examples of $-X^1R^{11}$ for R^2 include those listed above in relation to R^3.

Other examples for R^2 and R^3 include methoxy or 3,3,3-trifluoroethoxy.

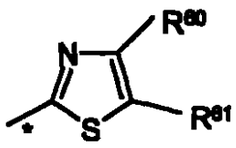
Preferably X is NH or O and is most preferably NH.

Examples of 5-membered aromatic rings R^5 include rings containing one or more heteroatoms selected from sulphur, oxygen and nitrogen. Such rings include pyrrole, pyrazole, pyrazolone, imidazole, oxazole, furan, tetrazole, triazole, thiazole, thiophene, or thiadiazole, any of which may be optionally substituted. In particular, R^5 includes at least one nitrogen or sulphur heteroatoms. Preferred rings for R^5 include pyrrole, pyrazole, imidazole, triazole, thiazole, thiophene, or thiadiazole.

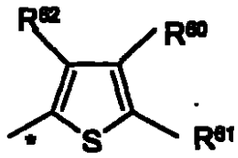
In a particular embodiment, R^5 is a sulphur containing ring. Suitably R^5 is optionally substituted thiazole, optionally substituted thiophene or optionally substituted thiadiazole and preferably, optionally substituted thiazole or optionally substituted thiophene.

More preferably, R^5 is a substituted thiazole or substituted thiophene group.

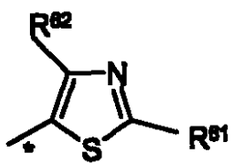
In particular, R^5 is a group of formula (a), (b), (c) or (d) and preferably (a) or (b):



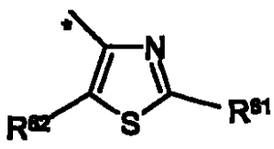
(a)



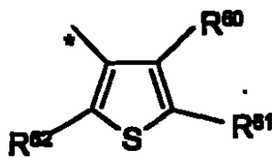
(b)



(c)



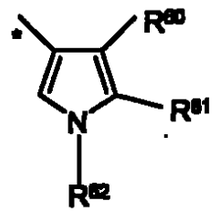
(d)

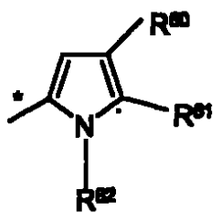


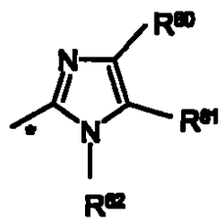
(e)

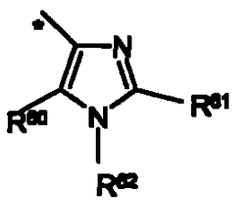
where R^{60}, R^{61} and R^{62} are independently selected from hydrogen or a substituent group and * indicates the point of attachment to the group X in formula (I). In particular, one of R^{60}, R^{61} or R^{62} is a substituent group and the others are either hydrogen or a small substituent such as C_{1-3} alkyl, for instance methyl. Suitably R^{62} is hydrogen. Preferably R^{61} is other than hydrogen,

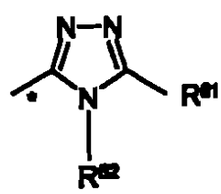
Alternatively, R^5 is an optionally substituted nitrogen containing ring such as a group of formula (f), (g), (h), (i) or (j):


(f)


(g)

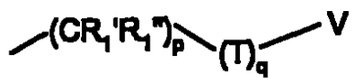

(h)


(I)


(J)

Suitable substituents for groups R^j include optionally substituted hydrocarbyl, optionally substituted heterocylyl or a functional group as defined above.

In particular, R^{60}, R^{61} or R^{62} is a group of sub-formula (k)


(k)

where p and q are independently 0 or 1 and wherein R_1' and R_1'' are independently hydrogen, hydroxy, optionally substituted alkyl, optionally substituted cycloalkyl, halogen, cyano, optionally substituted alkyl, optionally substituted alkyenyl. The optionally substituted alkyl or alkynyl may be substituted with halo, nitro, cyano, hydroxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulfamoyl, C_{1-4} alkyl, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N-(C_{1-4} alkyl), N(C_{1-4} alkyl)$_2$, C_{1-4} alkanoylamino, (C_{1-4} alkanoyl)$_2$amino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4})$_2$carbamoyl, C_{1-4})S, C_{1-4}S(O), (C_{1-4}alkyl)S(O)$_2$, (C_{1-4}) alkoxycarbonyl, N-(C_{1-4} alkyl)sulfamoyl, N,N-C_{1-4} alkyl)sulfamoyl, C_{1-4} alkylsolfonylamino, or heterocyclyl. R is preferably C_{1-4} alkyl, C_{2-4}alkenyl, or C_{2-4} alkynyl, and R_1' can form with R_1'' a 3 to 6 membered ring.

T is C=O, SO_n, C(=NOR)CO, C(O)C(O), C=NCN, CV=NO or wherein n = 0, 1 or 2 and V is independently R^{63} or N(R^{63})R^{64} wherein R^{63} and R^{64} are independently selected

from hydrogen, optionally substituted hydrocarbyl or optionally substituted heterocyclyl, or R^{63} and R^{64} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring.

Examples of groups for R^{63} and R^{64} include the group $-(CH_2)_qR^{70}$ where q and R^{70} are as defined below in relation to formula (II).

Suitably one of R^{63} or R^{64} is hydrogen, or methyl, ethyl or propyl optionally substituted with hydroxy and preferably one of R^{63} or R^{64} is hydrogen. In this case, the other is suitably a larger substituent for example of at least 4 carbon or heteroatoms, and is optionally substituted hydrocarbyl or optionally substituted heterocyclyl. Particular optionally substituted hydrocarbyl groups for R^{63} or R^{64} include alkyl, cycloalkyl, alkenyl, or aryl any of which is optionally substituted with a functional group as defined above, or in the case of aryl groups, with an alkyl group and in the case of alkyl group, with an aryl or heterocyclic group either of which may themselves be optionally substituted with alkyl or a functional group. Examples of optionally substituted aryl groups R^{63} or R^{64} include phenyl optionally substituted with one or more groups selected from C_{1-6} alkyl group such as methyl or ethyl (either of which may be optionally substituted with a functional group such as hydroxy), or a functional group as defined above (such as halo like fluoro, chloro or bromo, hydroxy, alkoxy such as methoxy, trifluoromethyl, nitro, cyano, trifluromethoxy, $CONH_2$, $C(O)CH_3$, amino, or dimethylamino).

When R^{63} or R^{64} is an optionally substituted alkyl group, it is suitably a C_{1-6}alkyl group, optionally substituted with one or more functional groups (such as cyano, hydroxy, alkoxy, in particular methoxy, COOalkyl such as $COOCH_3$), or aryl optionally substituted with a functional group as defined above (in particular in relation to R^{63} or R^{64} themselves, or an optionally substituted heterocyclic group such as N-methyl pyrrole.

When R^{63} and R^{64} is optionally substituted cycloalkyl, it is suitable cyclohexyl optionally substituted with a functional group such as hydroxy.

When R^{63} and R^{64} is optionally substituted alkenyl, it is suitably prop-2-enyl.

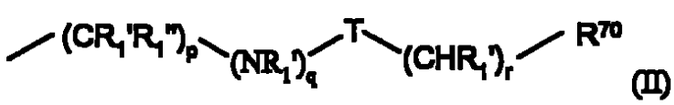
When R^{63} or R^{64} is optionally substituted heterocyclyl, or R^{63} and R^{64} together form a heterocyclic group, then this may be aromatic or non-aromatic and includes in particular, piperidine, piperazine, morpholino, pyrrolidine or pyridine any of which may be optionally substituted with a functional group such as hydroxy, alkoxy such as methoxy, or alkyl such as methyl which may itself be substituted with for instance a hydroxy group.

Alternatively at least one of R^{60}, R^{61} or R^{62} is a functional group, and in particular, one of R^{60}, R^{61} or R^{62} is a functional group a group of formula $(CR_2)_pC(O)_xR^{77}$ where R, p, x and R^{77} are as defined above, and in particular x is 2 and R^{77} is hydrogen or alkyl such as methyl.

Alternatively, R^5 is substituted by one or more groups selected from nitro, halo, C_{1-6}alkyl, optionally substituted C_{1-6} alkoxy, C_{1-4}alkoxymethyl, di(C_{1-4}alkoxy)methyl, C_{1-6}alkanoyl, trifluoromethyl, cyano, amino, C_{2-6}alkenyl, C_{2-6}alkynyl, a phenyl group, a benzyl group or a 5-6-membered heterocyclic group with 1-3 heteroatoms, selected independently from O, S and N, which heterocyclic group may be aromatic or non-aromatic and may be saturated (linked via a ring carbon or nitrogen atom) or unsaturated (linked via a ring carbon atom), and which phenyl, benzyl or heterocyclic group may bear on one or more ring carbon atoms up to 5 substituents selected from hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino, nitro, C_{2-4}alkanoyl, C_{1-4}alkanoylamino, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, carbamoyl, N-C_{1-4}alkylcarbamoyl, N,N-di(C_{1-4}alkyl)carbamoyl, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl, N,N-di(C_{1-4}alkyl)aminosulphonyl, C_{1-4}alkylsulphonylamino, and a satirated heterocyclic group selected from morpholino, thiomorpholino, pyrrolidinyl, piperazinyl, piperidinyl imidazolidinyl and pyrazolidinyl, which saturated heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino, nitro and C_{1-4}alkoxycarbonyl.

Suitably R^5 is substituted with at least one group which has at least 4 atoms which may be carbon or heteroatoms forming a chain. A particular example of such a substituent is optionally substituted alkoxy or alkoxy methyl. Suitable substituents for the alkoxy group include those listed above in relation to R^{77}, R^{78} and R^{79}.

A further particular substituent group for R^5 is a group of sub-formula (II)



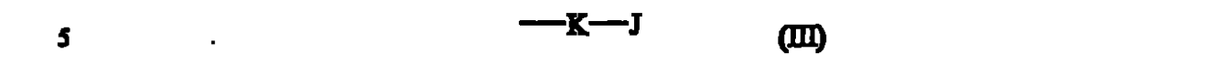
(II)

where p and q are independently 0 or 1, and r is 0, 1, 2, 3 or 4 and, R1', R1'' and T are as previously defined above;

R^{70} is hydrogen, hydroxy (other than where q is 0), C_{1-6}alkyl, C_{1-6}alkoxy, amino, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, hydroxyC_{2-6}alkoxy, C_{1-6}alkoxyC_{2-6}alkoxy,

aminoC$_{2-6}$alkoxy, *N*-C$_{1-6}$alkylaminoC$_{2-6}$alkoxy, *N*,*N*-(C$_{1-6}$alkyl)$_2$aminoC$_{2-6}$alkoxy or C$_{3-7}$cycloalkyl,

or R^{70} is of the Formula (III):

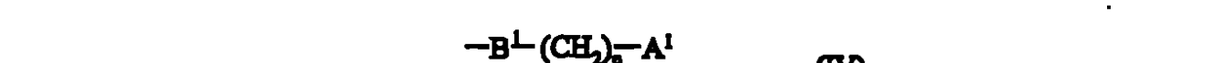


—K—J (III)

wherein J is aryl, heteroaryl or heterocyclyl and K is a bond, oxy, imino, *N*-(C$_{1-6}$alkyl)imino, oxyC$_{1-6}$alkylene, iminoC$_{1-6}$alkylene, *N*-(C$_{1-6}$alkyl)iminoC$_{1-6}$alkylene, -NHC(O) -, -SO$_2$NH-, -NHSO$_2$- or -NHC(O)-C$_{1-6}$alkylene-,

and any aryl, heteroaryl or heterocyclyl group in a R^{70} group may be optionally substituted by one or more groups selected from hydroxy, halo, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy, carbamoyl, formyl, sulphamoyl, C$_{1-6}$alkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, C$_{1-6}$alkoxy, -O-(C$_{1-3}$alkyl)-O-, C$_{1-6}$alkylS(O)$_n$- (wherein n is 0-2), *N*-C$_{1-6}$alkylamino, *N*,*N*-(C$_{1-6}$alkyl)$_2$amino, C$_{1-6}$alkoxycarbonyl, *N*-C$_{1-6}$alkylcarbamoyl, *N*,*N*-(C$_{1-6}$alkyl)$_2$carbamoyl, C$_{2-6}$alkanoyl, C$_{1-6}$alkanoyloxy, C$_{1-6}$alkanoylamino, *N*-C$_{1-6}$alkylsulphamoyl, *N*,*N*-(C$_{1-6}$alkyl)$_2$sulphamoyl, C$_{1-6}$alkylsulphonylamino and C$_{1-6}$alkylsulphonyl-*N*-(C$_{1-6}$alkyl)amino,

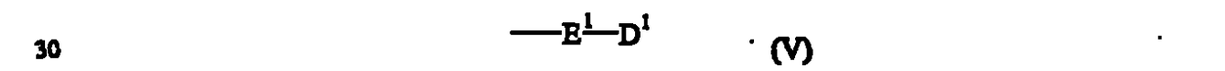
or any aryl, heteroaryl or heterocyclyl group in a R^{70} group may be optionally substituted with one or more groups of the Formula (IV):



—B^1—(CH$_2$)$_p$—A^1 (IV)

wherein A^1 is halo, hydroxy, C$_{1-6}$alkoxy, cyano, amino, *N*-C$_{1-6}$alkylamino, *N*,*N*-(C$_{1-6}$alkyl)$_2$amino, carboxy, C$_{1-6}$alkoxycarbonyl, carbamoyl, *N*-C$_{1-6}$alkylcarbamoyl or *N*,*N*-(C$_{1-6}$alkyl)$_2$carbamoyl, p is 1 - 6, and B^1 is a bond, oxy, imino, *N*-(C$_{1-6}$alkyl)imino or -NHC(O)-, with the proviso that p is 2 or more unless B^1 is a bond or -NHC(O)-;

or any aryl, heteroaryl or heterocyclyl group in a R^{70} group may be optionally substituted with one or more groups of the Formula (V):



—E^1—D^1 (V)

wherein D^1 is aryl, heteroaryl or heterocyclyl and E^1 is a bond, C_{1-6}alkylene, oxyC_{1-6}alkylene, oxy, imino, *N*-(C_{1-6}alkyl)imino, iminoC_{1-6}alkylene, *N*-(C_{1-6}alkyl)-iminoC_{1-6}alkylene, C_{1-6}alkylene-oxyC_{1-6}alkylene, C_{1-6}alkylene-iminoC_{1-6}alkylene, C_{1-6}alkylene-*N*-(C_{1-6}alkyl)-iminoC_{1-6}alkylene, -NHC(O)-, -$NHSO_2$-, -SO_2NH- or -NHC(O)-C_{1-6}alkylene-, and any aryl, heteroaryl or heterocyclyl group in a substituent on D^1 may be optionally substituted with one or more groups selected from hydroxy, halo, C_{1-6}alkyl, C_{1-6}alkoxy, carboxy, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-C_{1-6}alkylcarbamoyl, *N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{2-6}alkanoyl, amino, *N*-C_{1-6}alkylamino and *N*,*N*-(C_{1-6}alkyl)$_2$amino,

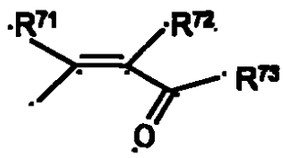
and any C_{3-7}cycloalkyl or heterocyclyl group in a R^{70} group may be optionally substituted with one or two oxo or thioxo substituents,

and any of the R^{70} groups defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, C_{1-6}alkoxy, *N*-C_{1-6}alkylamino, *N*,*N*-(C_{1-6}alkyl)$_2$amino and heterocyclyl.

A preferred example of a substituent of formula (II) is a group where q is 0.

A particular example of a group R^{70} in formula (II) is phenyl.

Another preferred substituent group for R^5 is a group of formula (VI)



(VI)

where R^{71} and R^{72} are independently selected from hydrogen or C_{1-4}alkyl, or R^{71} and R^{72} together form a bond, and R^{73} is a group OR^{74}, $NR^{75}R^{76}$ where R^{74}, R^{75} and R^{76} are independently selected from optionally substituted hydrocarbyl or optionally substituted heterocyclic groups, and R^{75} and R^{76} may additionally form together with the nitrogen atom to which they are attached, an aromatic or non-aromatic heterocyclic ring which may contain further heteroatoms.

Suitable optional substituents for hydrocarbyl or heterocyclic groups R^{74}, R^{75} and R^{76} include functional groups as defined above. Heterocyclic groups R^{74}, R^{75} and R^{76} may further be substituted by hydrocarbyl groups.

In particular, R^{71} and R^{72} in sub-formula (VI) are hydrogen.

Particular examples of R^{73} are groups OR^{74} where R^{74} is C_{1-4}alkyl.

Further examples of R^{73} are groups of formula $NR^{75}R^{76}$ where one of R^{75} or R^{76} is hydrogen and the other is optionally substituted C_{1-6}alkyl, optionally substituted aryl or optionally substituted heterocyclyl.

In particular, one of R^{75} or R^{76} is hydrogen and the other is C_{1-6}alkyl optionally substituted with trifluoromethyl, C_{1-3} alkoxy such as methoxy, cyano, thioC_{1-4}alkyl such as methylthio, or heterocyclyl optionally substituted with hydrocarbyl, such as indane, furan optionally substituted with C_{1-4} alkyl such as methyl.

In another embodiment, one of R^{75} or R^{76} is hydrogen and the other is an optionally substituted heterocyclic group such as pyridine, or a phenyl group optionally substituted with for example one or more groups selected from halo, nitro, alkyl such as methyl, or alkoxy such as methoxy.

Suitable pharmaceutically acceptable salts of compounds of Formula (I) or Formula (IA) include acid addition salts such as methanesulfonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulphuric acid. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. Where the compound of Formula (I) or Formula (IA) includes an acid functionality, salts may be base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N,N*-dibenzylethylamine or amino acids for example lysine. A preferred pharmaceutically acceptable salt is a sodium salt.

An *in vivo* hydrolysable ester of a compound of the Formula (I) or Formula (IA) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol.

Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkyl esters such as methyl or ethyl esters, C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxy-carbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the Formula (I) or Formula (IA) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

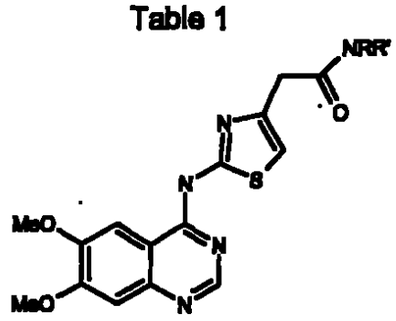
Suitable amides are derived from compounds of Formula (I) or Formula (IA) which have a carboxy group which is derivatised into an amide such as a N-C_{1-6}alkyl and N,N-di-(C_{1-6}alkyl)amide such as N-methyl, N-ethyl, N-propyl, N,N-dimethyl, N-ethyl-N-methyl or N,N-diethylamide.

Prefecred compounds of Formula (I) or Formula (IA) are those that are stable in mouse, rat, or human serum, preferably those that are stable in human serum.

Esters which are not *in vivo* hydrolysable may be useful as intermediates in the production of the compounds of Formula (I) or Formula (IA).

Particular examples of compounds of Formula (I) or Formula (IA) are set out in Tables 1 to 30 below.

Table 1



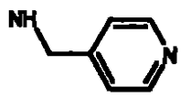
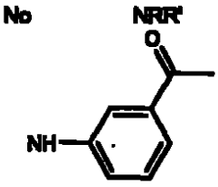
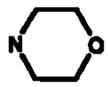
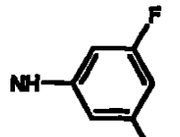
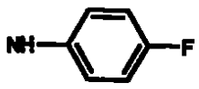
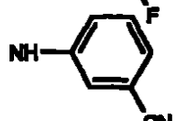
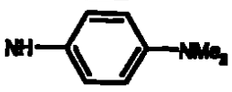
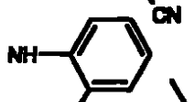
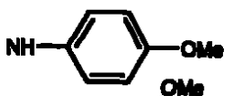
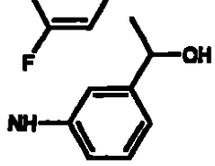
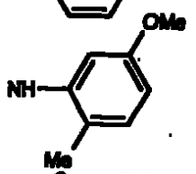
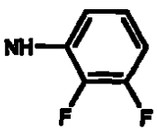
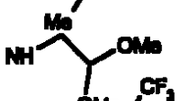
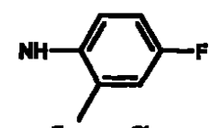
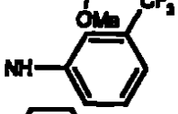
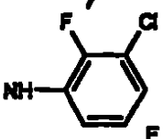
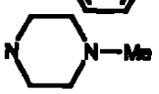
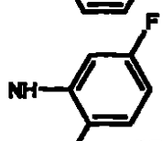
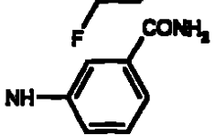
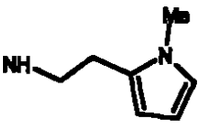
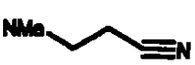
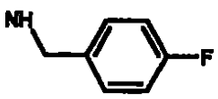
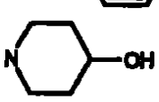
Compound No	NRR'	Compound No	NRR'
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3		17	
4		18	
5		19	
6		20	
7		21	
8		22	
9		23	
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11		25	
12			
13			
14			

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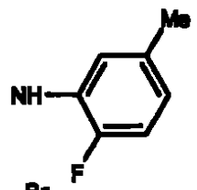
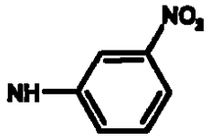
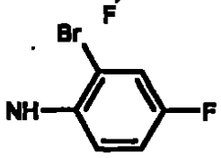
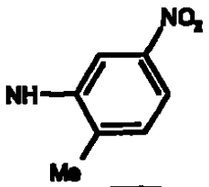
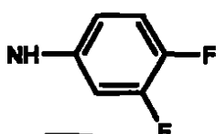
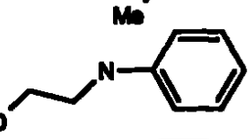
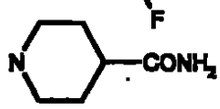
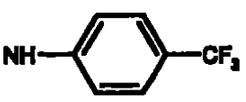
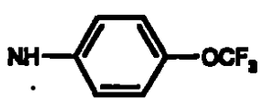
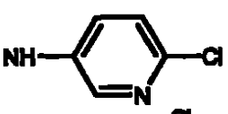
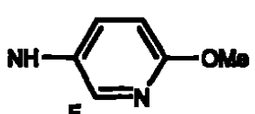
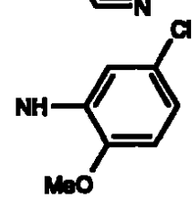
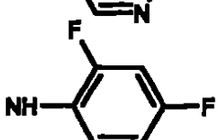
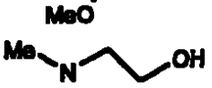
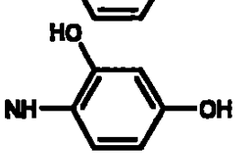
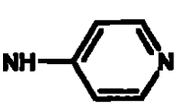
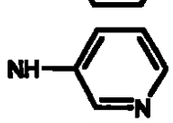
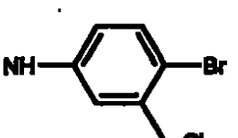
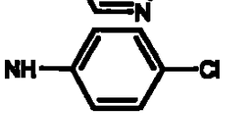
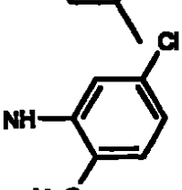
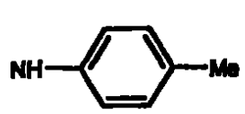
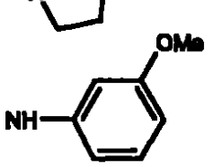
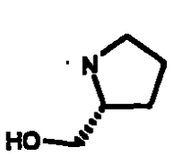
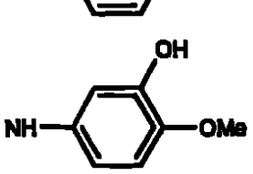
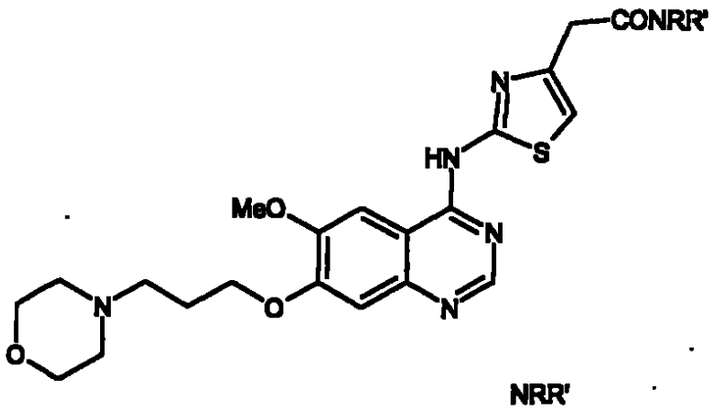
Compound No	NRR'	Compound No.	NRR'
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27		40	
28		41	
29		42	
30		43	
31		44	
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33		46	
34		47	
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36		49	
37		50	
38			

Table 2



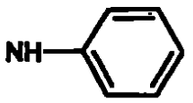
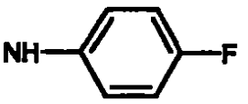
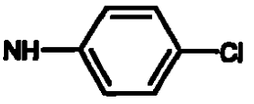
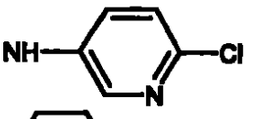
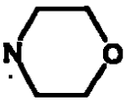
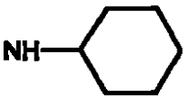
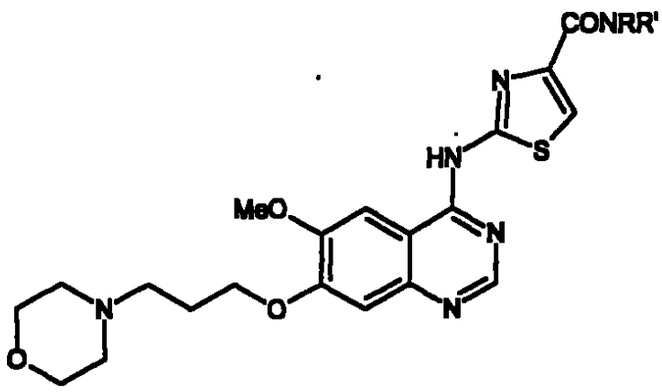
Compound No	NRR'
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52	
53	
54	
55	
56	
57	
58	

Table 3



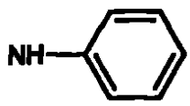
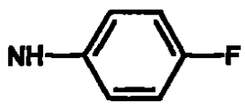
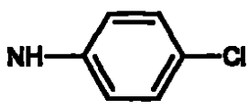
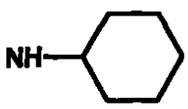
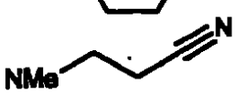
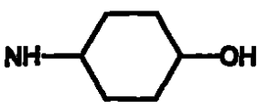
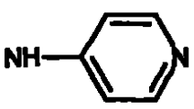
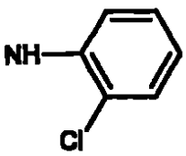
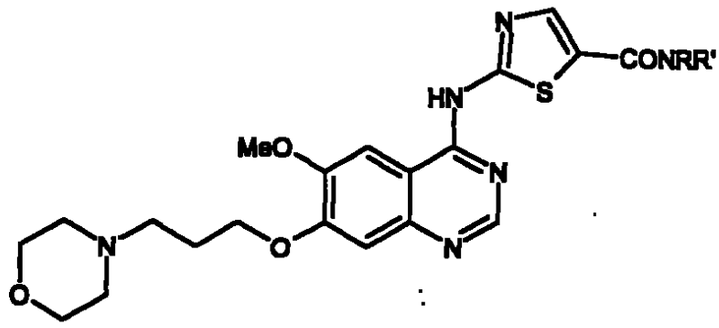
Compound No	NRR'
59	
60	
61	
62	
63	
64	
65	
66	

Table 4



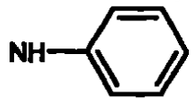
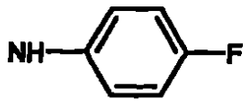
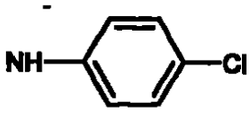
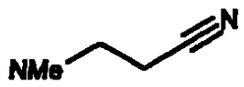
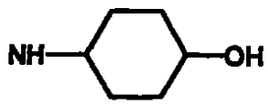
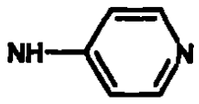
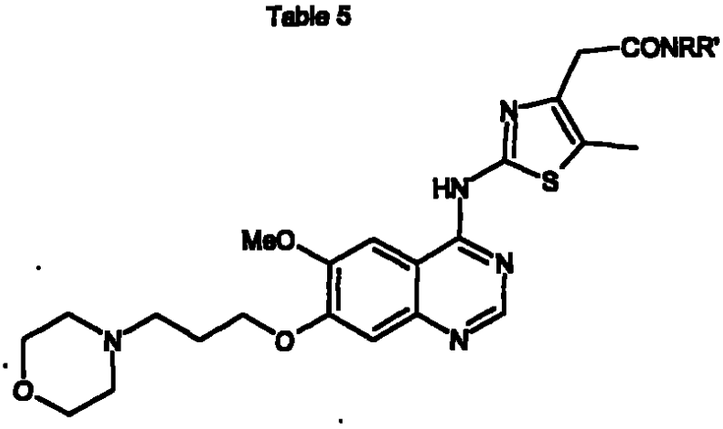
Compound No	NRR'
67	
68	
69	
70	
71	
72	
73	

Table 5



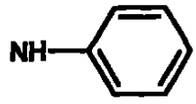
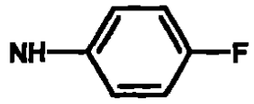
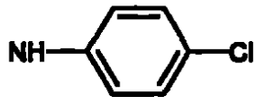
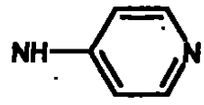
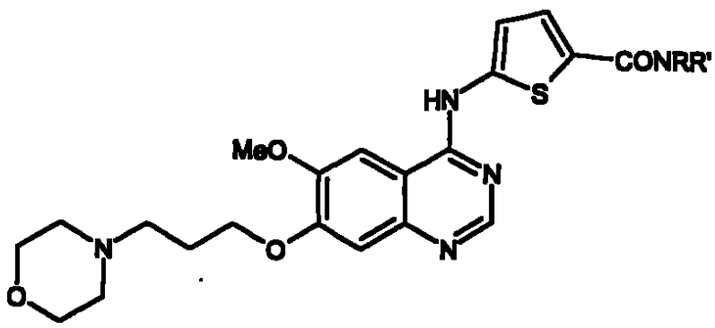
Compound No	NRR'
74	
75	
76	
77	
78	

Table 6



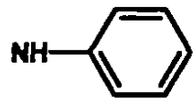
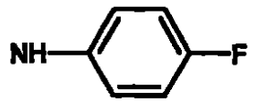
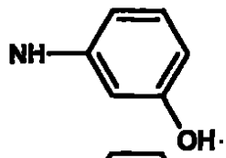
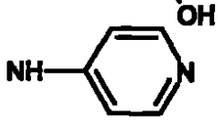
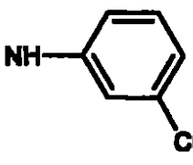
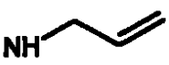
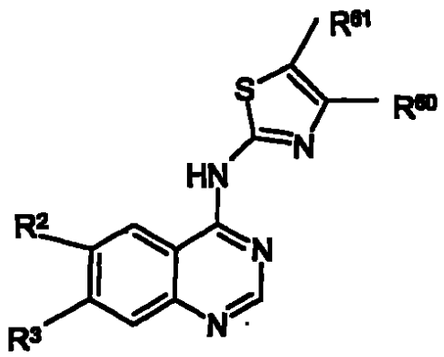
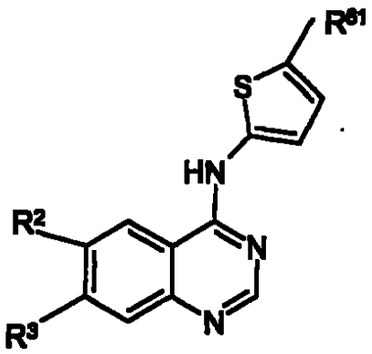
Compound No.	NRR'
79	
80	
81	
82	
83	
84	
85	
86	

Table 7



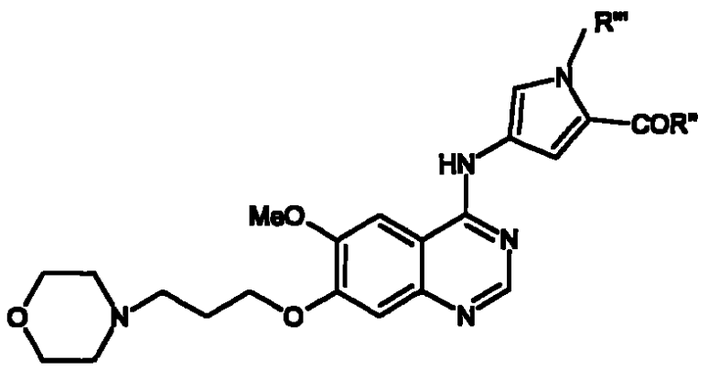
No.	R^2	R^3	R^{60}	R^{61}
200	OCH_3	OCH_3	$CH_2COOCH_2CH_3$	H
201	OCH_3	OCH_3	CH_2COOH	H
202	OCH_3	OCH_3	CH_3	$COOCH_2CH_3$
203	OCH_3	$O(CH_2)_3$-N-morpholino	CH_3	$COOCH_2CH_3$
204	OCH_3	$O(CH_2)_3$-N-morpholino	CH_3	COOH
205	OCH_3	$O(CH_2)_3$-N-morpholino	$CH_2COOCH_2CH_3$	H
206	OCH_3	$O(CH_2)_3$-N-morpholino	$COOCH_2CH_3$	H
207	OCH_3	$O(CH_2)_3$-N-morpholino	COOH	H
208	OCH_3	$O(CH_2)_3$-N-morpholino	H	$COOCH_2CH_3$
209	OCH_3	$O(CH_2)_3$-N-morpholino	H	COOH
210	OCH_3	$O(CH_2)_3$-N-morpholino	$CH_2COOCH_2CH_3$	CH_3
211	OCH_3	$O(CH_2)_3$-N-morpholino	CH_2COOH	CH_3

Table 8



No.	R^2	R^3	R^{61}
212	OCH_3	$O(CH_2)_3$-N-morpholino	COOH
213	OCH_3	OCH_3	$COOCH_2CH_3$
214	OCH_3	OCH_3	COOH

Table 9



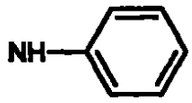
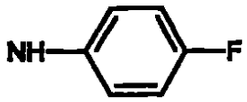
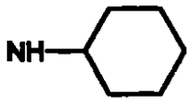
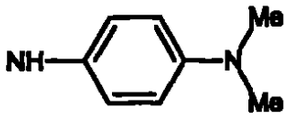
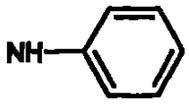
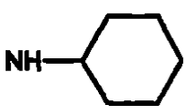
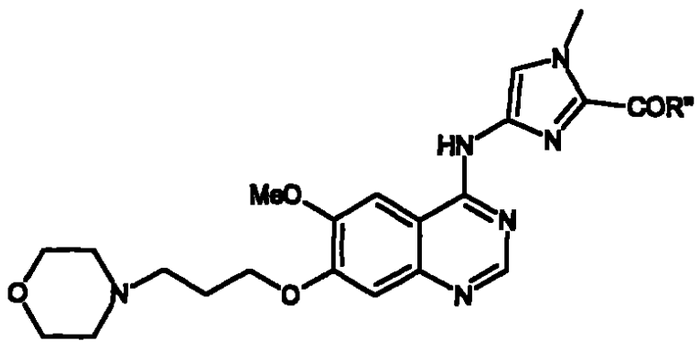
Compound No	R'''	R''
250	CH_3	OCH_3
251	CH_3	OH
252	CH_3	
253	CH_3	
254	CH_3	
255	CH_3	
256	H	OCH_2CH_3
257	H	OH
258	H	
259	H	

Table 10



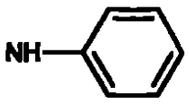
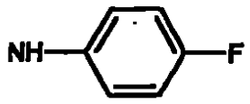
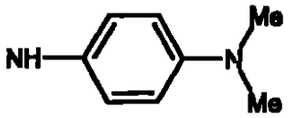
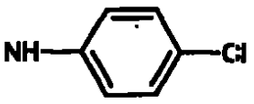
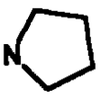
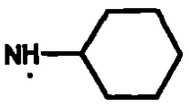
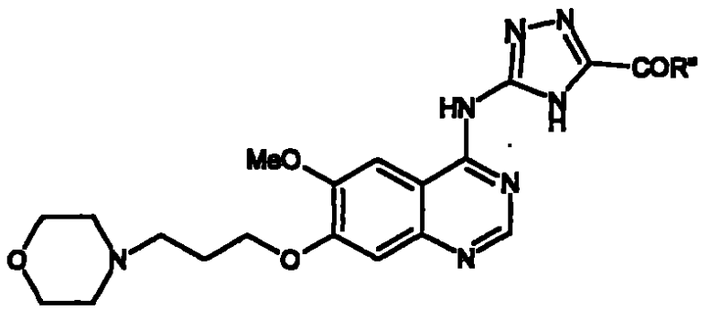
Compound No	R"
260	$COOCH_3$
261	COOH
262	
263	
264	
265	
266	
267	

Table 11



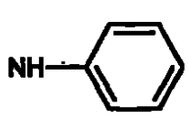
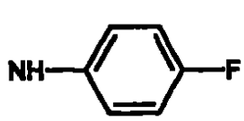
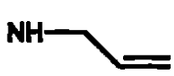
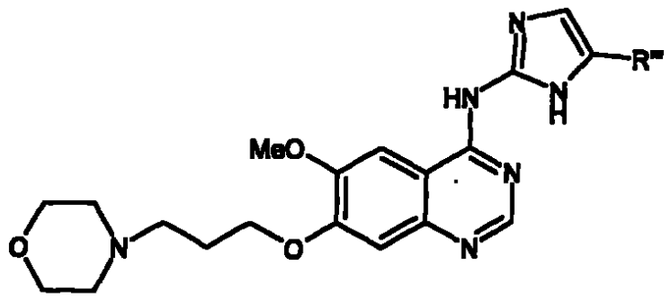
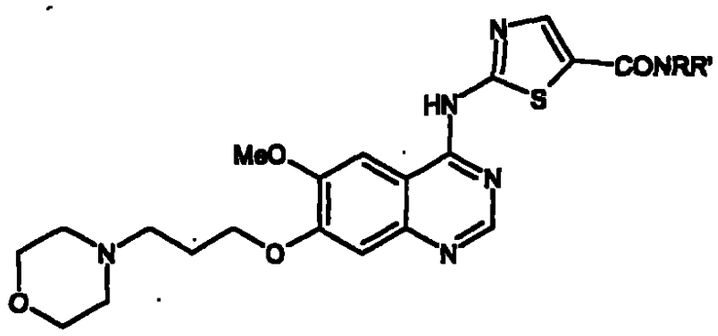
Compound No	R"
268	$COOCH_2CH_3$
269	COOH
270	
271	
272	

Table 12



Compound No.	R''''
300	H
301	$COOCH_2CH_3$

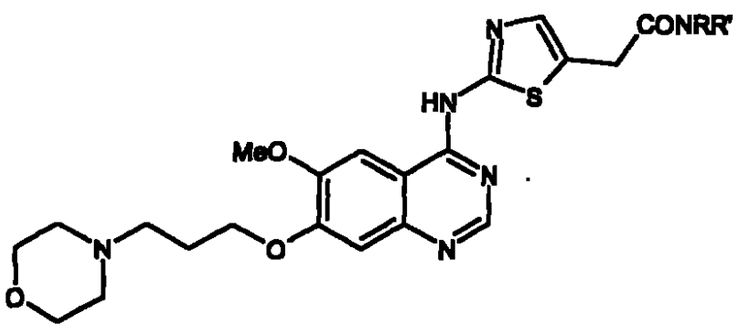
TABLE 13.



N°	NRR'	N°	NRR'
302	4-methoxyanilins	320	2-methyl-4-fluoroaniline
303	4-methylaniline	321	2-fluoro-5-methylaniline
304	2-aminopyridine	322	4-fluorobenzylamine
305	2-aminobenzyl alcohol	323	3,4-difluorobenzylamine
306	4-methoxybenzylamine	324	3-methylaniline
307	3-nitroaniline	325	2-(methylthio)aniline
308	Aminoacetonitrile	326	5-aminoindole
309	2-methyl-5-nitroaniline	327	3-aminobenzonitrile
310	Cyclopropylamine	328	2,4-difluorobenzylamine
311	4-nitrobenzylamine	329	3-(2-aminoethyl)pyridine
312	2-anilinoethanol	330	N-methylisobutylamine
313	Furfurylamine	331	2-aminobenzylamine
314	3-chloroaniline	332	3-methylbutylamine

315	2-methoxyaniline	333	1-aminomethyl-1-cyclohexanol
316	thiophene-2-methylamine	334	2-aminomethylpyrazine
317	Neopentylamine	335	3-methoxyaniline
318	2,6-difluorobenzylamine	336	4-chlorobenzylamine
319	2-methylallylamine		

TABLE 14



N°	NRR'	N°	NRR'
337	Aniline	357	2-methoxyaniline
338	3-chloro-4-fluoroaniline	358	2-fluoroaniline
339	4-chloroaniline	359	thiophene-2-methylamine
340	3,4-difluoroaniline	360	2-amino-1-phenylethanol
341	3-methoxyaniline	361	3-(1-hydroxyethyl)aniline
342	2-chloroaniline	362	neopentylamine

343 4-methoxyaniline

344 4-methylaniline

345 2-methylaniline

346 2-aminopyridine

347 2-aminobenzylalcohol

348 2-amino-3-methyl-1-butanol

349 2-anilino ethanol

350 3-chloro-4-methylaniline

351 3-nitroaniline

352 aminoacetonitrile

353 2-methyl-5-nitroaniline

354 2-amino-5-chloropyridine

355 4-trifluoromethylaniline

356 3-chloroaniline

363 3-fluoro-4-methoxyaniline

364 2-methyl-4-fluoroaniline

365 2,5-difluoroaniline

366 2-fluoro-4-chloroaniline

367 2-fluoro-4-methylaniline

368 3-methylaniline

369 2-(methylthio)aniline

370 5-aminoindole

371 2,4-difluoroaniline

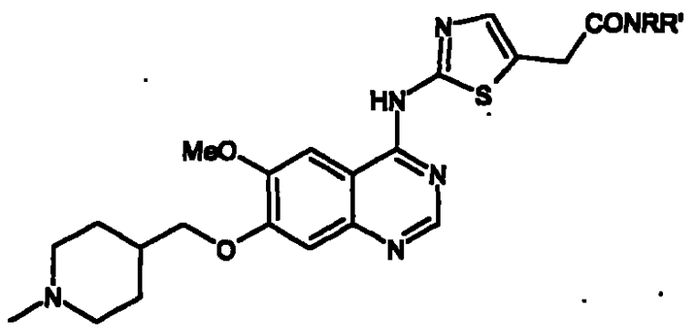
372 2-fluoro-4-methylaniline

373 3-cyanoaniline

374 2-methyl-5-fluoroaniline

375 2-methyl-5-chloroaniline

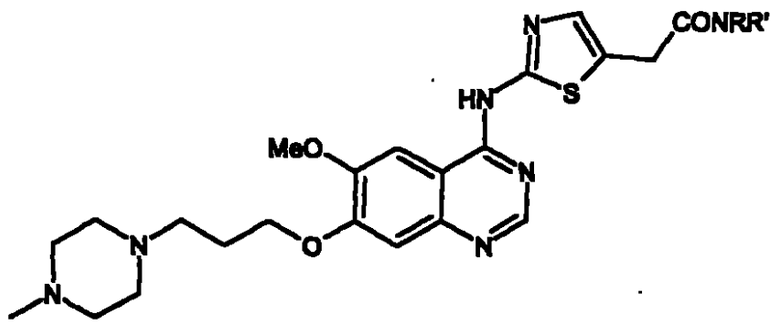
TABLE 15



N°	NRR'	N°	NRR'
376	aniline	390	3-fluoro-4-methoxyaniline
377	3-chloro-4-fluoroaniline	391	2-methyl-4-fluoroaniline
378	2-aminopyridine	392	2-amino-4-methylpyridine
379	3,4-difluoroaniline	393	2,5-difluoroaniline
380	2-chloroaniline	394	2-fluoro-4-chloroaniline
381	4-methylaniline	395	2-fluoro-5-methylaniline
382	2-methylaniline	396	3-methylaniline
383	4-chloroaniline	397	2,4-difluoroaniline
384	4-fluoroaniline	398	2-fluoro-4-methylaniline
385	2-amino-6-methylpyridine	399	3-cyanoaniline
386	3-methoxyaniline	400	2-methyl-5-fluoroaniline
387	2-amino-5-chloropyridine	401	3,5-difluoroaniline
388	3-chloroaniline	402	3-fluoroaniline

389 2-fluoroaniline

TABLE 16



N°	NRR'	N°	NRR'
403	Aniline		
404	3,4-difluoroaniline		
405	2-aminopyridine	418	2-fluoro-4-methylaniline
406	3-chloro-4-fluoroaniline	419	3-fluoro-4-methoxyaniline
407	2-chloroaniline		
408	4-methylaniline	420	2-methyl-4-fluroaniline
409	2-methylaniline	421	2-amino-4-methylpyridine
410	4-chloroaniline	422	2,5-difluoraniline
411	4-fluoroaniline	423	2-fluoro-4-chloroaniline
412	2-amino-6-methylpyridine	424	2-fluoro-5-methylaniline
413	3-methoxyaniline	425	3-methylaniline
414	2-amino-5-chloropyridine	426	2,4-difluoroaniline
415	3-chloroaniline	427	2-methyl-5-fluoroaniline

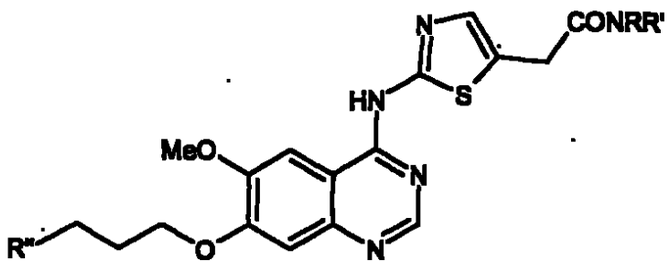
416 2-fluoroaniline

417 3-cyanoaniline

428 3,5-difluoroaniline

429 3-fluoroaniline

TABLE 17



N°	R"	NRR'
430	pyrrolidine	3-chloroaniline
431	pyrrolidine	3,4-difluoroaniline
432	dimethylamine	3,5-difluoroaniline
433	2-amino-2-methyl-1-propanol	3-chloro-4-fluoroaniline
434	2-amino-2-methyl-1-propanol	3-fluoroaniline
435	4-hydroxypiperidine	3,4-difluoroaniline
436	N,N-dimethylethylenediamine	3,4-difluoroaniline
437	piperidine	3,4-difluoroaniline
438	2-methylaminoethanol	3,4-difluoroaniline
439	1,2-diamino-2-methylpropane	3,4-difluoroaniline
440	cyclohexylamine	3,4-difluoroaniline
441	N,N,N'-trimethylethylenediamine	3,4-difluoroaniline
442	D-prolinol	3,4-difluoroaniline

443	L-prolinol	3,4-difluoroaniline
444	3-pyrrolidinol	3,4-difluoroaniline
445	1-(2-aminoethyl)pyrrolidine	3,4-difluoroaniline
446	1-acetylpiperazine	3,4-difluoroaniline
447	1-(2-morpholinoethyl)piperazine	3,4-difluoroaniline
448	2-(2-hydroxyethyl)piperidine	3,4-difluoroaniline
449	1-(2-hydroxyethyl)piperazine	3,4-difluoroaniline
450	cyclopentylamine	3,4-difluoroaniline
451	4-(2-hydroxyethyl)piperidine	3,4-difluoroaniline
452	L-alanine tert-butyester	3,4-difluoroaniline
453	3-hydroxypiperidine	3,4-difluoroaniline
454	4-hydroxymethylpiperidine	3,4-difluoroaniline
455	1-amino-2-propanol	3,4-difluoroaniline
456	L-alanine-tert-butylester	3-chloroaniline
457	2-methylaminoethanol	3-chloroaniline
458	1,2-diamino-2-methylpropane	3-chloroaniline
459	cyclohexylamine	3-chloroaniline
460	N,N-dimethylethylenediamine	3-chloroaniline
461	N,N,N'-trimethylethylenediamine	3-chloroaniline
462	D-prolinol	3-chloroaniline

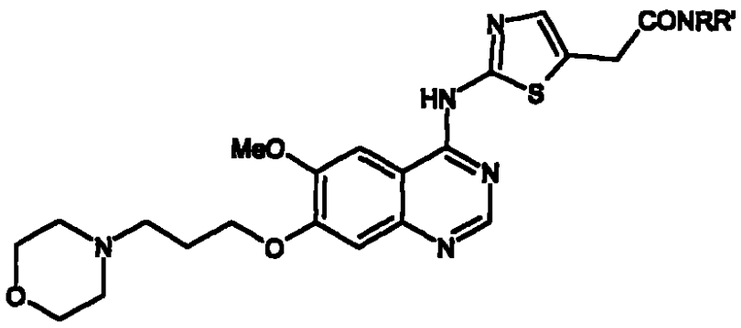
463	L-prolinol	3-chloroaniline
464	4-hydroxypiperidine	3-chloroaniline
465	3-pyrrolidinol	3-chloroaniline
466	1-(2-aminoethyl)pyrrolidine	3-chloroaniline
467	4-hydroxymethylpiperidine	3-chloroaniline
468	1-(2-hydroxyethyl)piperazine	3-chloroaniline
469	cyclopentylamine	3-chloroaniline
470	4-(2-hydroxyethyl)piperidine	3-chloroaniline
471	3-hydroxypiperidine	3-chloroaniline
472	(S)-1-amino-2-porpanol	3-chloroaniline
473	(R)-1-amino-2-propanol	3-chloroaniline
474	piperazine	3-chloroaniline
475	2-(2-hydroxyethyl)piperidine	3-chloroaniline
476	2-amino-2-methyl-1-propanol	3-chloroaniline
477	1-(2-dimethylaminoethyl)piperazine	3-chloroaniline
478	dimethylamine	3-chloroaniline
479	aminomethylcyclopropane	3-chloroaniline
480	piperidine	3-chloroaniline
481	1-(2-dimethylaminoethyl)piperazine	3,5-difluoroaniline
482	(S)-(+)-2-Pyrrolidine methanol	3,5-difluoroaniline

483	4-hydroxypiperidine	3,5-difluoroaniline
484	3-pyrrolidinol	3,5-difluoroaniline
485	1-(2-aminoethyl)pyrrolidine	3,5-difluoroaniline
486	4-hydroxymethylpiperidine	3,5-difluoroaniline
487	2-(2-hydroxyethyl)piperidine	3,5-difluoroaniline
488	1-(2-hydroxyethyl)piperazine	3,5-difluoroaniline
489	4-(2-hydroxyethyl)piperidine	3,5-difluoroaniline
490	3-hydroxypiperidine	3,5-difluoroaniline
491	N,N,N'-trimethylethylenediamine	3,5-difluoroaniline
492	piperidine	3,5-difluoroaniline
493	pyrrolidine	3,5-difluoroaniline
494	2-amino-2-methyl-1-propanol	3,5-difluoroaniline
495	2-methylaminoethanol	3,5-difluoroaniline
496	N,N-dimethylethylenediamine	3,5-difluoroaniline
497	(S)-(+)-1-amino-2-propanol	3,5-difluoroaniline
498	(R)-(-)-1-amino-2-propanol	3,5-difluoroaniline
499	piperazine	3,5-difluoroaniline
500	N-allylpiperazine	3,5-difluoroaniline
501	(R)-(-)-2-pyrrolidinemethanol	3,5-difluoroaniline
502	cyclopentylamine	3,5-difluoroaniline

503	2-methylaminoethanol	3-chloro-4-fluoroaniline
504	N,N,N'-trimethylethylenediamine	3-chloro-4-fluoroaniline
505	N-allylpiperazine	3-chloro-4-fluoroaniline
506	4-hydroxypiperidine	3-chloro-4-fluoroaniline
507	3-pyrrolidinol	3-chloro-4-fluoroaniline
508	1-(2-aminoethyl)pyrrolidine	3-chloro-4-fluoroaniline
509	N-acetylpiperazine	3-chloro-4-fluoroaniline
510	2-(2-hydroxyethyl)piperidine	3-chloro-4-fluoroaniline
511	1-(2-hydroxyethyl)piperazine	3-chloro-4-fluoroaniline
512	cyclopentylamine	3-chloro-4-fluoroaniline
513	4-(2-hydroxyethyl)piperidine	3-chloro-4-fluoroaniline
514	3-hydroxypiperidine	3-chloro-4-fluoroaniline
515	4-hydroxymethylpiperidine	3-chloro-4-fluoroaniline
516	1-amino-2-propanol	3-chloro-4-fluoroaniline
517	piperazine	3-chloro-4-fluoroaniline
518	1-(2-morpholinoethyl)piperazine	3-chloro-4-fluoroaniline
519	pyrrolidine	3-chloro-4-fluoroaniline
520	2-methylaminoethanol	3-fluoroaniline
521	1,2-diamino-2-methylpropane	3-fluoroaniline
522	N,N-dimethylethylenediamine	3-fluoroaniline

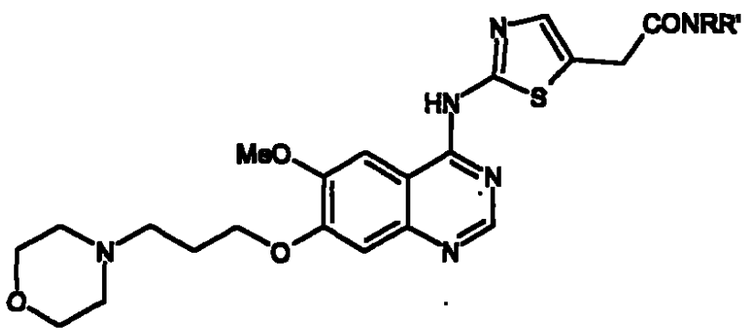
523	N,N,N'-trimethylethylenediamine	3-fluoroaniline
524	N-allylpiperazine	3-fluoroaniline
525	4-hydroxypiperidine	3-fluoroaniline
526	3-pyrrolidinol	3-fluoroaniline
527	1-(aminoethyl)pyrrolidine	3-fluoroaniline
528	N-acetylpiperazine	3-fluoroaniline
529	1-(2-hydroxyethyl)piperazine	3-fluoroaniline
530	cyclopentylamine	3-fluoroaniline
531	4-(2-hydroxyethyl)piperidine	3-fluoroaniline
532	3-hydroxypiperidine	3-fluoroaniline
533	4-hydroxymethylpiperidine	3-fluoroaniline
534	1-amino-2-propanol	3-fluoroaniline
535	(R)-(-)-2-pyrrolidinemethanol	3-fluoroaniline
536	(S)-(+)-2-pyrrolidinemethanol	3-fluoroaniline
537	piperazine	3-fluoroaniline
538	1-(2-morpholinoethyl)piperazine	3-fluoroaniline

TABLE 18



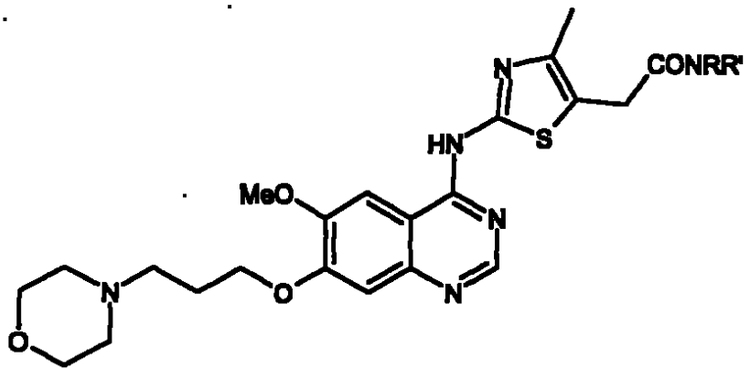
N°	NRR'
539	N-ethylaniline
540	3-chloro-4-fluoro-N-methylaniline
541	ethyl-2-(3-chloro-4-fluoroanilino)acetate
542	2-anilinoacetronitrile
543	3-anilinopropanitrile
544	N-(2-tert-butoxyethyl)-3-chloro-4-fluoroaniline
545	N-allylaniline
546	N-ethyl-3,4-(methylmedioxy)aniline
547	ethyl-4-(N-butylamino)benzate
548	N-ethyl-M-toluidine
549	N-(2-hydroxy"thyl)-3-chloro-4-fluoroaniline

TABLE 18



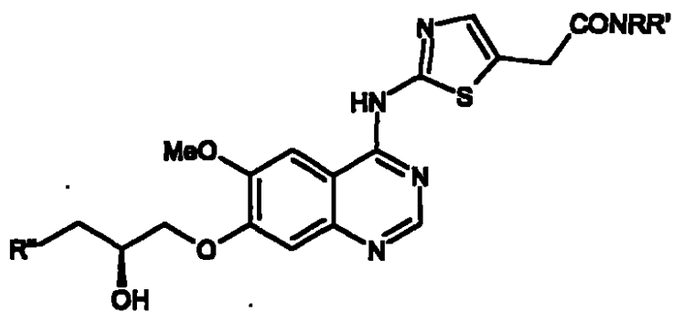
N°	NRR'
550	N-ethylaniline
551	3-chloro-4-fluoro-N-methylaniline
552	ethyl-2-(3-chloro-4-fluoroanilino)acetate
553	2-anilinoacetronitrile
554	3-anilinopropanitrile
555	N-(2-tert-butoxyethyl)-3-chloro-4-fluoroaniline
556	N-allylaniline
557	N-ethyl-3,4-(methylmedioxy)aniline
558	ethyl-4-(N-butylamino)benzate
559	N-ethyl-M-toluidine
560	N-(2-hydroxy"thyl)-3-chloro-4-fluoroaniline

TABLE 19



N°	NRR'
561	aniline
562	3-chloro-4-fluoroaniline
563	2-aminopyridine
564	3,4-difluoroaniline

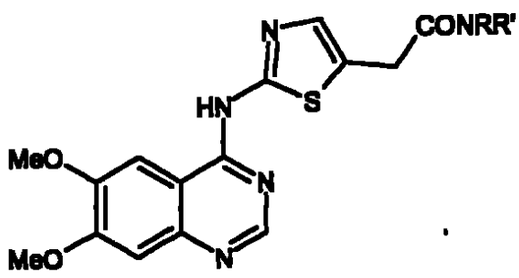
TABLE 20



N°	R""	NRR'
565	piperidine	3-chloro-4-fluoroaniline
566	pyrrolidine	3-chloro-4-fluoroaniline
567	4-hydroxypiperidine	3-chloro-4-fluoroaniline
568	piperazine	3-chloro-4-fluoroaniline
569	cyclopentylamine	3-chloro-4-fluoroaniline
570	2-amino-2-methyl-1-propanol	3-chloro-4-fluoroaniline
571	piperidine	3,4-difluoroaniline
572	pyrrolidine	3,4-difluoroaniline
573	4-hydroxypiperidine	3,4-difluoroaniline
574	cyclopentylamine	3,4-difluoroaniline

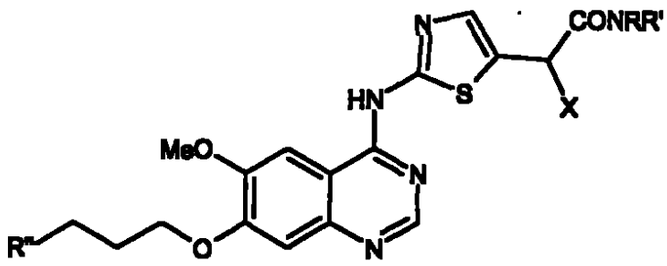
575	pyrrolidine	3-chloroaniline
576	4-hydroxypiperidine	3-chloroaniline
577	cyclopentylamine	3-chloroaniline
578	2-amino-2-methyl-1-propanol	3-chloroaniline
579	piperazine	3-chloroaniline
580	OMe	3-chloroaniline
581	piperidine	3-chloroaniline
582	piperidine	3,5-difluoroaniline
583	pyrrolidine	3,5-difluoroaniline
584	2-amino-2-methyl-1-propanol	3,5-difluoroaniline
585	piperazine (acetate)	3,5-difluoroaniline
586	piperazine	3,5-difluoroaniline
587	pyrrolidine	3-fluoroaniline
588	piperidine	3-fluoroaniline
589	piperazine	3-fluoroaniline
590	piperazine (acetate)	3-fluoroaniline
591	cyclopentylamine	3-fluoroaniline

TABLE21



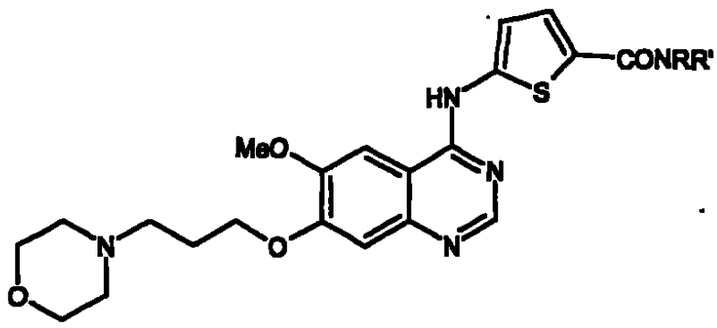
N°	NRR'
592	3,5-difluoroaniline
593	3-chloroaniline
594	3-chloro-4-fluoroaniline
595	3,4-difluoroaniline

TABLE 22



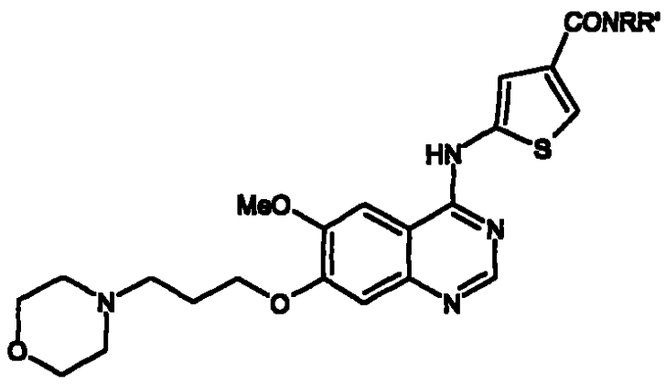
N°	R'''	Y	NRR'
596	morpholine	OH	aniline
597	morpholine	OH	3,4-difluoroaniline
598	N-Me-piperazine	OH	3,4-difluoroaniline
599	piperidine	OH	3-fluoroaniline
600	piperidine	OH	3-chloroaniline
601	N-Me-piperazine	=N-OH	3,4-difluoroaniline

TABLE 23



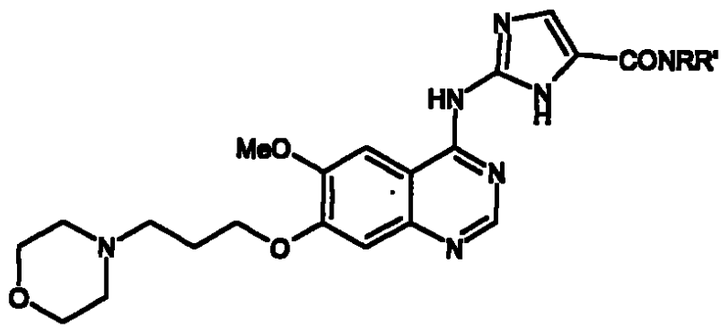
Nº	NRR'	Nº	NRR'
602	2-aminopyridine	610	2-methoxyaniline
603	4-methylaniline	611	3-(2-hydroxyethyl)aniline
604	2-methylaniline	612	3-fluoro-4-methoxyaniline
605	3-methoxyaniline	613	2-methyl-4-fluoroaniline
606	2-hydroxymethylaniline	614	2-fluoro-5-methylaniline
607	3-nitroaniline	615	3-cyanoaniline
608	4-trifluoromethylaniline	616	isoamylamine
609	3-chloroaniline	617	2-chloroaniline

TABLE 24



Nº	NRR'
618	aniline
619	4-fluoroaniline
620	3-hydroxyaniline
621	3-(methylthio)aniline
622	4-fluoro-3-chloroaniline
623	2,4-difluorobenzylamine
624	3-fluoroaniline

TABLE 25

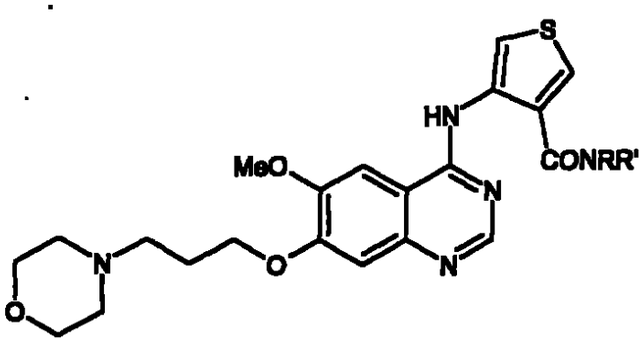


N°	NRR'
625	aniline
626	4-fluoroaniline
627	allylamine

30

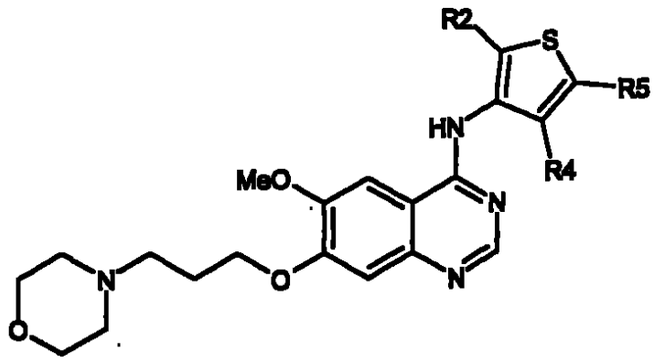
31

TABLE 26



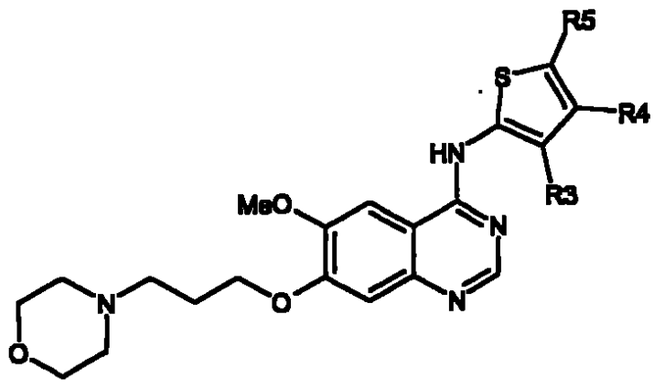
Nº	NRR'
628	aniline
629	allylamine

TABLE 27



Nº	R_2	R_4	R_5
630	COOMe	H	H

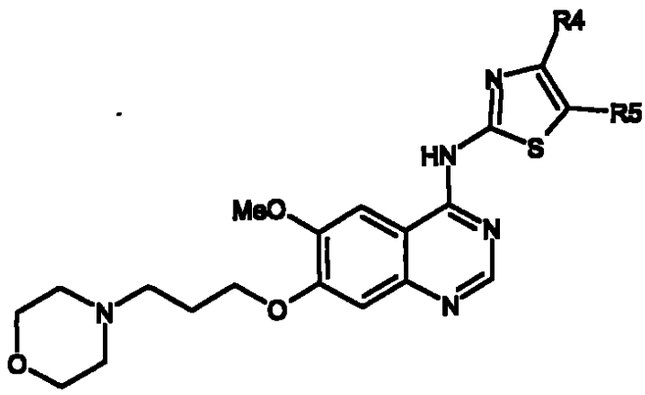
TABLE 28



Nº	R_3	R_4	R_5
631	CONH2	H	isopropyl
632	H	H	COO allyl

633	CONH2	H	H
634	CONH2	H	ethyl

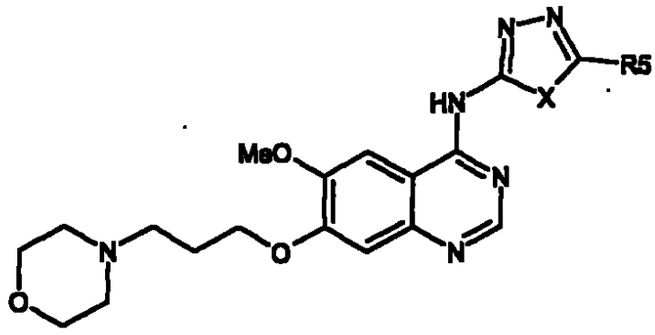
TABLE 29



	R4	R5
635	Ph	H
636	Me	COCH3
637	CF3	COOEt
638	Ph	COOEt
639	-(CH2)4-	
640	4-acetylaminophenyl	H
641	CF3	Ph
642	CF3	H
643	tert-butyl	H
644	Me	Me
645	Me	H
646	Me	-C(=N-OH)-Me
647	H	-NHCOO-tert-butyl
648	Me	-C(=NOMe)-Me
649	Me	-C(=NOPh)-Me
650	H	4-methoxyphenyl
651	H	Ph
652	H	Et
653	H	isopropyl

654	H	-CH2Ph
655	H	Me
657	H	n-butyl
658	H	CHO
659	H	-CH=N-OH

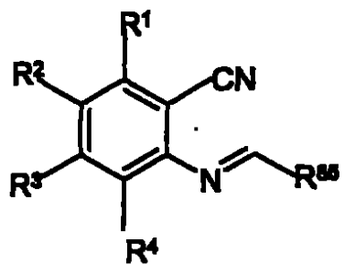
TABLE 30



	X	R5
660	S	tert-butyl
661	S	cyclopropyl
662	S	-S-CH2-CH3
662	S	-Ph
664	NH	-NH-Ph

Other compounds of Formula (I) or Formula (IA), in particular those in which R^5 carries a carboxy or carboxyl ester substituent are described below in the Examples.

Compounds of Formula (I) or Formula (IA) may be prepared by various methods which would be apparent from the literature. For example compounds of formula (I) where X is NH may be prepared by reacting a compound of formula (VII)



(VII)

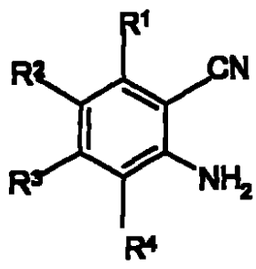
where R^1, R^2, R^3, and R^4 are as defined in relation to formula (I) and R^{85} is a group $NR^{86}R^{87}$ where R^{86} and R^{87} are independently selected from alkyl such as methyl , with a compound of formula (VIII)

$$H_2N\text{-}R^{5'} \qquad \text{(VIII)}$$

where $R^{5'}$ is a group R^5 as defined in relation to formula (I) or a precursor group thereof; and thereafter if desired or necessary, converting a precursor group $R^{5'}$ to a group R^5 and/or modifying substituents on the group R^5. The reaction is suitably effected in an organic solvent such as an acetic acid at elevated temperatures, conveniently at the reflux temperature of the solvent.

Examples of reactions in which a precursor group $R^{5'}$ is converted to a group R^5 and/or substituents on the group R^5 are modified are standard chemical reactions, such as conversion of esters to acids, and thereafter, if required to the preferred amides. Examples of such reactions are provided hereinafter.

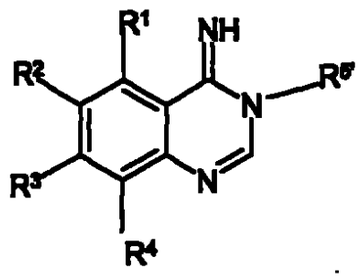
Compounds of formula (VII) are suitably prepared by reacting a compound of formula (IX)



(IX)

with an appropriate acetal such as N,N-dimethylformamide dimethyl acetal. The reaction is suitably effected in an organic solvent such as benzene, at elevated temperature, conveniently at the reflux temperature of the solvent.

Alternatively, compounds of formula (I) where X is NH may be prepared by rearranging a compound of formula (X)

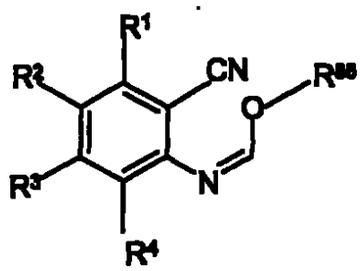


(X)

where R^1, R^2, R^3 and R^4 are as defined in relation to formula (I) and $R^{5'}$ is as defined in relation to formula (VIII) above, and thereafter if desired or necessary, converting a precursor group $R^{5'}$ to a group R^5 and/or modifying substituents on the group R^5, for example as described generally above.

The rearrangement reaction is suitably effected in an organic solvent such as an alkyl alcohol, in particular methanol, ethanol or cyclohexanol, acetic acid, or dimethylformamide, using a strong base such as sodium hydroxide, sodium acetate, sodium methylate, or dimethylamine. Elevated temperatures, for example of from 20°-120°C and preferably at about 75°C are employed.

Compounds of formula (X) are suitably obtained by reacting a compound of formula (XI)



(XI)

where R^1, R^2, R^3 and R^4 are as defined in relation to formula (I) and R^{86} is an alkyl group such as methyl; with a compound of formula (XII)

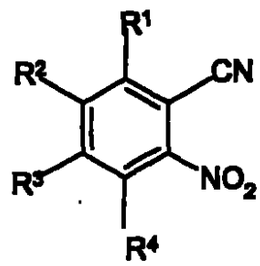
$$H_2N\text{-}R^{5'}$$

(XII)

where $R^{5'}$ is as defined in relation to formula (VIII). The reaction is suitably effected in an organic solvent such as methylene chloride, in the presence of a salt such as pyridinium hydrochloride. Moderate temperatures for example of from 0°-50°C and conveniently ambient temperature are employed.

Compounds of formula (XI) are suitably prepared by reacting a compound of formula (IX) as defined above, with a trialkylorthoformate such as trimethylorthoformate. The reaction is suitably effected at elevated temperature, for example of from 50°C to 120°C, and preferably at about 100°C, in the presence of a catalytic amount of an acid such as p-toluene sulphonic acid.

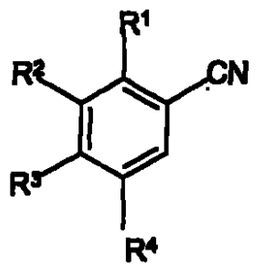
Compounds of formula (IX) are either known compounds or they can be prepared by conventional methods. In particular, compounds of formula (IX) may be prepared by reduction of the corresponding nitro compound of formula (XIII)



(XIII)

where R^1, R^2, R^3 and R^4 are as defined in relation to formula (I). Suitable reaction conditions are illustrated hereinafter.

Compounds of formula (XIII) may be obtained by nitration of a compound of formula (XIV)



(XIV)

Example 42.

An analogous reaction to that described in General Scheme 1, starting with 4-trifluoromethylaniline (43 mg, 0.26 mmol) yielded Compound 42 in Table 1(86 mg, 73 %).
MS ES^+ : 490 $(M+H)^+$

Example 43.

An analogous reaction to that described in General Scheme 1, starting with 3-amino-6-chloropyridine (33 mg, 0.26 mmol) yielded Compound 43 in Table 1(90 mg, 82 %).
^{1}HNMR (DMSO-d_6, TFA) : 3.92 (s, 2H) ; 3.96 (s, 3H) ; 4.0 (s, 3H) ; 7.27 (s, 1H) ; 7.28 (s, 1H) ; 7.46 (d, 1H) ; 7.98 (s, 1H) ; 8.1 (d, 1H) ; 8.65 (d, 1H) ; 9.1 (s, 1H).
MS ES^+ : 457,459 $(M+H)^+$

Example 44.

An analogous reaction to that described in General Scheme 1, starting with 2-methoxy-5-chloroaniline (42 mg, 0.26 mmol) yielded Compound 44 in Table 1(90 mg, 77 %).
MS ES^+ : 486, 488 $(M+H)^+$

Example 45.

An analogous reaction to that described in General Scheme 1, starting with 2-methylaminoethanol (20 mg, 0.26 mmol) yielded Compound 45 in Table 1(83 mg, 86 %).
MS ES^+ : 404 $(M+H)^+$

Example 46.

An analogous reaction to that described in General Scheme 1, starting with 4-aminopyridine (25 mg, 0.26 mmol) yielded Compound 46 in Table 1(101 mg, 100 %).
MS ES^+ : 423 $(M+H)^+$

Example 47.

An analogous reaction to that described in General Scheme 1, starting with 3-methyl-4-bromoaniline (49 mg, 0.26 mmol) yielded Compound 47 in Table 1(120 mg, 97 %).
MS ES^+ : 516, 517 $(M+H)^+$

Example 48.

An analogous reaction to that described in General Scheme 1, starting with 2-chloro-5-methoxyaniline (42 mg, 0.26 mmol) yielded Compound 48 in Table 1(65 mg, 56 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.73 (s, 2H) ; 3.98 (m, 9H) ; 6.78 (m, 1H) ; 7.28 (s, 2H) ; 7.39 (d, 1H) ; 7.50 (d, 1H) ; 7.98 (s, 1H) ; 9.10 (s, 1H).

MS ES$^+$: 486, 488 $(M,H)^+$

Example 49.

An analogous reaction to that described in General Scheme 1, starting with 4-aminotoluene (28 mg, 0.26 mmol) yielded Compound 49 in Table 1(89 mg, 85 %).

MS ES$^+$: 436 $(M,H)^+$

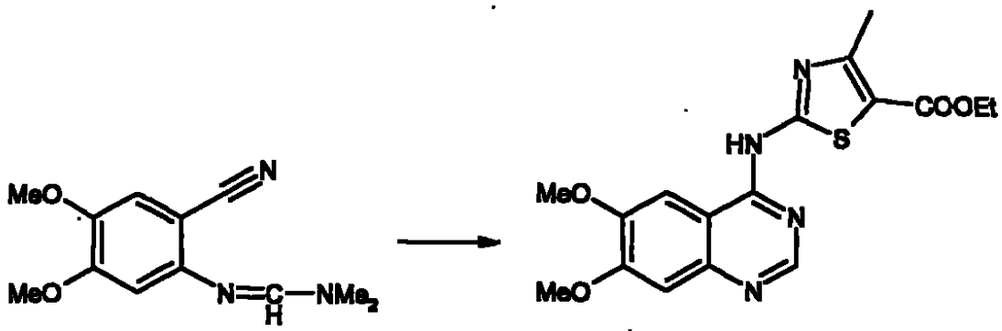
Example 50.

An analogous reaction to that described in General Scheme 1, starting with R(-)-2-pyrrolidinemethanol (27 mg, 0.26 mmol) yielded Compound 50 in Table 1(81 mg, 78 %).

MS ES$^+$: 430 $(M,H)^+$

Example 50A.

Preparation of Compound 202

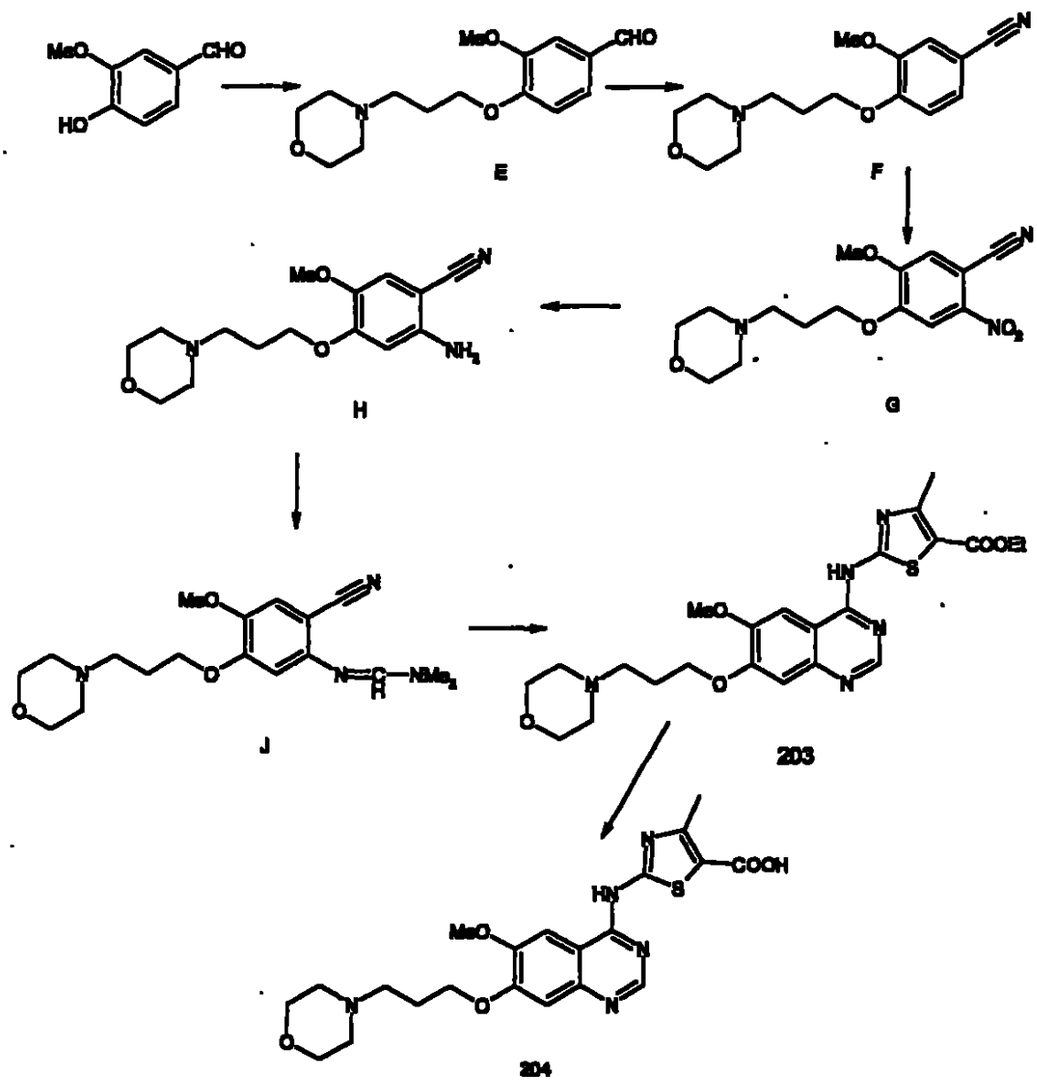


Amidine B (117 mg, 0.5 mmol) in acetic acid (12 ml) was reacted with ethyl-2-amino-4-methylthiazol-5-carboxylate (112 mg, 0.6 mmol) at 130°C for 3 hours. The solvent was evaporated, the residue was taken up into ethanol, and stirred for 10 minutes with a solution of $NaHCO_3$. The solid was recovered by filtration, washed with water, ether and dried under vacuum, to give title compound as a yellow solid (157 mg, 84 %).

^{1}HNMR (DMSO-d_6) : 1.31 (t, 3H) ; 2.6 (s, 3H) ; 3.96 (s, 6H) ; 4.27 (q, 2H) ; 7.28 (s, 1H) ; 8.11 (s, 1H) ; 8.77 (s, 1H).

MS ES$^+$: 375 $(M,H)^+$

General Scheme 2



Compound E

Vanilline (30.4 g, 0.2 mol) was solubilized in DMF (200 ml) in presence of K_2CO_3 at 50°C. N-(3-chloropropyl)morpholine was slowly added over 30 minutes to this mixture, which was heated over night at 80°C. Formed KCl was removed by filtration, the solvent was evaporated, and the residual orange oil dissolved in AcOEt, washed with water 2x, dried over $MgSO_4$, filtered and concentrated. The residual oil crystallises to give title compound as a white solid (45.6 g, 82 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.22 (m, 2H) ; 3.13 (t, 2H) ; 3.32 (t, 2H) ; 3.52 (d, 2H) ; 3.67 (t, 2H) ; 3.84 (s, 3H) ; 4.02 (d, 2H) ; 4.18 (t, 2H) ; 7.20 (d, 1H) ; 7.43 (d, 1H) ; 7.58 (d, 1H) ; 9.90 (s, 1H).

MS ES^+ : 280 $(M,H)^+$

Compound F

The aldehyde E (5.6 g, 20 mmol) was added to a solution of sodium acetate (3.3 g, 40 mmol) and hydroxylamine hydrochloride (2.8 g, 40 mmol) in acetic acid (25 ml). The mixture was refluxed for 18 hours, cooled, diluted with water and extracted with methylene chloride, dried over $MgSO_4$, filtered, concentrated, to give title compound (5.1 g, 93 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.19 (m, 2H) ; 3.12 (t, 2H) ; 3.29 (t, 2H) ; 3.50 (d, 2H) ; 3.67 (t, 2H) ; 3.81 (s, 3H) ; 4.01 (d, 2H) ; 4.15 (t, 2H) ; 7.12 (d, 1H) ; 7.39 (s, 1H) ; 7.41 (d, 1H).

MS ES^+ : 277 $(M,H)^+$

Compound G

The nitrile F (37.2 g, 135 mmol) in acetic acid (100 ml) was added to a solution of nitric acid (d = 1.42) 180 ml, at such a rate to maintain the temperature below 30°C. The mixture was stirred at room temperature over night. A solution of potassium hydroxide (10N, 370 ml) was then added slowly to the solution at 0° leading to a final pH of 11-12. The reaction was extracted with CH_2Cl_2, the organic phases were dried over MgSO4, filtered, evaporated to give a yellow solid which was washed with ether, dried to give title compound (22 g, 50 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.2 (m, 2H) ; 3.13 (t, 2H) ; 3.3 (t, 2H) ; 3.53 (d, 2H) ; 3.67 (t, 2H) ; 3.99 (s, 3H) ; 4.01 (d, 2H) ; 4.31 (t, 2H) ; 7.74 (s, 1H) ; 7.90 (s, 1H).

Compound H

Compound G (21 g, 65 mmol) in solution in CH_2Cl_2 (250 ml), was reacted with sodium hydrosulfite (92 g, 458 mmol) in solution in water (250 ml) in presence of tetrabutyl ammonium chloride (12.7 g, 45.8 mmol) at room temperature, over night. Sodium hydroxide (2N) was then added, and the reaction mixture was extracted with CH_2Cl_2, the organic phase was washed with water, dried over $MgSO_4$, filtered, evaporated. The residue was purified by silica gel chromatography, eluent : AcOEt / CH_2Cl_2 : 50/50 followed by MeOH / AcOEt / CH_2Cl_2 5/45/50 to 20/30/50 to give title compound (12.5 g, 66 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.2 (m, 2H) ; 3.13 (t, 2H) ; 3.31 (t, 2H) ; 3.53 (d, 2H) ; 3.68 (t, 2H) ; 3.71 (s, 3H) ; 4.05 (m, 4H) ; 6.56 (s, 1H) ; 7.02 (s, 1H).

MS ES$^+$: 292$(M+H)^+$

Compound J

The amino nitrile H (2.91 g, 10 mmol) in solution in toluene (50 ml) was reacted with N,N-dimethylformamide dimethyl acetal (1.79 g, 15 mmol), at 105°C for 5 hours, in a Dean Stark equipped flask. The solvent was evaporated, the residue triturated with ether to give title compound (3.4 g, 98 %).

^{1}HNMR (DMSO-d_6) : 1.87 (m, 2H) ; 2.36 (m, 6H) ; 2.95 (s, 3H) ; 3.04 (s, 3H) ; 3.56 (t, 4H) ; 3.72 (s, 3H) ; 4.06 (t, 2H) ; 6.72 (s, 1H) ; 7.07 (s, 1H) ; 7.89 (s, 1H).

MS ES$^+$: 347 $(M+H)^+$

Compound 203

Amidine J (173 mg, 0.5 mmol) was dissolved in AcOH (1.7 ml) in presence of ethyl-2-amino-4-methyl thiazole-5-carboxylate (112 mg, 0.6 mmol) and heated at 130°C for 3 hours. The solvent was removed by evaporation, and the residual solid was stirred in ethanol and a diluted solution of $NaHCO_3$ for 10 minutes. The solid was washed with water, dried over P_2O_5 under vacuum, to give a yellow powder of title compound (170 mg, 70 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.32 (t, 3H) ; 2.30 (m, 2H) ; 2.68 (s, 3H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (m, 4H) ; 7.38 (s, 1H) ; 8.01 (s, 1H) ; 9.26 (s, 1H).

MS ES$^+$: 488 $(M+H)^+$

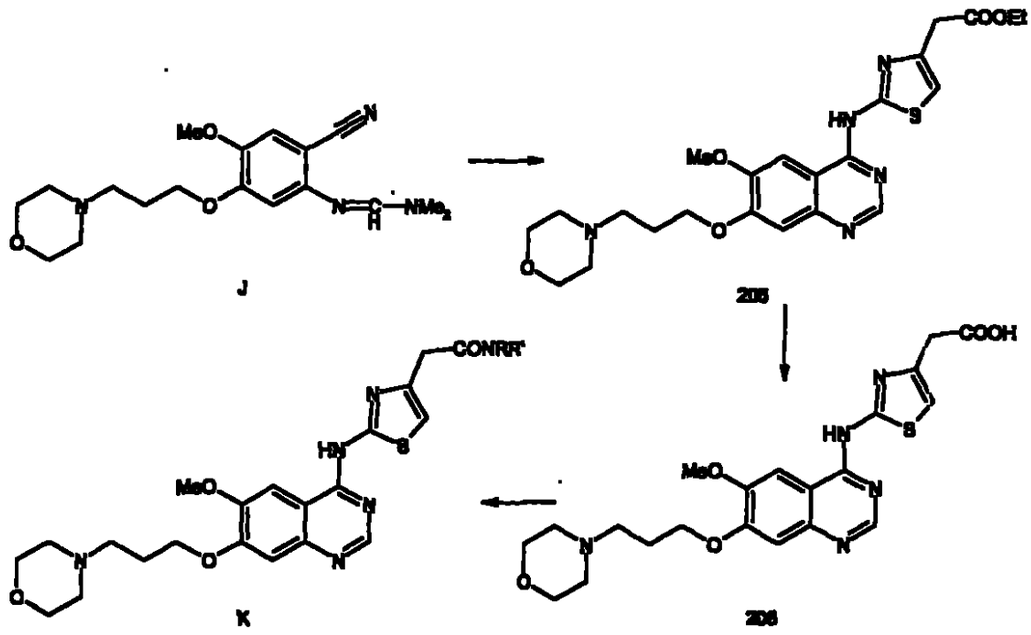
Compound 204

The ester 203 (122 mg, 0.25 mmol) was suspended in ethanol (5 ml) and reacted with sodium hydroxide (10N, 0.5 ml) at 80°C for 1 hour. The reaction mixture was cooled, acidified (pH 3.5), the yellow precipitate was filtered, washed with water, dried under vacuum, to give title compound (100 mg, 87 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.32 (m, 2H) ; 2.62 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.57 (d, 2H) ; 3.71 (t, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 7.35 (s, 1H) ; 7.98 (s, 1H) ; 9.23 (s, 1H).

MS ES$^+$: 460 $(M+H)^+$

General Scheme 3



Compound 205

Amidine J (2.08 g, 6 mmol) was reacted with ethyl 2-amino-4-thiazolacetate (1.34 g, 7.2 mmol) in acetic acid (2 ml) at 130°C for 4 hours, under argon. The solvent was evaporated, the residual oil was triturated in ether / petr. ether, and the solid filtered. This solid was suspended in water at pH 9 ($NaHCO_3$) and extracted with CH_2Cl_2, dried, evaporated, to give title compound (2 g, 68 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.87 (s, 2H) ; 4.0 (s, 3H) ; 4.04 (d, 2H) ; 4.15 (q, 2H) ; 4.31 (t, 2H) ; 7.28 (s, 1H) ; 7.34 (s, 1H) ; 8.06 (s, 1H) ; 9.15 (s, 1H).

MS ES$^+$: 488 $(M,H)^+$

Compound 206

Ester 205 (2 g, 4.1 mmol) was suspended in ethanol (20 ml). 2N sodium hydroxide (4.1 ml, 8.2 mmol) was added to the suspension which was stirred for 3 hours at room temperature. HCl 2N was added to the solution, the yellow precipitate was filtered, washed with water, ethanol, ether and dried under vacuum, to give title compound (1.98 g, 99 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.55 (d, 2H) ; 3.71 (t, 2H) ; 3.79 (s, 2H) ; 4.0 (s, 3H) ; 4.03 (d, 2H) ; 4.31 (t, 2H) ; 7.25 (s, 1H) ; 7.34 (s, 1H) ; 8.01 (s, 1H) ; 9.12 (s, 1H).

MS ES$^+$: 460 $(M+H)^+$

Synthesis of amides K, general procedure

The acid 206 (83 mg, 0.17 mmol) in DMF (0.8 ml) was reacted with amine (0.17 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (78 mg, 0.204 mmol), DIEA (52 mg, 0.4 mmol), for 6 hours at room temperature. The reaction mixture was then treated with a solution of $NaHCO_3$ (6 ml) with stirring for 2 hours, washed with water, cooled to 5°C, and the solid filtered, triturated with ether, dried under vacuum over P2O5 to give title compounds.

Example 51.

An analogous reaction to that described in General Scheme 3, starting with aniline (19 mg, 0.2 mmol) yielded Compound 51 in Table 2 (73 mg, 81 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.29 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.88 (s, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.09 (t, 1H) ; 7.27 (s, 1H) ; 7.33 (m, 3H) ; 7.63 (d, 2H) ; 7.99 (s, 1H) ; 9.12 (s, 1H).

MS ES$^+$: 535 $(M+H)^+$.

Example 52.

An analogous reaction to that described in General Scheme 3, starting with 4-fluoroaniline (23 mg, 0.2 mmol) yielded Compound 52 in Table 2(79 mg, 84 %).

^{1}HNMR (DMSO-d_6-TFA) : 2.29 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.67 (t, 2H) ; 3.87 (s, 2H) ; 3.98 (s, 3H) ; 4.02 (d, 2H) ; 4.3 (t, 2H) ; 7.17 (t, 2H) ; 7.27 (s, 1H) ; 7.32 (s, 1H) ; 7.63 (m, 2H) ; 7.99 (s, 1H) ; 9.11 (s, 1H).

MS ES$^+$: 553 $(M+H)^+$.

Example 53.

An analogous reaction to that described in General Scheme 3, starting with 4-dimethylaminoaniline (28 mg, 0.2 mmol) yielded Compound 53 in Table 2(52 mg, 53 %).

^{1}HNMR (DMSO-d6-TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.19 (s, 6H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.30 (t, 2H) ; 7.28 (s, 1H) ; 7.33 (s, 1H) ; 7.64 (d, 1H) ; 7.77 (d, 1H) ; 8.01 (s, 1H) ; 9.12 (s, 1H).

MS ES$^+$: 578 $(M+H)^+$

Example 54.

An analogous reaction to that described in General Scheme 3, starting with 4-chloroaniline (26 mg, 0.2 mmol) yielded Compound 54 in Table 2(72 mg, 75 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.31 (m, 2H) ; 3.14 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.89 (s, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.27 (s, 1H) ; 7.32 (s, 1H) ; 7.38 (d, 1H) ; 7.65 (d, 1H) ; 8.0 (s, 1H) ; 9.12 (s, 1H).

MS ES$^-$: 567, 569 $(M-H)^-$.

Example 55.

An analogous reaction to that described in General Scheme 3, starting with 3-amino-6-chloropyridine (26 mg, 0.2 mmol) yielded Compound 55 in Table 2(80 mg, 83 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.28 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.93 (s, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.3 (t, 2H) ; 7.29 (s, 1H) ; 7.33 (s, 1H) ; 7.49 (d, 1H) ; 8.01 (s, 1H) ; 8.09 (d, 1H) ; 8.66 (d, 1H) ; 9.13 (s, 1H).

MS ES$^+$: 570, 572 $(M+H)^+$.

Example 56.

An analogous reaction to that described in General Scheme 3, starting with morpholine (18 mg, 0.2 mmol) yielded Compound 56 in Table 2(14 mg, 16 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.6 (m, 12H) ; 3.9 (s, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.17 (s, 1H) ; 7.3 (s, 1H) ; 7.95 (s, 1H) ; 9.09 (s, 1H).

MS ES$^+$: 529 $(M+H)^+$

Example 57.

An analogous reaction to that described in General Scheme 3, starting with pyrrolidine (14 mg, 0.2 mmol) yielded Compound 57 in Table 2(73 mg, 84 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.82 (m, 2H) ; 1.93 (m, 2H) ; 2.28 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (m, 4H) ; 3.55 (m, 4H) ; 3.68 (t, 2H) ; 3.71 (s, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.3 (t, 2H) ; 7.17 (s, 1H) ; 7.3 (s, 1H) ; 7.94 (s, 1H) ; 9.08 (s, 1H).

MS ES$^+$: 513 $(M,H)^+$

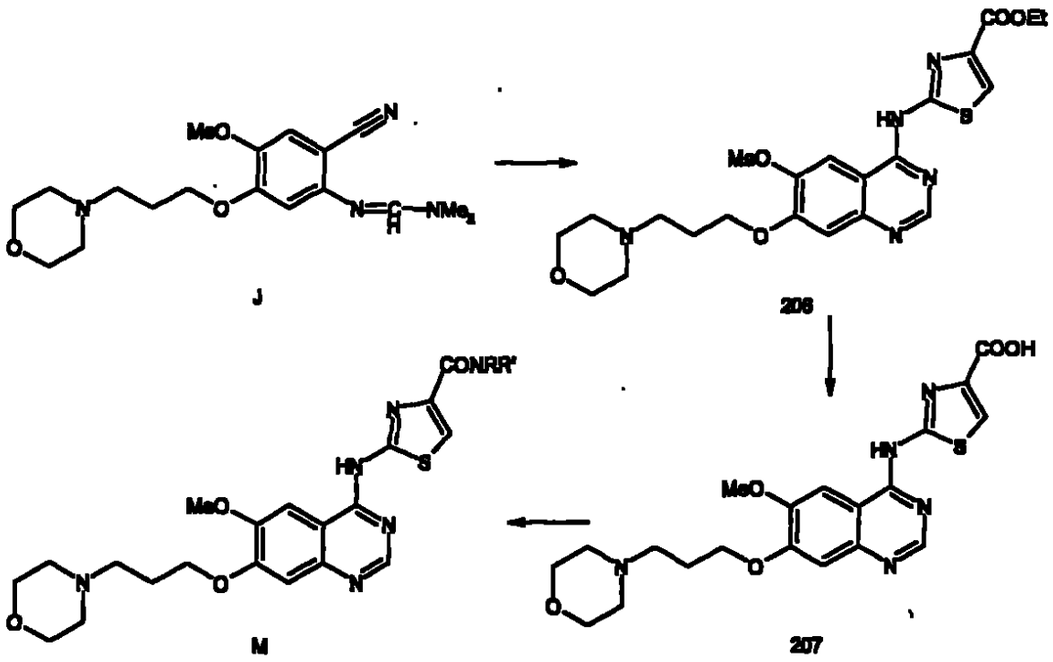
Example 58.

An analogous reaction to that described in General Scheme 3, starting with cyclohexylamine (20 mg, 0.2 mmol) yielded Compound 58 in Table 2 (80 mg, 87 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.25 (m, 4H) ; 1.75 (m, 4H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.56 (d, 2H) ; 3.6 (s, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.3 (t, 2H) ; 7.15 (s, 1H) ; 7.97 (s, 1H) ; 9.09 (s, 1H);

MS ES$^+$: 541 $(M,H)^+$

General Scheme 4



Compound 206

The amidine J (1.38 g, 4 mmol) in acetic acid (14 ml) was reacted with ethyl 2-amino-4-thiazolcarboxylate (0.72 g, 4.2 mmol) at 130°C for 6 hours. The solvent was evaporated, the residue dissolved in ethanol, and stirred with a saturated solution of $NaHCO_3$. The mixture

was extracted with CH_2Cl_2, dried, and purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH 98/2 → 90/10, to give title compound (0.738 g, 52 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.34 (t, 3H) ; 2.28 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (s, 3H) ; 4.04 (d, 2H) ; 4.34 (m, 4H) ; 7.45 (s, 1H) ; 8.33 (s, 1H) ; 8.44 (s, 1H) ; 9.26 (s, 1H).

MS ES$^+$: 474 $(M_1H)^+$

Compound 207

Ester 206 (946 mg, 2 mmol) in suspension in ethanol (20 ml) was treated with sodium hydroxide (6N, 4 ml) at 75°C for 45 minutes. The reaction mixture was then cooled to room temperature, acidified (pH 3) with 6N HCl. The precipitate was filtered, washed with ethanol, triturated with ether, dried under vacuum, to give title compound (795 mg, 80 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.34 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.76 (t, 2H) ; 4.03 (m, 5H) ; 4.35 (t, 2H) ; 7.48 (s, 1H) ; 8.26 (s, 1H) ; 8.41 (s, 1H) ; 9.29 (s, 1H).

Synthesis of amides of general structure M, general procedure

The acid 207 (79 mg, 0.16 mmol) in DMF (1 ml) was reacted with amine (0.19 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (73 mg, 0.19 mmol), DIEA (52 mg, 0.4 mmol), for 1 hour at room temperature. The reaction mixture was then treated with a solution of $NaHCO_3$ (5 ml) with stirring for 0.5 hour, and the solid filtered, dried under vacuum over P_2O_5. For the compounds which did not precipitate, the solution was concentrated to dryness, the residues were washed with methylene chloride / methanol, filtered. Alumine was added to the methylene chloride / methanol solution and the solvent evaporated. Purification of the compounds was carried out by chromatography over alumine, eluent CH_2Cl_2 ; CH_2Cl_2 / MeOH : 95/5, to give title compounds.

Example 59.

An analogous reaction to that described in General Scheme 4, starting with aniline (18 mg, 0.19 mmol) yielded Compound 59 in Table 3(50 mg, 60 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.34 (t, 2H) ; 7.14 (t, 1H) ; 7.39 (t, 2H) ; 7.45 (s, 1H) ; 7.8 (d, 2H) ; 8.29 (s, 1H) ; 8.41 (s, 1H) ; 9.29 (s, 1H).

MS ES$^+$: 521 $(M+H)^+$.

Example 60.

An analogous reaction to that described in General Scheme 4, starting with 4-fluoroaniline (21 mg, 0.19 mmol) yielded Compound 60 in Table 3(70 mg, 82 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.33 (t, 2H) ; 3.56 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (d, 2H) ; 4.04 (s, 3H) ; 4.35 (t, 2H) ; 7.22 (t, 2H) ; 7.45 (s, 1H) ; 7.83 (m, 2H) ; 8.28 (s, 1H) ; 8.4 (s, 1H) ; 9.27 (s, 1H).

MS ES$^+$: 539 $(M+H)^+$

Example 61.

An analogous reaction to that described in General Scheme 4, starting with 4-chloroaniline (24 mg, 0.19 mmol) yielded Compound 61 in Table 3(70 mg, 79 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.68 (t, 2H) ; 4.04 (m, 5H) ; 4.35 (t, 2H) ; 7.45 (m, 3H) ; 7.84 (d, 2H) ; 8.29 (s, 1H) ; 8.4 (s, 1H) ; 9.27 (s, 1H).

MS ES$^+$: 555, 557 $(M+H)^+$

Example 62.

An analogous reaction to that described in General Scheme 4, starting with cyclohexylamine (19 mg, 0.19 mmol) yielded Compound 62 in Table 3(60 mg, 72 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.32 (m, 5H) ; 1.62 (m, 1H) ; 1.73 (m, 2H) ; 1.87 (m, 2H) ; 2.33 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.75 (m, 1H) ; 4.03 (s, 3H) ; 4.05 (d, 2H) ; 4.33 (t, 2H) ; 7.42 (s, 1H) ; 8.07 (s, 1H) ; 8.32 (s, 1H) ; 9.24 (s, 1H).

MS ES$^+$: 527 $(M+H)^+$

Example 63.

An analogous reaction to that described in General Scheme 4, starting with 3-(methylamino)-propionitrile (16 mg, 0.19 mmol) yielded Compound 63 in Table 3(40 mg, 49 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 2.88 5m, 3H) ; 3.14 (m, 4H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.71 (t, 2H) ; 3.75 (m, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.44 (s, 1H) ; 7.85 (s, 1H) ; 8.37 (s, 1H) ; 9.27 (s, 1H).

MS ES$^+$: 512 $(M+H)^+$

Example 64.

An analogous reaction to that described in General Scheme 4, starting with 4-hydroxypiperidine (19 mg, 0.19 mmol) yielded Compound 64 in Table 3(45 mg, 54 M).
^{1}HNMR (DMSOd$_6$, TFA) : 1.36 (m, 2H) ; 1.78 (m, 2H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.29 (m, 2H) ; 3.37 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.77 (m, 2H) ; 3.84 (m, 1H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.42 (s, 1H) ; 7.75 (s, 1H) ; 8.35 (s, 1H) ; 9.27 (s, 1H).
MS ES$^+$: 529 $(M+H)^+$.

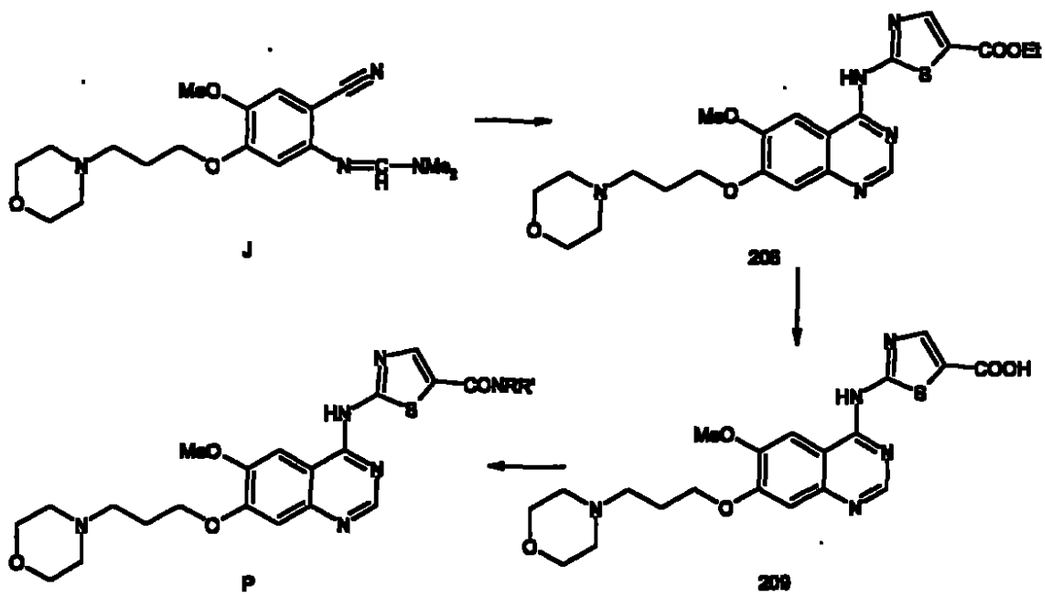
Example 65.

An analogous reaction to that described in General Scheme 4, starting with 4-aminopyridine (18 mg, 0.19 mmol) yielded Compound 65 in Table 3(35 mg, 42 %).
^{1}HNMR (DMSO-d$_6$, TFA) : 2.29 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (m, 5H) ; 4.34 (t, 2H) ; 7.48 (s, 1H) ; 8.41 (d, 2H) ; 8.43 (s, 1H) ; 8.52 (s, 1H) ; 8.81 (d, 2H) ; 9.24 (s, 1H).
MS ES$^+$: 522 $(M+H)^+$

Example 66.

An analogous reaction to that described in General Scheme 4, starting with 2-chloroaniline (24 mg, 0.19 mmol) yielded Compound 66 in Table 3 (25 mg, 28 %).
^{1}HNMR (DMSO-d$_6$, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (d, 2H) ; 4.05 (s, 3H) ; 4.35 (t, 2H) ; 7.24 (t, 1H) ; 7.42 (t, 1H) ; 7.47 (s, 1H) ; 7.6 (d, 1H) $(M+H)^+$.

General Scheme 5



Compound 208

The amidine J (1.52 g, 4.4 mmol) in AcOH (15 ml) was reacted with ethyl 2-amino-5-thiazolcarboxylate (757 mg, 4.4 mmol) at 130°C under argon for 3 hours. The solvent was evaporated, the residual oil was dissolved in methylene chloride and purified by silica gel chromatography, eluent CH_2Cl_2, CH_2Cl_2 / MeOH : 95/5, to give title compound as a yellow solid (1.44 g, 70 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.33 (t, 3H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.35 (m, 4H) ; 7.41 (s, 1H) ; 8.14 (s, 1H) ; 8.44 (s, 1H) ; 9.3 (s, 1H).

MS ES$^+$: 474 $(M+H)^+$

Compound 209

Ester 208 (1.6 g, 3.4 mmol) in suspension in ethanol (32 ml) was reacted with sodium hydroxide (6N, 6 ml) at 75°C for 1 hour. The cooled solution was acidified with HCl (6N) to pH 4. The solid was filtered, washed with EtOH, ether, dried, to give a yellow solid (1.65 g, 86 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.28 (m, 2H) ; 3.12 (t, 2H) ; 3.32 (t, 2H) ; 3.51 (d, 2H) ; 3.66 (t, 2H) ; 3.97 (s, 3H) ; 3.99 (d, 2H) ; 4.31 (t, 2H) ; 7.37 (s, 1H) ; 8.06 (s, 1H) ; 8.32 (s, 1H) ; 9.24 (s, 1H).

MS ES$^+$: 446 $(M+H)^+$

Synthesis of amides of general structure P, general procedure

The acid **209** (95 mg, 0.17 mmol) in DMF, 1 ml was reacted with amine (0.2 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (91 mg, 0.24 mmol), DIEA (110 mg, 0.85 mmol) for 14 hours at room temperature and 5 hours at 50°C. The reaction mixture was then treated with a solution of $NaHCO_3$ (1 ml) with stirring for 0.5 hour, and concentrated. The residue was washed with methylene chloride / methanol (1/1, 25 ml). Alumine was added to the organic phase, which was then evaporated. Purification of the compound was carried out by chromatography over alumine, eluent CH_2Cl_2, CH_2Cl_2 / MeOH / 95/5, to give title compounds.

Example 67.

An analogous reaction to that described in General Scheme 5, starting with aniline (19 mg, 0.2 mmol) yielded Compound 67 in Table 4 (30 mg, 34 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.14 (t, 1H) ; 7.39 (m, 3H) ; 7.73 (d, 2H) ; 8.05 (s, 1H) ; 8.61 (s, 1H) ; 9.28 (s, 1H).

MS ES$^+$: 521 $(M+H)^+$

Example 68.

An analogous reaction to that described in General Scheme 5, starting with 4-fluoroaniline (23 mg, 0.2 mmol) yielded Compound 68 in Table 4(58 mg, 64 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.20 (t, 1H) ; 7.38 (s, 1H) ; 7.73 (m, 1H) ; 8.05 (s, 1H) ; 8.57 (s, 1H) ; 9.28 (s, 1H).

MS ES$^+$: 539 $(M+H)^+$

Example 69.

An analogous reaction to that described in General Scheme 5, starting with 4-chloroaniline (26 mg, 0.2 mmol) yielded Compound 69 in Table 4(32 mg, 34 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.32 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 7.39 (s, 1H) ; 7.44 (d, 2H) ; 7.76 (d, 2H) . 8.06 (s, 1H) ; 8.6 (s, 1H) ; 9.29 (s, 1H).

MS ES$^+$: 555, 557 $(M+H)^+$

Example 70.

An analogous reaction to that described in General Scheme 5, starting with allylamine (12 mg, 0.2 mmol) yielded Compound 70 in Table 4(32 mg, 39 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.7 (t, 2H) ; 3.92 (d, 2H) ; 4.0 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 5.16 (d, 1H) ; 5.25 (d, 1H) ; 5.9 (m, 1H) ; 7.38 (s, 1H) ; 8.02 (s, 1H) ; 8.36 (s, 1H) ; 9.24 (s, 1H).

MS ES$^+$: 485 $(M+H)^+$

Example 71.

An analogous reaction to that described in General Scheme 5, starting with 3-(methylamino)-propionitrile (17 mg, 0.2 mmol) yielded Compound 71 in Table 4(32 mg, 39 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 2.89 (m, 3H) ; 3.15 (t, 2H) ; 3.34 (m, 4H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.8 (m, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 7.38 (s, 1H) ; 8.07 (s, 1H) ; 8.22 (s, 1H) ; 9.25 (s, 1H).

MS ES$^+$: 512 $(M+H)^+$.

Example 72.

An analogous reaction to that described in General Scheme 5, starting with 4-hydroxypiperidine (20 mg, 0.2 mmol) yielded Compound 72 in Table 4(12 mg, 13 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.45 (m, 2H) ; 1.82 (m, 2H) ; 2.31 (m, 2H) ; 3.15 (m, 4H) ; 3.35 (t, 2H) ; 3.4 (m, 2H) ; 3.54 (d, 2H) ; 3.7 (t, 2H) ; 3.79 (m, 1H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.38 (s, 1H) ; 8.06 (s, 1H) ; 8.09 (s, 1H) ; 9.23 (s, 1H).

MS ES$^+$: 529 $(M+H)^+$

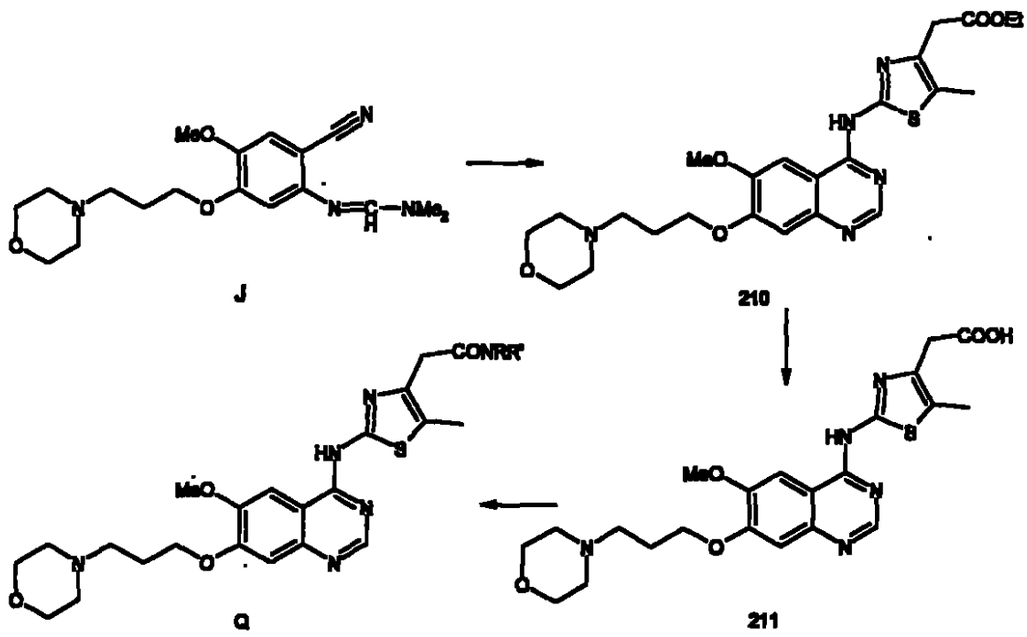
Example 73.

An analogous reaction to that described in General Scheme 5, starting with 4-aminopyridine (19 mg, 0.2 mmol) yielded Compound 73 in Table 4 (50 mg, 57 %).

^{1}HNMR (DMSO-d_6-TFA) : 2.29 (m, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.7 (t, 2H) ; 4.02 (s, 3H) ; 4.03 (d, 2H) ; 4.34 (t, 2H) ; 7.46 (s, 1H) ; 8.15 (s, 1H) ; 8.27 (d, 2H) ; 8.78 (s, 1H) ; 8.8 (d, 2H) ; 9.31 (s, 1H).

MS ES$^+$: 522 $(M+H)^+$

General Scheme 6



Compound 210

Amidine J (450 mg, 1.3 mmol) was reacted with methyl 2-amino-5-methyl-4-thiazolacetate (242 mg, 1.3 mmol) in acetic acid (5 ml) at 130°C for 3 hours, under argon. The solvent was evaporated, ethylacetate and water were added to the residual oil, the pH adjusted to 9 with a saturated solution of sodium bicarbonate and the mixture extracted with ethylacetate. The organic phase was washed with a saturated solution of sodium chloride, dried over magnesium sulphate, filtered, concentrated. The residual oil was purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH : 98/2 to 95/5 to give title compound (380 mg, 60 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 2.35 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.68 (s, 3H) ; 3.83 (s, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.31 (s, 1H) ; 7.96 (s, 1H) ; 9.06 (s, 1H).

MS ES$^+$: 488 $(M+H)^+$

Compound 211

Ester 210 (360 mg, 0.74 mmol) in ethanol (10 ml) was reacted with sodium hydroxide (6N, 1 ml) at room temperature for 1 hour. HCl (6N) was then added to the solution cooled to 0°C, and the pH adjusted to 3-4. The solid was recovered by filtration, washed with ethanol, ether, dried under vacuum, to give title compound as a dihydrochloride (550 mg, 83 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.34 (m, 5H) ; 3.13 (t, 2H) ; 3.32 (t, 2H) ; 3.52 (d, 2H) ; 3.74 (s, 2H) ; 3.78 (t, 2H) ; 3.98 (s, 3H) ; 4.01 (d, 2H) ; 4.31 (t, 2H) ; 7.37 (s, 1H) ; 7.91 (s, 1H) ; 9.03 (s, 1H).

MS ES$^+$: 474 $(M+H)^+$

Synthesis of amides of general structure O, general procedure

The acid 211 (87 mg, 0.13 mmol) in DMF (1 ml) was reacted with amine (0.169 mmol) in presence of O-(7-azabensotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (69 mg, 0.182 mmol), diisopropylethylamine (84 mg, 0.65 mmol) over night, at room temperature. The reaction mixture was diluted with water (5 ml) and a concentrated solution of sodium bicarbonate (1 ml). The solid was filtered, washed with water, ethanol, ether, and dried under vacuum, to give title compounds. For the compounds which did not precipitate, the solution was concentrated to dryness, the residues were washed with methylene chloride, methanol, filtered. Alumine was added to the methylene chloride / methanol solution, and the solvent was evaporated. Purification of the compounds was carried out by chromatography over alumine, eluent CH_2Cl_2 / MeOH : 98/2 to 95/5, to give title compounds.

Example 74.

An analogous reaction to that described in General Scheme 6, starting with aniline (16 mg, 0.17 mmol) yielded Compound 74 in Table 17 (50 mg, 70 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.28 (m, 2H) ; 2.37 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.56 (d, 2H) ; 3.68 (t, 2H) ; 3.84 (s, 2H) ; 3.96 (s, 3H) ; 4.03 (d, 2H) ; 4.28 (t, 2H) ; 7.07 (t, 1H) ; 7.29 (s, 1H) ; 7.3 (t, 2H) ; 7.61 (d, 2H) ; 7.89 (s, 1H) ; 9.02 (s, 1H).

MS ES$^+$: 549 $(M+H)^+$

Example 75.

An analogous reaction to that described in General Scheme 6, starting with 4-fluoroaniline (19 mg, 0.17 mmol) yielded Compound 75 in Table 17 (50 mg, 67 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 2.38 (s, 3H) ; 3.16 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.84 (s, 2H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.16 (t, 2H) ; 7.29 (s, 1H) ; 7.64 (m, 2H) ; 7.9 (s, 1H) ; 9.03 (s, 1H).

MS ES$^+$: 567 $(M+H)^+$.

Example 76.

An analogous reaction to that described in General Scheme 6, starting with 4-chloroaniline (22 mg, 0.17 mmol) yielded Compound 76 in Table 17(45 mg, 59 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.28 (m, 2H) ; 2.37 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.85 (s, 2H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.37 (d, 2H) ; 7.65 (d, 2H) ; 7.9 (s, 1H) ; 9.03 (s, 1H).

MS ES$^+$: 583 $(M_+H)^+$

Example 77.

An analogous reaction to that described in General Scheme 6, starting with 4-hydroxypiperidine (17 mg, 0.17 mmol) yielded Compound 77 in Table 17(45 mg, 62 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.42 (m, 2H) ; 1.82 (m, 2H) ; 2.31 (m, 5H) ; 3.08 (m, 1H) ; 3.16 (t, 2H) ; 3.27 (m, 1H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.78 (m, 2H) ; 3.83 (s, 2H) ; 3.92 (m, 1H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.28 (s, 1H) ; 7.85 (s, 1H) ; 9.0 (s, 1H).

MS ES$^+$: 557 $(M_+H)^+$.

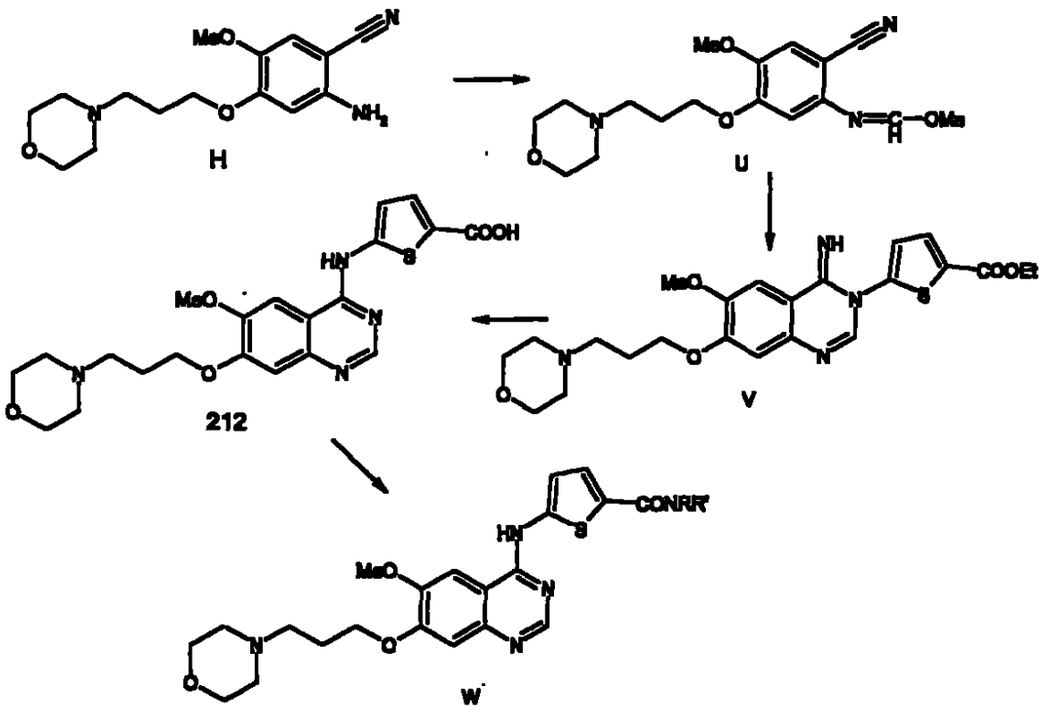
Example 78.

An analogous reaction to that described in General Scheme 6, starting with 4-aminopyridine (16 mg, 0.17 mmol) yielded Compound 78 in Table 17(35 mg, 49 %).

^{1}HNMR (DMSO-d6, TFA) : 2.29 (m, 2H) ; 2.39 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.96 (s, 3H) ; 4.02 (d, 2H) ; 4.04 (s, 2H) ; 4.29 (t, 2H) ; 7.33 (s, 1H) ; 7.92 (s, 1H) ; 8.1 (d, 2H) ; 8.76 (d, 2H) ; 9:06 (s, 1H).

MS ES$^+$: 550 $(M_+H)^+$.

General Scheme 7



Compound U

The amino nitrile H (2.91 g, 10 mmol) was reacted with trimethylorthoformate (10 ml) in presence of p-toluene-sulfonic acid (38 mg, 2 mmol) at 80°C for 6 hours. The solvent was evaporated, the residue crystallised from ether to give title compound (3.01 g, 90.4 %).

^{1}HNMR (DMSO-d_6) : 1.9 (t, 2H) ; 2.4 (m, 6H) ; 3.58 (t, 4H) ; 3.78 (s, 3H) ; 3.85 (s; 3H) ; 4.08 (t, 2H) ; 6.88 (s, 1H) ; 7.28 (s, 1H) ; 8.2 (s, 1H).

MS ES$^+$: 334 $(M+H)^+$

Compound V

Imidate U (0.25 g, 0.75 mmol) in CH_2Cl_2 (5 ml) was reacted with ethyl 2-amino-5-thiophenecarboxylate (0.13 g, 0.79 mmol) in presence of pyridinium hydrochloride (0.09 g, 0.75 mmol), at room temperature over night. Ethyl acetate was then added, and the solid was recovered by filtration, washed with ethyl acetate, dried under vacuum, to give product (0.23 g, 65 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.33 (t, 3H) ; 2.28 (m, 2H) ; 3.12 (t, 2H) ; 3.32 (t, 2H) ; 3.53 (d, 2H) ; 3.73 (t, 2H) ; 3.96 (s, 3H) ; 4.02 (d, 2H) ; 4.37 (m, 4H) ; 7.45 (s, 1H) ; 7.67 (d, 1H) ; 7.95 (d, 1H) ; 8.12 (s, 1H) ; 8.52 (s, 1H).

MS ES$^+$: 473 $(M+H)^+$

Compound 212

Ester V (1.1 g, 2.3 mmol) in methanol (20 ml) was treated with sodium hydroxide (2N, 20 ml) at 75°C for 4 hours, and at room temperature over night. Methanol was evaporated, and the remaining aqueous solution was kept for 24 hours at 5°C. The solid was filtered, washed with water, MeOH / CH_2Cl_2 : 1/1, dried under vacuum to give title compound (0.9 g, 87 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.31 (m, 2H) ; 3.14 (t, 2H) ; 3.33 (t, 2H) ; 3.53 (d, 2H) ; 3.76 (t, 2H) ; 4.01 (d, 2H) ; 4.07 (s, 3H) ; 4.33 (t, 2H) ; 7.44 (s, 1H) ; 7.54 (d, 1H) ; 7.68 (d, 1H) ; 8.54 (s, 1H) ; 9.22 (s, 1H).

MS ES$^+$: 445 $(M+H)^+$

Synthesis of amides of general structure W, general procedure

Acid 212 (80 mg, 0.18 mmol) in DMF (1.5 ml) was reacted with amine (0.216 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (80 mg, 0.21 mmol), DIEA (80 µl, 0.46 mmol), for 3 hours at room temperature. The reaction mixture was then treated with a solution of $NaHCO_3$ (2 ml) with stirring for 0.5 hour, the solid filtered, washed with water, ether, dried under vacuum over P_2O_5, to give title compound.

Example 79.

An analogous reaction to that described in General Scheme 7, starting with aniline (17 µl, 0.186 mmol) yielded Compound 79 in Table 18 (80 mg, 86 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.32 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.53 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (d, 2H) ; 4.03 (s, 3H) ; 4.3 (t, 2H) ; 7.7 (t, 1H) ; 7.32 (m, 4H) ; 7.73 (d, 2H) ; 7.98 (d, 1H) ; 8.18 (s, 1H) ; 9.22 (s, 1H).

MS ES$^+$: 520 $(M+H)^+$

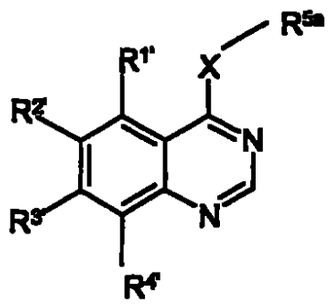
for example, using nitric acid as the nitrating agent. Again, suitable reaction conditions are illustrated hereinafter.

The nitrile of formula (XIV) may be derived by reaction of the corresponding formamide with hydroxylamine as illustrated hereinafter.

Compounds of Formula (I) and Formula (IA) are inhibitors of aurora 2 kinase. As a result, these compounds can be used to treat disease mediated by these agents, in particular proliferative disease.

According to a further aspect of the present invention there is provided a method for inhibiting aurora 2 kinase in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of Formula (I) or Formula (IA), or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

Certain compounds of formula (I) are novel and these form a further aspect of the invention. Thus the invention further comprises a compound of formula (IA)



(IA)

or a salt, ester or amide thereof;

where X is as defined in relation to formula (I);

$R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ are equivalent to R^1, R^2, R^3, R^4 as defined in relation to formula (I) and R^{5a} is an optionally substituted 5-membered heteroaromatic ring, subject to the following provisos:

(i) that where R^{5a} is a pyrazole group, it carries a substitutent of formula (k), (II) of (VI) above,

(ii) that where X is NH and R^{5a} is a substituted pyrazolone or tetrazolyl group, at least one of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ is other than hydrogen; or

(iii) that where X is O and R^{5a} is 1-methyl-4-nitro-1H-imidazol-5-yl, at least one of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ is other than hydrogen.

Preferably at least one of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ is other than hydrogen.

Suitably R^{5a} is selected from the groups of sub-formulae (a)-(j) as set out above.

Preferably R^{5a} is pyrrole, imidazole, triazole, thiazole, thiophene, or thiadiazole, any of which may be optionally substituted.

In particular, R^{5a} is substituted by at least one group of formula (k), (II) of (VI) above.

Other preferred or particular groups and substitutents in formula (IA) are as set out for the equivalent groups in formula (I) above.

According to a further aspect of the invention there is provided a compound of the formula (IA) as defined herein, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, for use in a method of treatment of the human or animal body by therapy. In particular, the compounds are used in methods of treatment of proliferative disease such as cancer and in particular cancers such as colorectal or breast cancer where aurora 2 is upregulated.

The invention also provides a pharmaceutical composition comprising a compound of formula (IA) as defined herein, or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof, in combination with at pharmaceutically acceptable carrier.

Preferred or particular compounds of formula (IA) for use in the compositions of the invention are as described above in relation to preferred compounds of formula (I).

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal track, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents

may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

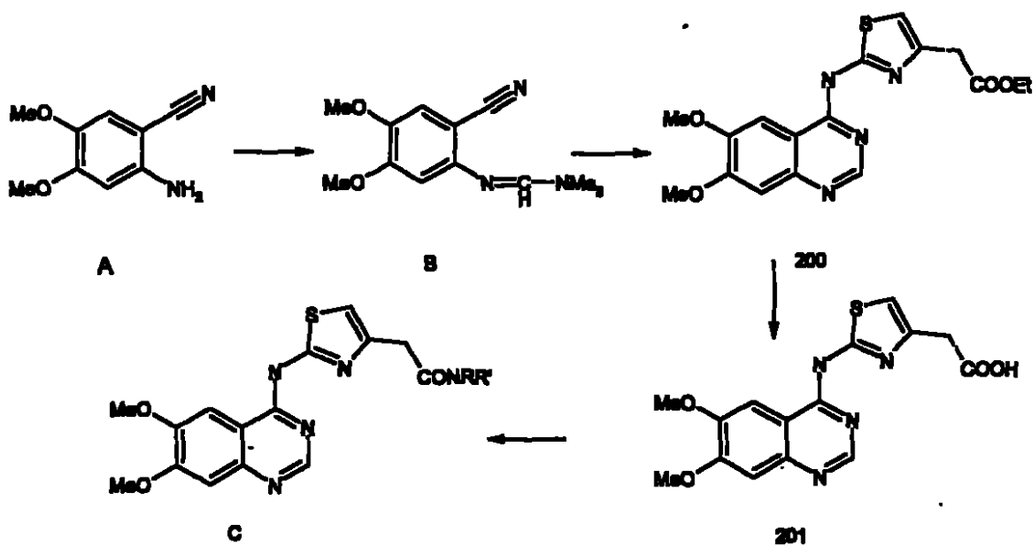
The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the Formula I are useful in treating diseases or medical conditions which are due alone or in part to the effects of aurora 2 kinase.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

A further aspect of the invention comprises a compound of Formula (I) or Formula (IA) as defined above, or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, for use in the preparation of a medicament for the treatment of proliferative disease. Preferred compounds of Formula (I) or Formula (IA) for this purpose are as described above.

The following Examples illustrate the invention.

General Scheme 1



Compound B

The amino nitrile A (534 mg, 3 mmol) in benzene (15 ml) was reacted with N,N-dimethylformamide dimethyl acetal (535 mg, 4.5 mmol) at 90°C, in a Dean Stark equipped flask. After 4.5 hours reflux, the solution was concentrated, and the residual oil triturated with ether to give the title compound as a solid (680 mg, 90 %).

^{1}HNMR ($CDCl_3$) : 3.08 (s, 6H) ; 3.86 (s, 3H) ; 3.91 (s, 3H) ; 6.48 (s, 1H) ; 6.94 (s, 1H) ; 7.58 (s, 1H).

MS ES^+ : 234 $(M+H)^+$

Compound 200

A mixture of amidine B (1.4 g, 6 mmol), ethyl 2-amino-4-thiazoleacetate (1.4 g, 7.5 mmol) in acetic acid (14 ml) was heated at 130°C for 3 hours. The solvent was removed under vacuum, the residue was triturated in ethanol (5 ml) and a solution of $NaHCO_3$ (pH 8) for 10 minutes. The solid was recovered by filtration, washed with water, dissolved in CH_2Cl_2, and dried over $MgSO_4$. CH_2Cl_2 was evaporated, the residual oil treated with ether and pet. ether to give title compound (1.8 g, 80 %).

^{1}H NMR (DMSO-d_6) : 1.2 (t, 3H) ; 3.74 (s, 2H) ; 3.95 (s, 6H) ; 4.1 (q, 2H) ; 7.02 (s, 1H) ; 7.26 (s, 1H) ; 8.14 (s, 1H) ; 8.68 (s, 1H).

Compound 201

Ester 200 (1.8 g, 4.8 mmol) was reacted with 2N NaOH (4.8 ml, 9.6 mmol) in ethanol (20 ml) at room temperature for 2 hours. The mixture was cooled to room temperture, acidified with EtOH, HCl (2N) to pH 3. Stirring was carried on for 15 minutes, and a yellow solid of title compound was recovered by filtration (1.7 g, 100 %).

^{1}HNMR (DMSO-d_6) : 3.71 (s, 2H) ; 3.96 (s, 3H) ; 3.97 (s, 3H) ; 7.11 (s, 1H) ; 7.28 (s, 1H) ; 8.3 (brs, 1H) ; 8.88 (s, 1H).

Synthesis of amide 5, general procedure

The acid 201 (86.5 mg, 0.25 mmol) in DMF (1 ml) was reacted with various amines (2.6 mmol) in presence of O-(7-azabenzotriazol-1yl) N,N,N',N',-tetramethyluronium hexafluorophosphate (98 mg, 0.26 mmol), DIEA (33 mg, 0.26 mmol) at room temperature for 0.5 hour. A solution of $NaHCO_3$ (1 ml) and water (7 ml) was added to the mixture. The mixture was left overnight, and the precipitated solid was then recovered by filtration, washed with water and dried under vacuum in presence of P_2O_5, to give compounds of formula C as listed below.

Example 1.

Using the reaction described in the General Scheme 1, starting with 4-aminomethyl pyridine (27 mg, 0.25 mmol) yielded Compound No. 1 in Table 1 (50 mg, 46 %).

^{1}HNMR (DMSO-d_6) : 3.64 (s, 2H) ; 3.95 (s, 3H) ; 3.96 (s, 3H) ; 4.32 (d, 2H) ; 6.98 (s, 1H) ; 7.26 (m, 3H) ; 8.15 (s, 1H) ; 8.49 (m, 3H) ; 8.68 (s, 1H).

Example 2.

An analogous reaction to that described in the General Scheme 1, starting with morpholine (23 mg, 0.26 mmol) yielded Compound No 2 in Table 1 (70 mg, 67 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.55 (br m, 8H) ; 3.88 (s, 2H) ; 3.97 (s, 3H) ; 4.0 (s, 3H) ; 7.15 (s, 1H) ; 7.27 (s, 1H) ; 7.92 (s, 1H) ; 9.07 (s, 1H).

Example 3.

An analogous reaction to that described in the General Scheme 1, starting with 4-fluoroaniline (29 mg, 0.26 mmol) yielded the Compound No. 3 in Table 1 (75 mg, 68 %).

^{1}H NMR (DMSO-d_6) : 3.74 (s, 2H) ; 3.93 (s, 6H) ; 7.00 (s, 1H) ; 7.15 (t, 2H) ; 7.25 (s, 1H) ; 7.64 (m, 2H) ; 8.12 (s, 1H) ; 8.67 (s, 1H) ; 10.20 (s, 1H).

MS ES$^+$: 440 $(M+H)^+$

Example 4.

An analogous reaction to that described in the General Scheme 1, starting with N,N-dimethyl-1,4-phenylenediamine (35 mg, 0.26 mmol) yielded Compound 4 in Table 1 (65 mg, 56 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.2 (s, 6H) ; 3.9 (s, 2H) ; 3.97 (s, 3H) ; 4.0 (s, 3H) ; 7.27 (s, 1H) ; 7.3 (s, 1H) ; 7.65 (d, 2H) ; 7.8 (d, 2H) ; 7.99 (s, 1H).

MS ES$^+$: 465 $(M+H)^+$

Example 5.

An analogous reaction to that described in the General Scheme 1, starting with 4-methoxy-aniline (32 mg, 0.26 mmol) yielded Compound 5 in Table 1 (80 mg, 71 %).

^{1}HNMR (DMSO-d_6) : 3.71 (s, 5H) ; 3.93 (s, 3H) ; 3.94 (s, 3H) ; 6.88 (d, 2H) ; 6.99 (s, 1H) ; 7.25 (s, 1H) ; 7.53 (d, 2H) ; 8.13 (s, 1H) ; 8.67 (s, 1H) ; 9.99 (s, 1H).

MS ES$^+$: 452 $(M+H)^+$

Example 6.

An analogous reaction to that described in the General Scheme 1, starting with 5-methoxy-2-methylaniline (36 mg, 0.26 mmol) yielded Compound 6 in Table 1 (87 mg, 75 %).

^{1}HNMR (DMSO-d_6) : 2.13 (s, 3H) ; 3.69 (s, 3H) ; 3.81 (s, 2H) ; 3.96 (s, 6H) ; 6.65 (m, 1H) ; 7.05 (m, 1H) ; 7.09 (d, 1H) ; 7.21 (s, 1H) ; 7.26 (s, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H) ; 9.3 (s, 1H).

MS ES$^+$: 466 $(M+H)^+$

Example 7.

An analogous reaction to that described in the General Scheme 1, starting with aminoacetaldehyde dimethyl acetal (27 mg, 0.26 mmol) yielded Compound 7 in Table 1 (80 mg, 74 %).

^{1}HNMR (DMSO-d_6) : 3.2 (t, 2H) ; 3.29 (s, 3H) ; 3.31 (s, 3H) ; 3.55 (s, 2H) ; 3.94 (s, 6H) ; 4.37 (t, 1H) ; 6.92 (s, 1H) ; 7.26 (s, 1H) ; 8.02 (t, 1H) ; 8.14 (s, 1H) ; 8.67 (s, 1H).

MS ES$^+$: 434 $(M+H)^+$

Example 8.

An analogous reaction to that described in the General Scheme 1, starting with 3-trifluoromethylaniline (42 mg, 0.26 mmol) yielded Compound 8 in Table 1 (72 mg, 59 %).

^{1}HNMR (DMSO-d_6) : 3.80 (s, 2H) ; 3.93 (s, 3H) ; 3.94 (s, 3H) ; 7.04 (s, 1H) ; 7.26 (s, 1H) ; 7.41 (d, 1H) ; 7.55 (t, 1H) ; 7.81 (d, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H) ; 10.50 (s, 1H).

MS ES$^+$: 490 $(M+H)^+$

Example 9.

An analogous reaction to that described in General Scheme 1, starting with N-methylpiperazine (26 mg, 0.26 mmol) yielded Compound 9 in Table 1(65 mg, 61 %).

^{1}HNMR (DMSO-d_6) : 2.73 and 2.77 (two t, 4H) ; 2.86 and 3.10 (two s, 3H) ; 3.56 and 3.74 (two t, 4H) ; 3.79 and 3.84 (two s, 2H) ; 3.95 (s, 6H) ; 6.95 (m, 1H) ; 7.26 (s, 1H) ; 8.14 (s, 1H) ; 8.68 (s, 1H).

MS ES$^+$: 429 $(M+H)^+$

Example 10.

An analogous reaction to that described in General Scheme 1, starting with 2-methoxyethylamine (20 mg, 0.26 mmol) yielded Compound 10 in Table 1(68 mg, 67 %).
^{1}HNMR (DMSO-d_6) : 3.25 (s, 3H) ; 3.3 (m, 6H) ; 3.54 (s, 2H) ; 3.94 (s, 6H) ; 6.92 (s, 1H) ; 7.26 (s, 1H) ; 8.0 (t, 1H) ; 8.14 (s, 1H) ; 8.67 (s, 1H).
MS ES$^+$: 404 $(M+H)^+$

Example 11.

An analogous reaction to that described in General Scheme 1, starting with 2-(2-aminoethyl)-N-methylpyrrole (32 mg, 0.26 mmol) yielded Compound 11 in Table 1(93 mg, 82 %).
^{1}HNMR (DMSO-d_6) : 3.3 (m, 4H) ; 3.5 (s, 2H) ; 3.94 (s, 6H) ; 5.78 (s, 1H) ; 5.84 (m, 1H) ; 6.58 (s, 1H) ; 6.89 (s, 1H) ; 7.24 (s, 1H) ; 8.01 (t, 1H) ; 8.13 (s, 1H) ; 8.66 (s, 1H).
MS ES$^+$: 453 $(M+H)^+$

Example 12.

An analogous reaction to that described in the General Scheme 1, starting with 3-(methylamino)propionitrile (22 mg, 0.26 mmol) yielded Compound 12 in Table 1(60 mg, 58 %).
^{1}HNMR (DMSO-d_6) : 2.15 (s, 3H) ; 3.45 (m, 4H) ; 3.77 (s, 2H) ; 3.96 (s, 6H) ; 6.91 (s, 1H) ; 7.25 (s, 1H) ; 8.14 (s, 1H) ; 8.67 (s, 1H).
MS ES$^+$: 413 $(M+H)^+$

Example 13.

An analogous reaction to that described in General Scheme 1, starting with 4-fluorobenzylamine (33 mg, 0.26 mmol) yielded Compound 13 in Table 1(81 mg, 81 %).
^{1}HNMR (DMSO-d_6) : 3.59 (s, 2H) ; 3.95 (m, 6H) ; 4.27 (d, 2H) ; 6.94 (s, 1H) ; 7.15 (m, 2H) ; 7.26 (s, 1H) ; 7.31 (m, 2H) ; 7.95 (s, 1H) ; 8.14 (s, 1H) ; 8.41 (t, 1H) ; 8.67 (s, 1H).
MS ES$^+$: 454 $(M+H)^+$

Example 14.

An analogous reaction to that described in General Scheme 1, starting with 4-hydroxypiperidine (26 mg, 0.26 mmol) yielded Compound 14 in Table 1(86 mg, 80 %).

^{1}HNMR (DMSO-d_6) : 1.21 (m, 2H) ; 1.65 (m, 2H) ; 3.02 (m, 1H) ; 3.16 (m, 1H) ; 3.65 (m, 1H) ; 3.78 (m, 3H) ; 4.71 (d, 1H) ; 6.91 (s, 1H) ; 7.26 (s, 1H) ; 8.14 (s, 1H) ; 9.67 (s, 1H).
MS ES$^+$: 430 $(M+H)^+$

Example 15.

An analogous reaction to that described in General Scheme 1, starting with 3-aminoacetophenone (35 mg, 0.26 mmol) yielded Compound 15 in Table 1(92 mg, 79 %).
^{1}HNMR (DMSO-d_6) : 2.59 (s, 3H) ; 3.78 (s, 2H) ; 3.90 (s, 3H) ; 3.93 (s, 3H) ; 7.02 (s, 1H) ; 7.26 (s, 1H) ; 7.47 (t, 1H) ; 7.67 (d, 1H) ; 7.89 (d, 1H) ; 8.12 (s, 1H) ; 8.2 (s, 1H) ; 8.68 (s, 1H) ; 10.36 (s, 1H).
MS ES$^+$: 464 $(M+H)^+$.

Example 16.

An analogous reaction to that described in General Scheme 1, starting with 3,5-difluoroaniline (34 mg, 0.26 mmol) yielded Compound 16 in Table 1(71 mg, 64 %).
^{1}HNMR (DMSO-d_6, TFA) : 3.90 (s, 2H) ; 3.93 (s, 3H) ; 3.97 (s, 3H) ; 6.89 (m, 1H) ; 7.27 (s, 1H) ; 7.29 (s, 1H) ; 7.35 (m, 2H) ; 7.96 (m, 1H) ; 9.10 (s, 1H).
MS ES$^+$: 458 $(M+H)^+$

Example 17.

An analogous reaction to that described in General Scheme 1, starting with 3-cyanoaniline (31 mg, 0.26 mmol) yielded Compound 17 in Table 1(90 mg, 84 %).
MS ES$^+$: 447 $(M+H)^+$

Example 18.

An analogous reaction to that described in General Scheme 1, starting with 2-fluoroaniline (29 mg, 0.26 mmol) yielded Compound 18 in Table 1(86 mg, 82 %).
MS ES$^+$: 440 $(M+H)^+$

Example 19.

An analogous reaction to that described in General Scheme 1, starting with 3-(1-hydroxyethyl)aniline (36 mg, 0.26 mmol) yielded Compound 19 in Table 1(92 mg, 82 %).
MS ES$^+$: 466 $(M+H)^+$

Example 20.

An analogous reaction to that described in General Scheme 1, starting with 2,3-difluoroaniline (34 mg, 0.26 mmol) yielded Compound 20 in Table 1(51 mg, 47 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.98 (s, 3H) ; 4.01 (s, 3H) ; 4.03 (s, 2H) ; 7.19 (m, 2H) ; 7.27 (s, 1H) ; 7.29 (s, 1H) ; 7.73 (m, 1H) ; 7.99 (s, 1H) ; 9.11 (s, 1H).

MS ES$^+$: 458 $(M+H)^+$

Example 21.

An analogous reaction to that described in General Scheme 1, starting with 2-methyl-4-fluoroaniline (33 mg, 0.26 mmol) yielded Compound 21 in Table 1(94 mg, 86 %).

MS ES$^+$: 454 $(M+H)^+$

Example 22.

An analogous reaction to that described in General Scheme 1, starting with 2-fluoro-3-chloroaniline (38 mg, 0.26 mmol) yielded Compound 22 in Table 1(60 mg, 53 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.95 (s, 3H) ; 3.98 (s, 3H) ; 4.01 (s, 2H) ; 7.20 (m, 1H) ; 7.24 (s, 1H) ; 7.26 (s, 1H) ; 7.31 (m, 1H) ; 7.88 (m, 1H) ; 7.96 (s, 1H) ; 9.08 (s, 1H).

MS ES$^+$: 474 $(M+H)^+$

Example 23.

An analogous reaction to that described in General Scheme 1, starting with 2,5-difluoroaniline (34 mg, 0.26 mmol) yielded Compound 23 in Table 1(52 mg, 48 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.97 (s, 3H) ; 4.00 (s, 2H) ; 4.01 (s, 3H) ; 6.97 (m, 1H) ; 7.26 (s, 1H) ; 7.29 (s, 1H) ; 7.33 (m, 1H) ; 7.94 (m, 1H) ; 7.98 (s, 1H) ; 9.11 (s, 1H).

MS ES$^+$: 458$(M+H)^+$

Example 24.

An analogous reaction to that described in General Scheme 1, starting with 3-aminobenzamide (36 mg, 0.26 mmol) yielded Compound 24 in Table 1(94 mg, 84 %).

MS ES$^+$: 465 $(M+H)^+$

Example 25.

An analogous reaction to that described in General Scheme 1, starting with 4-aminophenol (29 mg, 0.26 mmol) yielded Compound 25 in Table 1(89 mg, 84 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.81 (s, 2H) ; 3.97 (s, 3H) ; 4.00 (s, 3H) ; 6.71 (d, 2H) ; 7.23 (s, 1H) ; 7.27 (s, 1H) ; 7.40 (d, 2H) ; 7.95 (s, 1H) ; 9.09 (s, 1H).

MS ES$^+$: 438 $(M+H)^+$

Example 26.

An analogous reaction to that described in General Scheme 1, starting with 2-fluoro-5-methylaniline (33 mg, 0.26 mmol) yielded Compound 26 in Table 1(88 mg, 81 %).

MS ES$^+$: 454 $(M+H)^+$

Example 27.

An analogous reaction to that described in General Scheme 1, starting with 2-bromo-4-fluoroaniline (50 mg, 0.26 mmol) yielded Compound 27 in Table 1(68 mg, 55 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.89 (s, 2H) ; 3.94 (s, 3H) ; 3.97 (s, 3H) ; 7.21 (m, 1H) ; 7.25 (s, 1H) ; 7.6 (s, 1H) ; 7.61 (m, 1H) ; 7.92 (m, 1H) ; 7.95 (s, 1H) ; 9.07 (s, 1H).

MS ES$^+$: 518, 520 $(M+H)^+$

Example 28.

An analogous reaction to that described in General Scheme 1, starting with 3,4-difluoroaniline (34 mg, 0.26 mmol) yielded Compound 28 in Table 1(81 mg, 74 %).

MS ES$^+$: 458 $(M+H)^+$

Example 29.

An analogous reaction to that described in General Scheme 1, starting with isonipecotamide (34 mg, 0.26 mmol) yielded Compound 29 in Table 1(96 mg, 88 %).

MS ES$^+$: 457 $(M+H)^+$

Example 30.

An analogous reaction to that described in General Scheme 1, starting with 4-trifluoromethoxyaniline (47 mg, 0.26 mmol) yielded Compound 30 in Table 1(105 mg, 87 %).
MS ES$^+$: 506 $(M+H)^+$

Example 31.

An analogous reaction to that described in General Scheme 1, starting with 5-amino-2-methoxypyridine (33 mg, 0.26 mmol) yielded Compound 31 in Table 1(86 mg, 79 %).
MS ES$^+$: 453 $(M+H)^+$

Example 32.

An analogous reaction to that described in General Scheme 1, starting with 2,4-difluoroaniline (34 mg, 0.26 mmol) yielded Compound 32 in Table 1(81 mg, 74 %).
MS ES$^+$: 458 $(M+H)^+$

Example 33.

An analogous reaction to that described in General Scheme 1, starting with 4-aminoresorcinol hydrochloride (43 mg, 0.26 mmol) yielded Compound 33 in Table 1(84 mg, 77 %).
MS ES$^+$: 454 $(M+H)^+$

Example 34.

An analogous reaction to that described in General Scheme 1, starting with 3-aminopyridine (25 mg, 0.26 mmol) yielded Compound 34 in Table 1(101 mg, 100 %).
MS ES$^+$: 423$(M+H)^+$

Example 35.

An analogous reaction to that described in General Scheme 1, starting with 4-chloroaniline (34 mg, 0.26 mmol) yielded Compound 35 in Table 1(109 mg, 100 %).
MS ES$^+$: 456, 458 $(M+H)^+$.

Example 36.

An analogous reaction to that described in General Scheme 1, starting with pyrrolidine (19 mg, 0.26 mmol) yielded Compound 36 in Table 1(33 mg, 35 %).

MS ES^+ : 400 $(M+H)^+$

Example 37.

An analogous reaction to that described in General Scheme 1, starting with 3-methoxyaniline (33 mg, 0.26 mmol) yielded Compound 37 in Table 1(94 mg, 87 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.72 (s, 3H) ; 3.87 (s, 2H) ; 3.96 (s, 3H) ; 4.0 (s, 3H) ; 6.64 (m, 1H) ; 7.14 (d, 1H) ; 7.21 (d, 1H) ; 7.22 (s, 1H) ; 7.24 (s, 1H) ; 7.27 (s, 1H) ; 7.95 (s, 1H) ; 9.09 (s, 1H).

MS ES^+ : 452 $(M+H)^+$

Example 38.

An analogous reaction to that described in General Scheme 1, starting with 3-hydroxy-4-methoxyaniline (37 mg, 0.26 mmol) yielded Compound 38 in Table 1(95 mg, 85 %).

MS ES^+ : 468 $(M+H)^+$

Example 39.

An analogous reaction to that described in General Scheme 1, starting with 3-nitroaniline (36 mg, 0.26 mmol) yielded Compound 39 in Table 1(87 mg, 78 %).

MS ES^+ : 467 $(M+H)^+$

Example 40.

An analogous reaction to that described in General Scheme 1, starting with 1-methyl-3-nitroaniline (40 mg, 0.26 mmol) yielded Compound 40 in Table 1(50 mg, 44 %).

MS ES^+ : 481 $(M+H)^+$

Example 41.

An analogous reaction to that described in General Scheme 1, starting with 2-anilinoethanol (36 mg, 0.26 mmol) yielded Compound 41 in Table 1(45 mg, 41 %).

MS ES^+ : 466 $(M+H)^+$

Example 80.

An analogous reaction to that described in General Scheme 7, starting with 4-fluoroaniline (24 mg, 0.216 mmol) yielded Compound 80 in Table 18 (62 mg, 64 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.05 (m, 5H) ; 4.33 (t, 2H) ; 7.21 (t, 2H) ; 7.33 (d, 1H) ; 7.4 (s, 1H) ; 7.77 (m, 2H) ; 7.98 (d, 1H) ; 8.2 (s, 1H) ; 9.25 (s, 1H).

MS ES$^+$: 538 $(M+H)^+$.

Example 81.

An analogous reaction to that described in General Scheme 7, starting with 3-aminophenol (24 mg, 0.216 mmol) yielded Compound 81 in Table 18 (60 mg, 66 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.7 (t, 2H) ; 4.04 (d, 2H) ; 4.06 (s, 3H) ; 4.33 (t, 2H) ; 6.53 (m, 1H) ; 7.13 (m, 2H) ; 7.3 (d, 1H) ; 7.36 (d, 1H) ; 7.4 (s, 1H) ; 7.96 (s, 1H) ; 8.0 (d, 1H) ; 8.26 (s, 1H) ; 9.25 (s, 1H).

MS ES$^+$: 536 $(M+H)^+$.

Example 82.

An analogous reaction to that described in General Scheme 7, starting with 4-aminopyridine (20 mg, 0.216 mmol) yielded Compound 82 in Table 18 (16 mg, 19 %).

^{1}HNMR (DMSO-d6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.32 (t, 2H) ; 7.01 (d, 1H) ; 7.03 (s, 1H) ; 8.18 (d, 1H) ; 8.22 (s, 1H) ; 8.3 (d, 2H) ; 8.76 (d, 2H) ; 9.3 (s, 1H).

MS ES$^+$: 521 $(M+H)^+$.

Example 83.

An analogous reaction to that described in General Scheme 7, starting with 4-amino-1-butanol (19 mg, 0.216 mmol) yielded Compound 83 in Table 18 (22 mg, 28 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.46 (m, 2H) ; 1.58 (m, 2H) ; 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.26 (t, 2H) ; 3.36 (t, 2H) ; 3.44 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (m, 5H) ; 4.32 (t, 2H) ; 7.26 (d, 1H) ; 7.39 (s, 1H) ; 7.7 (d, 1H) ; 8.19 (s, 1H) ; 9.21 (s, 1H).

MS ES$^+$: 516 $(M+H)^+$

Example 84.

An analogous reaction to that described in General Scheme 7, starting with 3-aminobenzamide (29 mg, 0.216 mmol) yielded Compound 84 in Table 18 (60 mg, 77 %).
^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.67 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.32 (t, 2H>) ; 7.34 (d, 1H) ; 7.39 (s, 1H) ; 7.42 (t, 1H) ; 7.62 (d, 1H) ; 7.96 (d, 1H) ; 8.05 (d, 1H) ; 8.21 (m, 2H) ; 9.27 (s, 1H).
MS ES$^+$: 563 $(M+H)^+$.

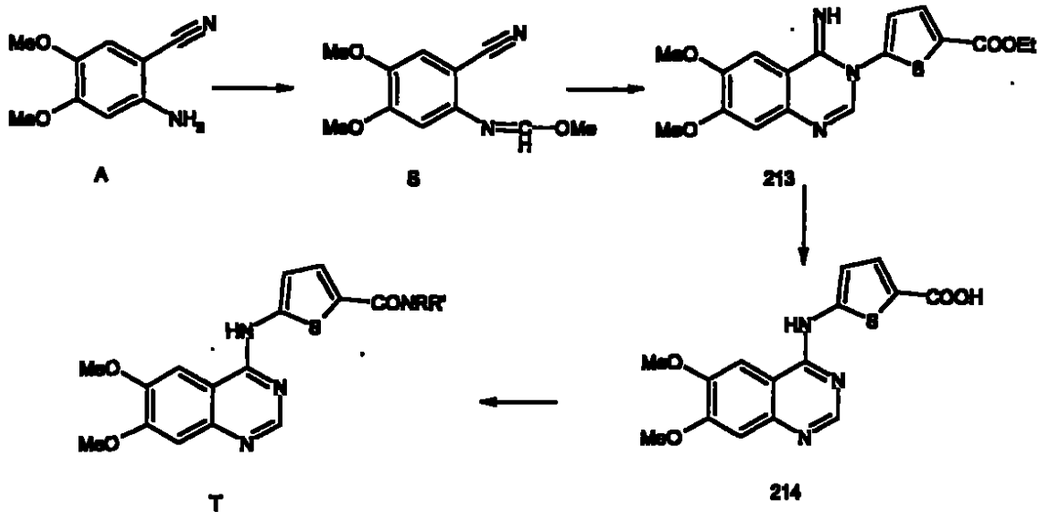
Example 85.

An analogous reaction to that described in General Scheme 7, starting with allylamine (12 mg, 0.216 mmol) yielded title Compound 85 in Table 18 (20 mg., 43 %).
^{1}HNMR (DMSO-d6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.91 (d, 2H) ; 4.04 (m, 5H) ; 4.32 (t, 2H) ; 5.12 (d, 1H) ; 5.2 (d, 1H) ; 5.91 (m, 1H) ; 7.26 (d, 1H) ; 7.38 (s, 1H) ; 7.75 (d, 1H) ; 8.19 (s, 1H) ; 9.22 (s, 1H).
MS ES$^+$: 484 $(M+H)^+$.

Example 86.

An analogous reaction to that described in General Scheme 7, starting with Methyl-4-aminobutyrate (25 mg, 0.216 mmol) yielded Compound 86 in Table 18 (18 mg, 23 %).
^{1}HNMR : 1.8 (t, 2H) ; 2.3 (m, 2H) ; 2.39 (t, 2H) ; 3.16 (t, 2H) ; 3.28 (t, 2H) ; 3.35 (t, 2H) ; 3.56 (d, 2H) ; 3.6 (s, 3H) ; 3.67 (t, 2H) ; 4.04 (m, 5H) ; 4.32 (t, 2H) ; 7.26 (d, 1H) ; 7.38 (s, 1H) ; 7.69 (d, 1H) ; 8.19 (s, 1H) ; 9.22 (s, 1H).
MS ES$^+$: 544 $(M+H)^+$.

General Scheme 8



Compound S

Aminonitrile A (1.78 g, 10 mmol) was treated with trimethylorthoformate (10 ml) and a catalytic amount of p-toluene sulfonic acid at 100°C for 1 hour. The mixture was cooled to room temperature, ethyl acetate was added, and the insoluble solid removed by filtration, the solvent was then evaporated, the residue triturated with ether to give title compound as a yellow solid (1.56 g, 71 %).

^{1}HNMR (DMSO-d_6) : 3.77 (s, 3H) ; 3.83 (s, 3H) ; 3.84 (s, 3H) ; 6.87 (s, 1H) ; 7.26 (s, 1H) ; 8.19 (s, 1H).

MS ES$^+$: 221 $(M_4H)^+$.

Compound 213

Imidate S (0.165 g, 0.75 mmol) was reacted with ethyl 2-amino-5-thiophenecarboxylate (0.13 g, 0.79 mmol) in methylene chloride (4 ml) in presence of pyridinium hydrochloride (88 mg, 0.75 mmol) at room temperature for 4 hours. The solvent was evaporated, and the residue was purified by silica gel chromatography, eluent : AcOEt / CH2Cl2, 1/1 ; followed by MeOH / AcOEt / CH2Cl2, 1/4/5, to give title compound (0.135 g , 50 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.33 (t, 3H) ; 3.95 (s, 3H) ; 4.03 (s, 3H) ; 4.38 (q, 2H) ; 7.43 (s, 1H) ; 7.67 (d, 1H) ; 7.95 (d, 1H) ; 8.05 (s, 1H) ; 8.52 (s, 1H).

MS ES$^+$: 360 $(M_4H)^+$

Compound 214

The ester 213 (72 mg, 0.2 mmol) in methanol (2 ml) was treated with sodium hydroxide (2N, 2 ml) at 75°C for 1.5 hour. The reaction mixture was cooled to room temperature, and the pH adjusted to 3 by addition of HCl 2N. The solid was recovered by filtration, washed with water, dried under vacuum in presence of P_2O_5, to give title compound (83 mg, 100 %).

^{1}HNMR (DMSO-d_6, TFA) : 4.02 (s, 3H) ; 4.04 (s, 3H) ; 7.38 (s, 1H) ; 7.42 (d, 1H) ; 7.68 (d, 1H) ; 8.35 (s, 1H) ; 9.21 (s, 1H).

MS ES$^+$: 332 $(M+H)^+$.

Example 87.

Synthesis of compound of General formula T where NRR' = NHPh (Compound 87)

Quinazoline 214 (45 mg, 0.108 mmol) in DMF (1 ml) was reacted with aniline (12 µl, 0.13 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (50 mg, 0.13 mmol), DIEA (75 µl, 0.43 mmol) for 1.5 hour at room temperature. A saturated solution of sodium bicarbonate (2 ml) was added to the mixture which was stirred for 0.5 hour. The solid was filtered, washed with water, and purified by chromatography over alumine, eluent AcOEt / CH_2Cl_2 : 1/1 to MeOH / AcOEt / CH_2Cl_2 : 1/4/5, to give title compound (15 mg, 34 %).

^{1}HNMR (DMSO-d_6) : 3.97 (s, 3H) ; 4.01 (s, 3H) ; 7.05 (d, 1H) ; 7.09 (t, 1H) ; 7.29 (s, 1H) ; 7.36 (t, 2H) ; 7.74 (d, 2H) ; 7.91 (d, 1H) ; 7.92 (s, 1H) ; 8.72 (s, 1H).

MS ES$^+$: 406 $(M+H)^+$

Example 88.

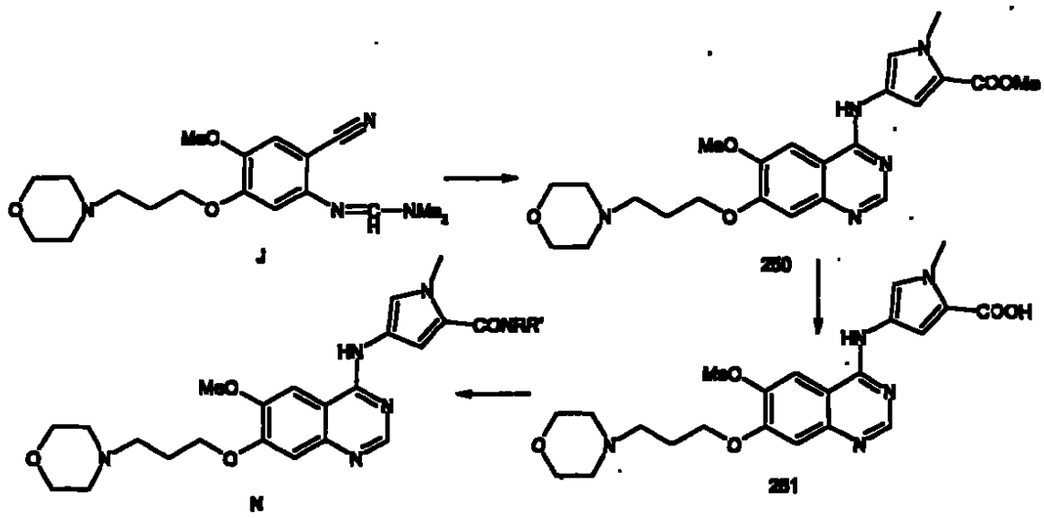
Synthesis of Compound 88 of General formula T where NRR' is NHPh(4-F)

An analogous reaction to that described in the Example 87, starting with quinazoline 213 (60 mg, 0.14 mmol), 4-fluoroaniline (17 µl, 0.17 mmol) yielded title compound (15 mg, 24 %).

^{1}HNMR (DMSO-d_6, TFA) : 4.04 (s, 3H) ; 4.06 (s, 3H) ; 7.18 (t, 2H) ; 7.32 (d, 1H) ; 7.35 (s, 1H) ; 7.75 (t, 2H) ; 7.98 (d, 1H) ; 8.17 (s, 1H) ; 9.23 (s, 1H).

MS ES$^+$: 425 $(M+H)^+$.

General Scheme 9



Example 89. Preparation of Compound 250 in Table 9

Amidine J (1.04 g, 3 mmol) in acetic acid (10 ml) was reacted with methyl 4-amino-1-methyl-2-pyrrolecarboxylate hydrochloride (686 mg, 3.6 mmol) and dimethylamine in methanol (1.25 M 2.9 ml, 3.6 mmol) at 130°C for 5.5 hours. The solvent was evaporated, water and an aqueous solution of sodium bicarbonate were added to the residue, the precipitate was filtered, dried under vacuum over P_2O_5. The solid was redissolved in a large volume of tetrahydrofuran, methylene chloride, methanol, the solution was concentrated, the solid filtered, washed with ether, dried, to give title compound (1.18 g, 86 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.8 (s, 3H) ; 3.95 (s, 3H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.26 (d, 1H) ; 7.32 (s, 1H) ; 7.69 (d, 1H) ; 8.06 (s, 1H) ; 8.94 (s, 1H).

MS ES$^+$: 456 $[M_+H]^+$

Example 90. Preparation of Compound 251 in Table 9

Ester 250 (1.34 g, 3 mmol) was treated with sodium hydroxide (6N, 3 ml) in ethanol (25 ml) at 75° for 2 hours. The solution was then cooled to room temperature, acidified to pH 3 with HCl (6N), the precipitate was recovered by filtration, washed with ethanol, ether, dried under vacuum to give title compound (636 mg, 42 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (m, 5H) ; 4.3 (t, 2H) ; 7.19 (s, 1H) ; 7.32 (s, 1H) ; 7.62 (s, 1H) ; 8.17 (s, 1H) ; 8.93 (s, 1H).

MS ES$^+$: 428 $[M+H]^+$

Example 91. Synthesis of amides N, general procedure

Acid 251 (79 mg, 0.15 mmol) in DMF (1 ml) was reacted with O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (62 mg, 0.165 mmol), the appropriate amine (1.65 mmol) and DIEA (68 mg, 0.525 mmol) at room temperature for 1.5 hour. The reaction mixture was then diluted with water (4 ml) and an aqueous solution of sodium bicarbonate (1 ml). The solid was recovered by filtration, redissolved in tetrahydrofuran, methylene chloride, and concentrated, the precipitated solid was recovered, washed with ether, dried under vacuum, to give title compound.

Example 92. Preparation of Compound 252 in Table 9

Compound of example 1 was obtained by reaction of the N-hydroxybenzotriazol ester of 3 (56 mg, 0.1 mmol) with aniline (11 mg, 0.12 mmol) in DMF (1 ml) at 105°C for 3 hours. Water was added to the cooled reaction mixture, which was extracted with ethylacetate, the organic phase was washed with water, dried over $MgSO_4$, filtered and concentrated to give title compound (12 mg, 23 %). The N-hydroxybenzotriazol ester was obtained as described in the general procedure of Example 91.

^{1}HNMR (DMSOd_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.08 (t, 1H) ; 7.33 (m, 3H) ; 7.4 (s, 1H) ; 7.63 (s, 1H) ; 7.74 (d, 2H) ; 8.1 (s, 1H) ; 8.93 (s, 1H).

MS ES+ : 517 $[M+H]^+$

Example 93. Preparation of Compound 253 in Table 9

An analogous reaction to that described in Example 92, but starting with 4-fluoroaniline (22 mg, 0.195 mmol) yielded title compound (40 mg, 57 %).

^{1}H NMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.72 (t, 2H) ; 3.97 (s, 3H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.3 (t, 2H) ; 7.18 (t, 2H) ; 7.34 (s, 1H) ; 7.4 (d, 1H) ; 7.63 (d, 1H) ; 7.76 (m, 1H) ; 8.11 (s, 1H) ; 8.94 (s, 1H).

MS ES$^+$: 535 $[M+H]^+$

Example 94. Preparation of Compound 254 in Table 9

An analogous reaction to that described in Example 92, but starting with cyclohexylamine (16 mg, 0.17 mmol) yielded title compound (60 mg, 76 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.14 (m, 1H) ; 1.3 (m, 4H) ; 1.62 (m, 1H) ; 1.8 (m, 4H) ; 2.29 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (m, 3H) ; 3.9 (s, 3H) ; 4.0 (s, 3H) ; 4.03 (d, 2H) ; 4.28 (t, 2H) ; 7.14 (d, 1H) ; 7.31 (s, 1H) ; 7.49 (d, 1H) ; 8.07 (s, 1H) ; 8.9 (s, 1H).

MS ES$^+$: 523 $[M+H]^+$

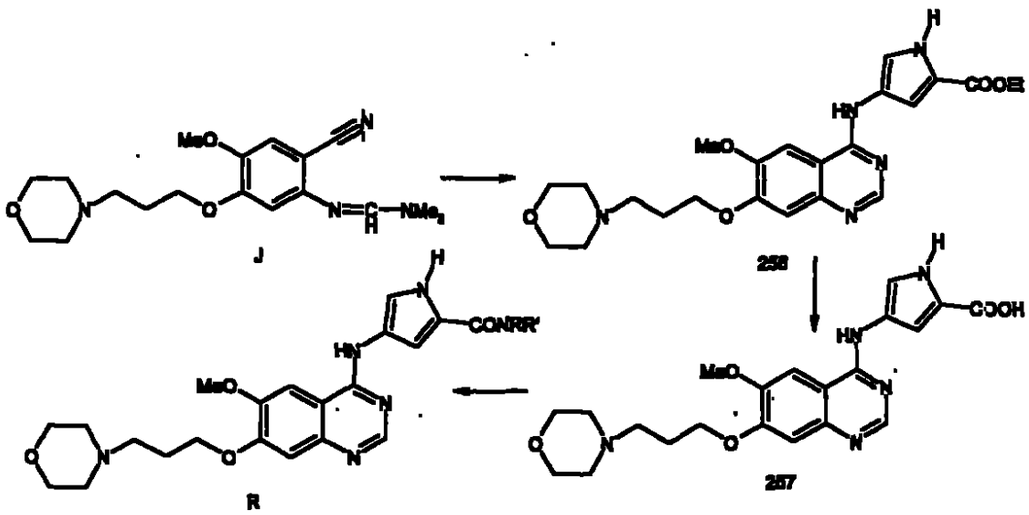
Example 95. Preparation of Compound 255 in Table 9

An analogous reaction to that described in the Example 92, but starting with N,N-dimethyl-1,4-phenylenediamine (23 mg, 0.17 mmol) yielded title compound (61 mg, 73 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.21 (s, 6H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.97 (s, 3H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.35 (s, 1H) ; 7.45 (d, 1H) ; 7.66 (m, 3H) ; 7.93 (d, 2H) ; 8.1 (s, 1H) ; 8.93 (s, 1H).

MS ES$^+$: 560 $[M+H]^+$

General Scheme 10



Example 96. Preparation of Compound 256 in Table 9

Amidine J (1.38 g, 4 mmol) in acetic acid (14 ml) was reacted with ethyl 4-amino-2-pyrrolecarboxylate (0.702 g, 4.56 mmol) at 130°C for 5 hours. The solution was concentrated,

the solid recovered by filtration and washed with ether. This solid was then treated with a diluted solution of sodium bicarbonate, filtered, washed with water and dried under vacuum over P_2O_5 to give title compound (1.34 g, 73 %).

^{1}H NMR (DMSO-d_6) : 1.3 (t, 3H) ; 1.95 (t, 2H) ; 2.38 (m, 4H) ; 2.44 (t, 2H) ; 3.58 (m, 4H) ; 3.94 (s, 3H) ; 4.16 (d, 2H) ; 4.23 (q, 2H) ; 7.05 (d, 1H) ; 7.14 (s, 1H) ; 7.59 (d, 1H) ; 7.75 (s, 1H) ; 8.46 (s, 1H) ; 9.53 (s, 1H) ; 11.72 (s, 1H).

MS ES$^+$: 456 $[M+H]^+$

Example 96. Preparation of Compound 257 in Table 9

Ester 256 (1.34 g, 3 mmol) in ethanol (25 ml) was treated with sodium hydroxide (6N, 3 ml) at 75°C for 2 hours. The solution was cooled, and acidified with hydrochloric acid (6N) to pH 3. The precipitate was filtered, washed with ethanol, ether, dried under vacuum over P_2O_5, to give title compound (0.63 g, 42 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (s, 3H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.19 (d, 1H) ; 7.32 (s, 1H) ; 7.62 (d, 1H) ; 8.17 (s, 1H) ; 8.93 (s, 1H).

MS ES$^+$: 428 $[M+H]^+$

Example 97. Preparation of Compound 258 in Table 9

Acid 256 (75 mg, 0.15 mmol) in DMF (0.7 ml) was reacted with O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (68 mg, 0.18 mmol), aniline (17 mg, 0.18 mmol) and DIEA (62 mg, 0.48 mmol) at room temperature over night. The reaction mixture was then diluted with a saturated solution of sodium bicarbonate (5 ml), and stirred for 1 hour. The solid was filtered, washed with water, dried under vacuum over P_2O_5, to give title compound (30 mg, 40 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.54 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.31 (t, 2H) ; 7.08 (t, 1H) ; 7.35 (m, 3H) ; 7.46 (d, 1H) ; 7.56 (d, 1H) ; 7.77 (d, 1H) ; 8.1 (s, 1H) ; 8.93 (s, 1H).

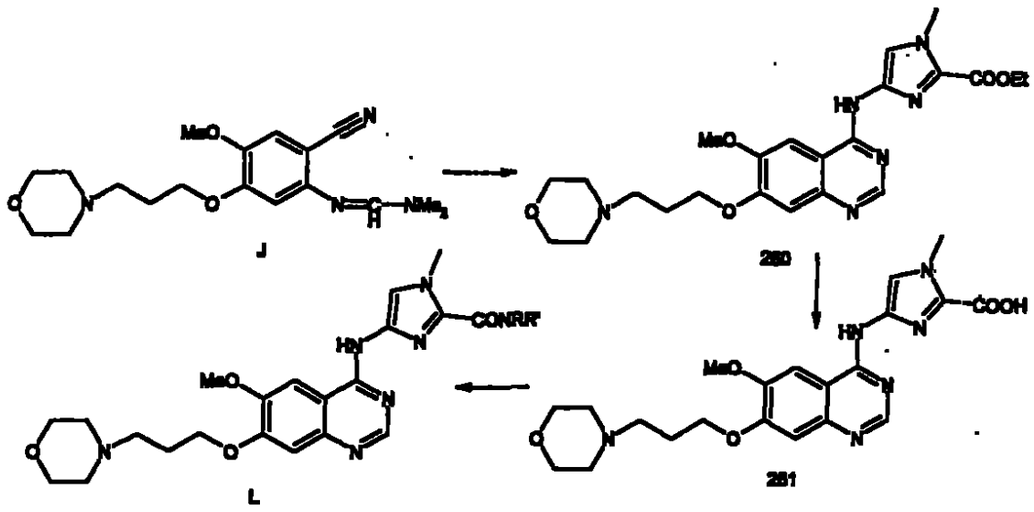
MS ES$^+$: 503 $[M+H]^+$

Example 98. Preparation of Compound 259 in Table 9

An analogous reaction to that described for the Example 97, but starting with cyclohexylamine (18 mg, 0.18 mmol) yielded title compound (30 mg, 39 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.13 (m, 1H) ; 1.3 (m, 4H) ; 1.63 (m, 1H) ; 1.8 (m, 4H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.76 (m, 1H) ; 4.0 (s, 1H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.2 (d, 1H) ; 7.3 (s, 1H) ; 7.43 (d, 1H) ; 8.0 (s, 1H) ; 8.9 (s, 1H).
MS ES$^+$: 509 $[M+H]^+$

General Scheme 11



Example 99. Preparation of Compound 260 in Table 10

Amidine J (1.04 g, 3 mmol) in acetic acid (10 ml) was reacted with ethyl 4-amino-1-methyl-2-imidazolecarboxylate hydrochloric acid (0.74 g, 3.6 mmol) in presence of dimethylamine / MeOH (1.25N, 2.9 ml, 3.6 mmol) at 130°C for 3 hours. The solvent was evaporated, the residue triturated with ether and filtered. The solid was suspended in water, the pH adjusted to 9 with an aqueous solution of sodium bicarbonate, the suspension was filtered, washed with water, dried under vacuum over P_2O_5, to give title compound (1.1 g, 78 %).
^{1}HNMR (DMSO-d_6) : 1.32 (t, 3H) ; 1.96 (m, 2H) ; 2.37 (m, 4H) ; 2.44 (t, 2H) ; 3.58 (m, 4H) ; 3.94 (s, 3H) ; 4.0 (s, 3H) ; 4.17 (t, 2H) ; 4.28 (q, 2H) ; 7.16 (s, 1H) ; 7.99 (s, 1H) ; 8.07 (s, 1H) ; 8.53 (s, 1H) ; 10.55 (s, 1H).

Example 100. Preparation of Compound 261 in Table 10

Ester 260 (1.1 g, 2.34 mmol) in ethanol (23 ml) was reacted with sodium hydroxyde (6N, 2.3 ml) at 80°C for 2.5 hours. The mixture was cooled, and acidified with hydrochloric acid (6N) to pH 3. The suspension was recovered by centrifugation, washed with ethanol, ether, dried under vacuum over P_2O_5, to give title compound (930 mg, 73 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.76 (t, 2H) ; 4.01 (s, 3H) ; 4.05 (m, 5H) ; 4.32 (t, 2H) ; 7.41 (s, 1H) ; 8.03 (s, 1H) ; 8.38 (s, 1H) ; 9.0 (s, 1H).

MS ES$^+$: 443 $[M+H]^+$

Example 101. Preparation of Compounds of General Structure L

Acid 261 (88 mg, 0.16 mmol) in DMF (1 ml) was reacted with O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate (73 mg, 0.19 mmol), the appropriate amine (0.18 mmol) and DIEA (82 mg, 0.4 mmol) at room temperature for 3 hours. The solution was then diluted with a saturated solution of sodium bicarbonate (4 ml) and stirred at room temperature for 3 hours. The precipitate was filtered, washed with water, dried under vacuum over P_2O_5, to give title compound.

Example 102. Preparation of Compound 262 in Table 10

An analogous reaction to that described in Example 101, but starting with aniline (17 mg, 0.18 mmol) yielded title compound (37 mg, 44 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (m, 5H) ; 4.06 (s, 3H) ; 4.31 (t, 2H) ; 7.13 (t, 1H) ; 7.38 (m, 3H) ; 7.78 (d, 2H) ; 7.99 (s, 1H) ; 8.27 (s, 1H) ; 9.01 (s, 1H).

MS ES$^+$: 518 $[M+H]^+$

Example 103. Preparation of Compound 263 in Table 10

An analogous reaction to that described in Example 101, but starting with 4-fluoroaniline (20 mg, 0.18 mmol) yielded title compound (84 mg, 97 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.1 (s, 3H) ; 4.31 (t, 2H) ; 7.21 (t, 2H) ; 7.39 (s, 1H) ; 7.82 (m, 2H) ; 7.98 (s, 1H) ; 8.32 (s, 1H) ; 9.01 (s, 1H).

MS ES$^+$: 536 $[M+H]^+$

Example 104. Preparation of Compound 264 in Table 10

An analogous reaction to that described in Example 101, but starting with N,N-dimethyl-1,4-phenylenediamine (24 mg, 0.18 mmol) yielded title compound (80 mg, 88 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.21 (s, 6H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (m, 5H) ; 4.1 (s, 3H) ; 4.31 (t, 2H) ; 7.4 (s, 1H) ; 7.66 (d, 2H) ; 7.98 (d, 2H) ; 8.01 (s, 1H) ; 8.32 (s, 1H) ; 9.01 (s, 1H).

MS ES$^+$: 561 $[M+H]^+$

Example 105. reparation of Compound 265 in Table 10

An analogous reaction to that described in Example 101, but starting with 4-chloroaniline (23 mg, 0.18 mmol) yielded title compound (55 mg, 62 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.1 (s, 3H) ; 4.32 (t, 2H) ; 7.39 (s, 1H) ; 7.43 (d, 2H) ; 7.84 (d, 2H) ; 7.99 (s, 1H) ; 8.32 (s, 1H) ; 9.01 (s, 1H).

MS ES$^+$: 552, 554 $[M+H]^+$

Example 106. Preparation of Compound 266 in Table 10

An analogous reaction to that described in Example 101, but starting with pyrrolidine (13 mg, 0.18 mmol) yielded title compound (50 mg, 62 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.85 (m, 4H) ; 2.28 (m, 2H) ; 3.15 (t, 2H) ; 3.32 (t, 2H) ; 3.5 (m, 4H) ; 3.66 (t, 2H) ; 3.89 (m, 5H) ; 3.98 (m, 5H) ; 4.27 (t, 2H) ; 7.33 (s, 1H) ; 7.85 (s, 1H) ; 8.29 (s, 1H) ; 8.96 (s, 1H).

MS ES$^+$: 496 $[M+H]^+$

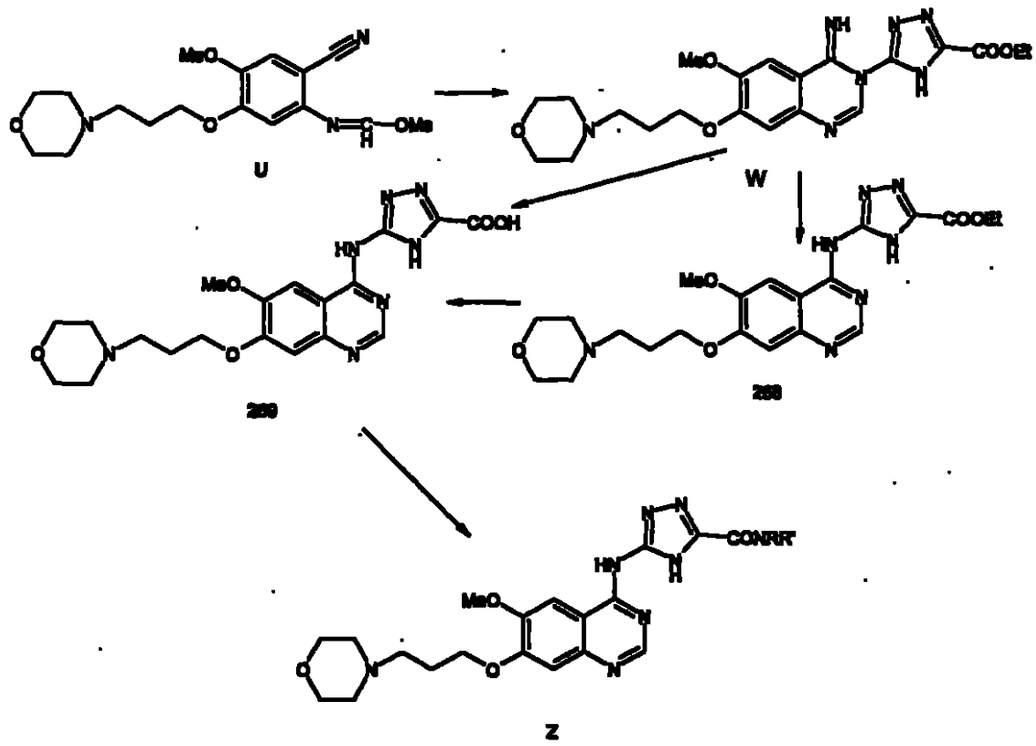
Example 107. Preparation of Compound 267 in Table 10

An analogous reaction to that described in Example 101, but starting with cyclohexylamine (18 mg, 0.18 mmol) yielded title compound (54 mg, 64 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.19 (m, 1H) ; 1.35 (m, 4H) ; 1.61 (m, 1H) ; 1.71 (m, 2H) ; 1.85 (m, 2H) ; 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.69 (t, 2H) ; 3.75 (m, 1H) ; 4.01 (s, 3H) ; 4.04 (m, 5H) ; 4.3 (t, 2H) ; 7.37 (s, 1H) ; 7.9 (s, 1H) ; 8.29 (s, 1H) ; 8.99 (s, 1H).

MS ES$^+$: 524 $[M+H]^+$

General Scheme 12



Example 108.

Step (a) Preparation of Intermediates of General formula W

Imidate U (2 g, 6 mmol) in dimethylformamide (40 ml) was reacted with ethyl 5-amino-4H-1,2,4-triazole-3-carboxylate hydrochloric acid (1.16 g, 6 mmol) in presence of sodium hydride (60 %, 504 mg, 12.6 mmol) at 110°C for 7 hours, under argon. The mixture was then cooled to room temperature, and acetic acid (1.03 ml, 18 mmol) was added, the solvent was evaporated under vacuum, the residue purified by silica gel chromatography, eluent : CH_2Cl_2 / MeOH, 90/10 to give title compound (1.07 g, 39 %).

^1H NMR (DMSO-d_6, TFA) : 1.39 (t, 3H) ; 2.28 (m, 2H) ; 3.15 (t, 2H) ; 3.32 (t, 2H) ; 3.56 (d, 2H) ; 3.68 (t, 2H) ; 3.98 (s, 3H) ; 4.05 (d, 2H) ; 4.37 (t, 2H) ; 4.52 (q, 2H) ; 7.49 (s, 1H) ; 8.12 (s, 1H) ; 8.71 (s, 1H).

MS ES^+ : 458 $[M+H]^+$

Step (b) : Preparation of Compound 268 in Table 11

Triazole ester W (80 mg, 0.17 mmol) in dimethylformamide (3 ml) was treated with dimethylamine acetate (0.52 mmol) at 70°C for 20 minutes. The mixture was cooled, the

solvent evaporated, and the residue purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH / NH3, 90/10/1 to give title product (60 mg, 75 %).

^{1}H NMR (DMSO-d_6, TFA) : 1.34 (t, 3H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.0 (s, 3H) ; 4.04 (d, 2H) ; 4.36 (m, 4H) ; 7.48 (s, 1H) ; 8.26 (s, 1H) ; 9.01 (s, 1H).

MS ES$^+$: 458 $[M+H]^+$

Example 109. Preparation of Compound 269 in Table 11

Triazole ester 268 (900 mg, 1.97 mmol) in methanol (20 ml), was treated with sodium hydroxyde (2N, 20 ml) at 80°C for 1.5 hour. The mixture was cooled, and acidified to pH 2.5 with hydrochloric acid (6N), the solid was recovered by filtration dried under vacuum over P_2O_5 to give title compound (843 mg, 100 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.37 (m, 2H) ; 3.12 (t, 2H) ; 3.3 (t, 2H) ; 3.5 (d, 2H) ; 3.87 (t, 2H) ; 3.97 (d, 2H) ; 4.01 (s, 3H) ; 4.35 (t, 2H) ; 7.63 (s, 1H) ; 8.32 (s, 1H) ; 8.97 (s, 1H).

MS ES$^+$: 430 $(M+H)^+$.

Example 110. Preparation of Compound 270 in Table 11

Acid 269 (120 mg, 0.28 mmol) in DMF (2 ml) was reacted with aniline (0.025 ml, 0.28 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N',-tetramethyluronium hexafluorophosphate (106 mg, 0.28 mmol) and DIEA (0.12 ml, 0.7 mmol) at room temperature for 4 hours. The solvent was evaporated, the residue dissolved in methylene chloride / methanol, and treated with a methanolic solution of dimethylamine (2M, 1 ml) at room temperature over night. The solvent was evaporated, and the residue purified by flash silica gel chromatography, eluent CH_2Cl_2 / MeOH, 90/10 to give title compound (12 mg, 9 %).

^{1}H NMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.18 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 7.16 (t, 1H) ; 7.39 (t, 2H) ; 7.45 (s, 1H) ; 7.83 (d, 2H) ; 8.2 (s, 1H) ; 8.95 (s, 1H).

MS ES$^+$: 505 $[M+H]^+$

Example 111. Preparation of Compound 271 in Table 11

An analogous reaction to that described in Example 110, but starting with 4-fluoroaniline (0.13 ml, 1.4 mmol) yielded title compound (44 mg, 18 %).

^{1}H NMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.0 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.23 (t, 2H) ; 7.44 (s, 1H) ; 7.86 (m, 1H) ; 8.18 (s, 1H) ; 8.93 (s, 1H).

MS ES$^+$: 523 $[M+H]^+$

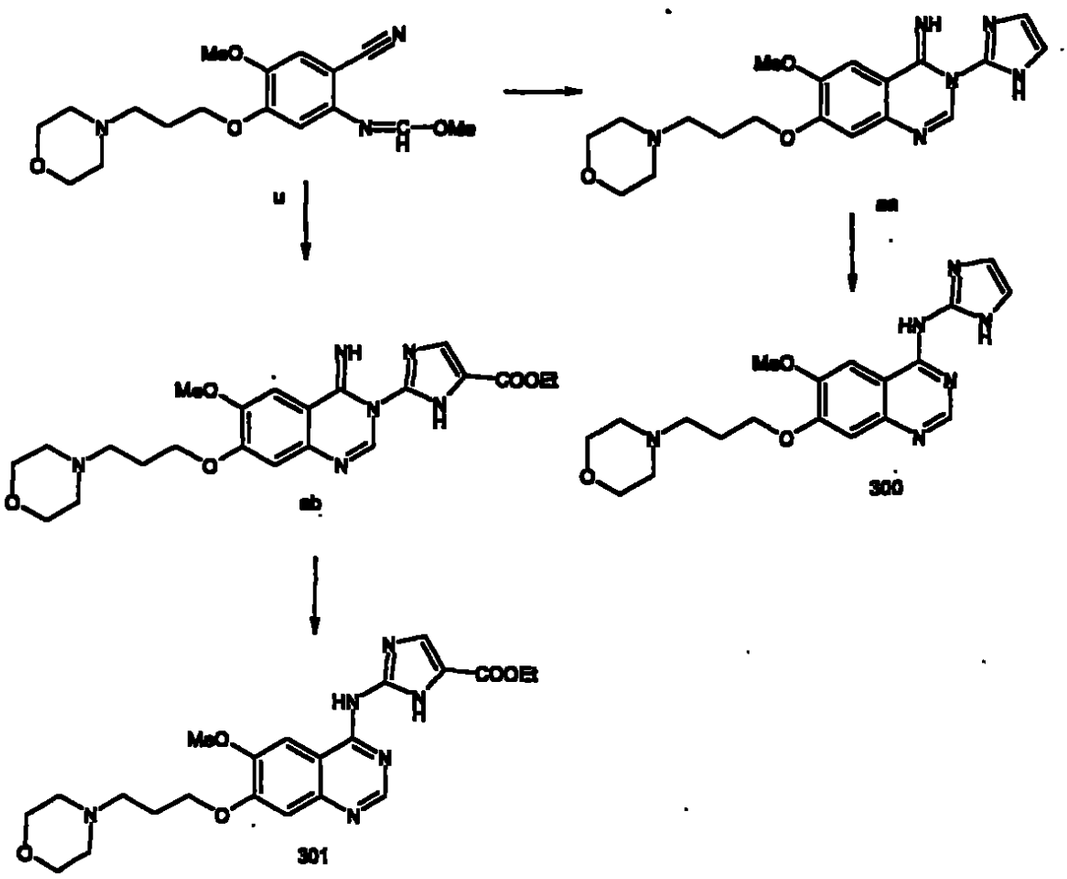
Example 112. Preparation of Compound 272 in Table 11

An analogous reaction to that described in Example 110 but starting with allylamine (0.13 ml, 1.75 mmol) yielded the title compound (26 mg, 10 %).

^{1}H NMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.34 ((, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.94 (d, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 5.13 (d, 1H) ; 5.18 (d, 1H) ; 5.92 (m, 1H) ; 7.41 (s, 1H) ; 8.17 (s, 1H) ; 8.91 (s, 1H).

MS ES$^+$: 469 $[M+H]^+$

General Scheme 13



Example 113. Preparation of Compound 300 in Table 12

Step 1 Preparation of Compound aa

Imidate u, (200 mg, 0.6 mmol) in DMF (4 ml) was condensed with 2-aminoimidazole, sulfate (160 mg, 0.6 mmol) in presence of sodium hydride (60 %, 50 mg, 1.26 mmol) at 90°C for 2 hours. The mixture was cooled, acetic acid (0.01 ml, 1.8 mmol) was added, the solvent was evaporated, and the residue purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH, 90/10 to give title compound (112 mg, 48 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.33 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.36 (t, 2H) ; 7.41 (s, 2H) ; 7.47 (s, 1H) ; 8.13 (s, 1H) ; 8.66 (s, 1H).

MS ES$^+$: 385 $[M_+H]^+$

Step 2: Preparation of Compound 300

Imidazole aa (105 mg, 0.273 mmol) in DMF (2 ml) was heated at 80°C for 0.3 hour in presence of dimethylamine acetate (0.819 mmol), the solvent was evaporated, and the residue was purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH sat. NH_3, 90/10 to give title compound (78 mg, 74 %).

^{1}HNMR (DMSO) : 1.96 (m, 2H) ; 2.39 (m, 4H) ; 2.46 (t, 2H) ; 3.6 (m, 4H) ; 3.9 (s, 3H) ; 4.18 (t, 2H) . 6.9 (s, 2H) ; 7.14 (s, 1H) ; 7.84 (s, 1H) ; 8.39 (s, 1H).

MS ES$^+$: 385 $[M_+H]^+$

Example 114 Preparation of Compound 301 in Table 12

Step 1: Preparation of Compound ab

Imidate u (250 mg, 0.751 mmol) in DMF (4 ml) was reacted with ethyl 2-aminoimidazole-4-carboxylate (117 mg, 0.751 mmol) in presence of sodium hydride (60 %, 30 mg, 0.826 mmol) at 100° C for 3 hours. The mixture was cooled, acetic acid (0.13 ml, 2.25 mmol) was added, the solvent was evaporated, and the residue purified by silica gel chromatography to give title compound (125 mg, 36 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.32 (t, 3H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (q, 2H) ; 4.37 (t, 2H) ; 7.49 (s, 1H) ; 8.11 (s, 1H) ; 8.2 (s, 1H) ; 8.65 (s, 1H).

MS ES$^+$: 457 $[M_+H]^+$

Step 2: Preparation of Compound 301 in Table 12

Imidazole 3 (122 mg, 0.268 mmol) in DMF (2 ml) was heated at 80°C for 0.3 hour in presence of dimethylamine acetate (0.802 mmol). The solvent was evaporated, and the residue was purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH sat. NH_3 95/5 to 90/10 to give title compound (105 mg, 86 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.32 (t, 3H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.94 (s, 3H) ; 4.03 (d, 2H) ; 4.27 (t, 2H) ; 4.33 (q, 2H) ; 7.27 (s, 1H) ; 7.84 (s, 1H) ; 7.92 (s, 1H) ; 8.76 (s, 1H).

MS ES$^+$: 457 $[M_4H]^+$

Example 115. Preparation of compound 302 in Table 13

An analogous reaction to that described in general scheme 5, starting with 4-methoxyaniline (32 mg, 0.26 mmol) yielded compound 302 in Table 13 (24 mg, 21%).

MS ES$^+$: 551 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.76 (s, 3H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 6.96 (d, 2H) ; 7.38 (s, 1H) ; 7.62 (d, 2H) ; 8.04 (s, 1H) ; 8.55 (s, 1H) 9.27 (s, 1H).

Example 116. Preparation of compound 303 in Table 13

An analogous reaction to that described in general scheme 5, starting with 4-methylaniline (28 mg, 0.26 mmol) yielded compound 303 in Table 13 (23 mg, 22%).

MS ES$^+$: 535 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.29 (s, 3H) ; 2.33 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.19 (d, 2H) ; 7.38 (s, 1H) ; 7.60 (d, 2H) ; 8.05 (s, 1H) ; 8.58 (s, 1H) ; 9.28 (s, 1H).

Example 117. Preparation of compound 304 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-aminopyridine (24 mg, 0.26 mmol) yielded compound 304 in Table 13 (12 mg, 11%).

MS ES$^+$: 522 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.34 (t, 2H) ; 7.33 (m, 1H) ; 7.41 (s, 1H) ; 8.07 (m, 2H) ; 8.09 (s, 1H) ; 8.46 (d, 1H) ; 8.81 (s, 1H) ; 9.30 (s, 1H).

Example 118. Preparation of compound 305 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-aminobenzyl alcohol (32 mg, 0.26 mmol) yielded compound 305 in Table 13 (54 mg, 60%).

MS ES$^+$: 551 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.33 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 3.78 (s, 2H) ; 4.02 (s, 3H) ; 4.05 (d, 2H) ; 4.34 (t, 2H) ; 6.73 (d, 1H) ; 7.30 (m, 2H) ; 7.39 (s, 1H) ; 7.40 (m, 1H) ; 8.07 (s, 1H) ; 8.62 (s, 1H) ; 9.3 (s, 1H).

Example 119. Preparation of compound 306 in Table 13

An analogous reaction to that described in general scheme 5, starting with 4-methoxybenzylamine (36 mg, 0.26 mmol) yielded compound 306 in Table 13 (29 mg, 26%).

MS ES$^+$: 565 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.28 (t, 2H) ; 3.14 (t, 2H) ; 3.31 (t, 2H) ; 3.50 (d, 2H) ; 3.68 (t, 2H) ; 3.69 (s, 3H) ; 3.94 (s, 3H) ; 3.98 (d, 2H) ; 4.26 (t, 2H) ; 4.37 (s, 2H) ; 6.89 (m, 2H) ; 7.12 (m, 2H) ; 7.35 (s, 1H) ; 7.90 (s, 1H) ; 8.31 (s, 1H) ; 9.15 (s, 1H).

Example 120. Preparation of compound 307 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3-nitroaniline (36 mg, 0.26 mmol) yielded compound 307 in Table 13 (27 mg, 24%).

MS ES$^+$: 566 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.30 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.40 (s, 1H) ; 7.71 (t, 1H) ; 7.99 (d, 1H) ; 8.08 (s, 1H) ; 8.14 (d, 1H) ; 8.64 (s, 1H) ; 8.71 (s, 1H) ; 9.31 (s, 1H).

Example 121. Preparation of compound 308 in Table 13

An analogous reaction to that described in general scheme 5, starting with aminoacetonitrile (24 mg, 0.26 mmol) yielded compound 308 in Table 13 (29 mg, 30%).

MS ES$^+$: 484 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.00 (s, 3H) ; 4.02 (d, 2H) ; 4.32 (t, 2H) ; 4.37 (s, 2H) ; 7.39 (s, 1H) ; 8.06 (s, 1H) ; 8.36 (s, 1H) ; 9.27 (s, 1H).

Example 122. Preparation of compound 309 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-methyl-5-nitroaniline (40 mg, 0.26 mmol) yielded compound 309 in Table 13 (14 mg, 12%).

MS ES$^+$: 580 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.39 (s, 1H) ; 7.58 (d, 1H) ; 8.04 (d, 1H) ; 8.08 (s, 1H) ; 8.34 (d, 1H) ; 8.62 (s, 1H) ; 9.29 (s, 1H).

Example 123. Preparation of compound 310 in Table 13

An analogous reaction to that described in general scheme 5, starting with cyclopropylamine (15 mg, 0.26 mmol) yielded compound 310 in Table 13 (6 mg, 6%).

MS ES$^+$: 485 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 0.68 (m, 2H) ; 0.74 (m, 2H) ; 2.27 (t, 2H) ; 2.67 (m, 1H) ; 3.12 (t, 2H) ; 3.31 (t, 2H) ; 3.51 (d, 2H) ; 3.69 (t, 2H) ; 3.95 (s, 3H) ; 3.98 (d, 2H) ; 4.29 (t, 2H) ; 7.32 (s, 1H) ; 7.96 (s, 1H) ; 8.24 (s, 1H) ; 9.20 (s, 1H).

Example 124. Preparation of compound 311 in Table 13

An analogous reaction to that described in general scheme 5, starting with 4-nitrobenzylamine (49 mg, 0.26 mmol) yielded compound 311 in Table 13 (5 mg, 4%).

MS ES$^+$: 580 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 4.63 (s, 2H) ; 7.38 (s, 1H) ; 7.62 (d, 2H) ; 8.04 (s, 1H) ; 8.23 (d, 2H) ; 8.40 (s, 1H) ; 9.25 (s, 1H).

Example 125. Preparation of compound 312 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-anilinoethanol (36 mg, 0.26 mmol) yielded compound 312 in Table 13 (49 mg, 44%).

MS ES$^+$: 565 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.7 (m, 4H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 4.49 (t, 2H) ; 7.15 (t, 1H) ; 7.26 (d, 2H) ; 7.41 (t, 2H) ; 7.43 (s, 1H) ; 8.15 (s, 1H) ; 8.48 (s, 1H) ; 9.31 (s, 1H).

Example 126. Preparation of compound 313 in Table 13

An analogous reaction to that described in general scheme 5, starting with furfurylamine (25 mg, 0.26 mmol) yielded compound 313 in Table 13 (20 mg, 19%).

MS ES$^+$: 525 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (d, 2H) ; 4.32 (t, 2H) ; 4.48 (s, 2H) ; 6.33 (d, 1H) ; 6.41 (d, 1H) ; 7.37 (s, 1H) ; 7.59 (s, 1H) ; 8.01 (s, 1H) ; 8.37 (s, 1H) ; 9.24 (s, 1H).

Example 127. Preparation of compound 314 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3-chloroaniline (33 mg, 0.26 mmol) yielded compound 314 in Table 13 (21 mg, 19%).

MS ES$^+$: 555, 557 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.54 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.32 (t, 2H) ; 7.20 (d, 1H) ; 7.39 (s, 1H) ; 7.42 (t, 1H) ; 7.63 (d, 1H) ; 7.91 (s, 1H) ; 8.07 (s, 1H) ; 8.61 (s, 1H) ; 9.30 (s, 1H).

Example 128. Preparation of compound 315 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-methoxyaniline (32 mg, 0.26 mmol) yielded compound 315 in Table 13 (67 mg, 61%).

MS ES$^+$: 551 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.87 (s, 3H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 6.99 (t, 1H) ; 7.13 (d, 1H) ; 7.23 (t, 1H) ; 7.40 (s, 1H) ; 7.66 (d, 1H) ; 8.04 (s, 1H) ; 8.64 (s, 1H) ; 9.27 (s, 1H).

Example 139. Preparation of compound 316 in Table 13

An analogous reaction to that described in general scheme 5, starting with thiophene-2-methylamine (29 mg, 0.26 mmol) yielded compound 316 in Table 13 (25 mg, 23%).

MS ES$^+$: 541 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.01 (s, 3H) ; 4.04 (d, 2H) ; 4.34 (t, 2H) ; 4.67 (s, 2H) ; 6.99 (m, 1H) ; 7.08 (m, 1H) ; 7.39 (s, 1H) ; 7.41 (d, 1H) ; 8.04 (s, 1H) ; 8.36 (s, 1H) ; 9.27 (s, 1H).

Example 140. Preparation of compound 317 in Table 13

An analogous reaction to that described in general scheme 5, starting with neopentylamine (23 mg, 0.26 mmol) yielded compound 317 in Table 13 (31 mg, 30%).

MS ES$^+$: 515 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 0.91 (s, 9H) ; 2.31 (t, 2H) ; 3.10 (s, 2H) ; 3.17 (t, 2H) ; 3.35 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.35 (s, 1H) ; 8.00 (s, 1H) ; 8.45 (s, 1H) ; 9.23 (s, 1H).

Example 141. Preparation of compound 318 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2,6-difluorobenzylamine (37 mg, 0.26 mmol) yielded compound 318 in Table 13 (35 mg, 31%).

MS ES$^+$: 571 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.31 (t, 2H) ; 4.54 (s, 2H) ; 7.11 (t, 2H) ; 7.36 (s, 1H) ; 7.42 (m, 1H) ; 8.00 (s, 1H) ; 8.35 (s, 1H) ; 9.24 (s, 1H).

Example 142. Preparation of compound 319 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-methylallylamine (28 mg, 0.26 mmol) yielded compound 319 in Table 13 (16 mg, 16%).

MS ES$^+$: 499 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 1.72 (s, 3H) ; 2.31 (t, 1H) ; 3.15 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.72 (s, 2H) ; 3.99 (s, 3H) ; 4.02 (d, 2H) ; 4.31 (t, 2H) ; 4.82 (s, 1H) ; 4.86 (s, 1H) ; 7.36 (s, 1H) ; 8.01 (s, 1H) ; 8.37 (s, 1H) ; 9.23 (s, 1H).

Example 143. Preparation of compound 320 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-methyl-4-fluoroaniline (33 mg, 0.26 mmol) yielded compound 320 in Table 13 (47 mg, 43%).

MS ES$^+$: 553 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.26 (s, 3H) ; 2.31 (t, 1H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 7.07 (m, 1H) ; 7.18 (d, 1H) ; 7.36 (m, 1H) ; 7.38 (s, 1H) ; 8.06 (s, 1H) ; 8.53 (s, 1H) ; 9.27 (s, 1H).

Example 144. Preparation of compound 321 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-fluoro-5-methylaniline (33 mg, 0.26 mmol) yielded compound 321 in Table 13 (60 mg, 54%).

MS ES$^+$: 553 $(M+H)^+$

Example 145. Preparation of compound 322 in Table 13

An analogous reaction to that described in general scheme 5, starting with 4-fluorobenzylamine (33 mg, 0.26 mmol) yielded compound 322 in Table 13 (33 mg, 30%).

MS ES$^+$: 553 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 1H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (d, 2H) ; 4.33 (t, 2H) ; 4.47 (s, 2H) ; 7.15 (t, 2H) ; 7.36 (s, 1H) ; 7.37 (m, 2H) ; 8.02 (s, 1H) ; 8.36 (s, 1H) ; 9.24 (s, 1H).

Example 146. Preparation of compound 323 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3,4-difluorobenzylamine (37 mg, 0.26 mmol) yielded compound 323 in Table 13 (17 mg, 15%).

MS ES$^+$: 571 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 4.48 (s, 2H) ; 7.21 (m, 1H) ; 7.38 (s, 1H) ; 7.38 (m, 2H) ; 8.03 (s, 1H) ; 8.38 (s, 1H) ; 9.24 (s, 1H).

Example 147. Preparation of compound 324 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3-methylaniline (28 mg, 0.26 mmol) yielded compound 324 in Table 13 (57 mg, 53%).

MS ES$^+$: 535 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.32 (m, 5H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (s, 3H) ; 4.04 (d, 2H) ; 6.95 (d, 1H) ; 7.24 (t, 1H) ; 7.38 (s, 1H) ; 7.53 (m, 2H) ; 8.04 (s, 1H) ; 8.59 (s, 1H) ; 9.28 (s, 1H).

Example 148. Preparation of compound 325 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-(methylthio)aniline (36 mg, 0.26 mmol) yielded compound 325 in Table 13 (73 mg, 64%).

MS ES$^+$: 567 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 2.44 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.22 (t, 1H) ; 7.37 (m, 4H) ; 8.06 (s, 1H) ; 8.52 (s, 1H) ; 9.27 (s, 1H).

Example 149. Preparation of compound 326 in Table 13

An analogous reaction to that described in general scheme 5, starting with 5-aminoindole (34 mg, 0.26 mmol) yielded compound 326 in Table 13 (16 mg, 15%).

MS ES$^+$: 560 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.32 (t, 2H) ; 7.36 (m, 5H) ; 7.94 (s, 1H) ; 8.04 (s, 1H) ; 8.28 (s, 1H) ; 9.28 (s, 1H).

Example 150. Preparation of compound 327 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3-aminobenzonitrile (31 mg, 0.26 mmol) yielded compound 327 in Table 13 (30 mg, 28%).

MS ES$^+$: 546 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.67 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.40 (s, 1H) ; 7.60 (m, 2H) ; 7.97 (m, 1H) ; 8.08 (s, 1H) ; 8.21 (s, 1H) ; 8.61 (s, 1H) ; 9.30 (s, 1H).

Example 151. Preparation of compound 328 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2,4-difluorobenzylamine (37 mg, 0.26 mmol) yielded compound 328 in Table 13 (27 mg, 24%).
MS ES$^+$: 571 $(M+H)^+$
^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 4.49 (s, 2H) ; 7.09 (m, 1H) ; 7.21 (m, 1H) ; 7.38 (s, 1H) ; 8.02 (s, 1H) ; 8.38 (s, 1H) ; 9.24 (s, 1H).

Example 152. Preparation of compound 329 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3-(2-aminoethyl)pyridine (32 mg, 0.26 mmol) yielded compound 329 in Table 13 (33 mg, 30%).
MS ES$^+$: 550 $(M+H)^+$
^{1}H NMR (DMSO-d6, TFA) : 2.33 (t, 2H) ; 3.11 (t, 2H) ; 3.18 (t, 2H) ; 3.35 (t, 2H) ; 3.57 (d, 2H) ; 3.66 (t, 2H) ; 3.68 (t, 2H) ; 4.01 (s, 3H) ; 4.05 (d, 2H) ; 4.34 (t, 2H) ; 7.41 (s, 1H) ; 8.05 (s, 1H) ; 8.08 (dd, 2H) ; 8.28 (s, 1H) ; 8.59 (d, 1H) ; 8.87 (d, 1H) ; 8.95 (s, 1H) ; 9.25 (s, 1H).

Example 153. Preparation of compound 330 in Table 13

An analogous reaction to that described in general scheme 5, starting with N-methylisobutylamine (23 mg, 0.26 mmol) yielded compound 330 in Table 13 (23 mg, 22%).
MS ES$^+$: 515 $(M+H)^+$
^{1}H NMR (DMSO-d6, TFA) : 0.88 (d, 6H) ; 2.02 (m, 1H) ; 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.27 (m, 5H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.37 (s, 1H) ; 8.03 (s, 1H) ; 8.18 (s, 1H) ; 9.23 (s, 1H).

Example 154. Preparation of compound 331 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-aminobenzylamine (32 mg, 0.26 mmol) yielded compound 331 in Table 13 (6 mg, 6%).
MS ES$^+$: 550 $(M+H)^+$
^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 4.47 (s, 2H) ; 7.41 (s, 1H) ; 7.46 (m, 4H) ; 8.06 (s, 1H) ; 8.42 (s, 1H) ; 9.24 (s, 1H).

Example 155. Preparation of compound 332 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3-methylbutylamine (23 mg, 0.26 mmol) yielded compound 332 in Table 13 (48 mg, 47%).

MS ES$^+$: 515 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 0.90 (d, 6H) ; 1.43 (q, 2H) ; 1.62 (m, 1H) ; 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.28 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (d, 2H) ; 4.31 (t, 2H) ; 7.35 (s, 1H) ; 8.00 (s, 1H) ; 8.31 (s, 1H) ; 9.23 (s, 1H).

Example 156. Preparation of compound 333 in Table 13

An analogous reaction to that described in general scheme 5, starting with 1-aminomethyl-1-cyclohexanol (43 mg, 0.26 mmol) yielded compound 333 in Table 13 (7 mg, 6%).

MS ES$^+$: 557 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 1.37 (m, 10H) ; 2.28 (t, 2H) ; 3.11 (t, 2H) ; 3.23 (s, 2H) ; 3.32 (t, 2H) ; 3.51 (d, 2H) ; 3.65 (t, 2H) ; 3.96 (s, 3H) ; 3.99 (d, 2H) ; 4.28 (t, 2H) ; 7.32 (s, 1H) ; 7.95 (s, 1H) ; 8.43 (s, 1H) ; 9.19 (s, 1H).

Example 157. Preparation of compound 334 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-aminomethylpyrazine (38 mg, 0.26 mmol) yielded compound 334 in Table 13 (25 mg, 24%).

MS ES$^+$: 537 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.33 (t, 2H) ; 3.13 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.05 (d, 2H) ; 4.30 (t, 2H) ; 4.65 (s, 2H) ; 7.38 (s, 1H) ; 8.03 (s, 1H) ; 8.40 (s, 1H) ; 8.57 (d, 1H) ; 8.62 (d, 1H) ; 8.70 (s, 1H) ; 9.24 (s, 1H).

Example 158. Preparation of compound 335 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3-methoxyaniline (32 mg, 0.26 mmol) yielded compound 335 in Table 13 (60 mg, 54%).

MS ES$^+$: 551 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.58 (d, 2H) ; 3.70 (t, 2H) ; 3.79 (s, 3H) ; 4.03 (s, 3H) ; 4.06 (d, 2H) ; 4.34 (t, 2H) ; 6.73 (d, 1H) ; 7.29 (d, 1H) ; 7.32 (d, 1H) ; 7.41 (m, 2H) ; 8.07 (s, 1H) ; 8.62 (s, 1H) ; 9.30 (s, 1H).

Example 159. Preparation of compound 336 in Table 13

An analogous reaction to that described in general scheme 5, starting with 4-chlorobenzylamine (19 mg, 0.26 mmol) yielded compound 336 in Table 13 (31 mg, 54%).
MS ES$^+$: 569, 571 $(M+H)^+$
^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 1H) ; 4.48 (s, 2H) ; 7.42 (m, 5H) ; 8.02 (s, 1H) ; 8.37 (s, 1H) ; 9.24 (s, 1H).

Example 160. Preparation of compound 337 in Table 14

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (78 mg, 0.17 mmol) in DMF (1 ml), was reacted with aniline (19 mg, 0.2 mmol) in presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (76 mg, 0.2 mmol) and DIEA (44 mg, 0.34 mmol) at 50°C over night. The reaction mixture was cooled, treated with $NaHCO_3$ (1 ml), concentrated. The yellow solid was recovered, dissolved in a mixture of CH_2Cl_2 / MeOH (60/40) 20 ml. Alumina (3 g) was added to the mixture, the solvent was evaporated, and the solid was added on top of an alumina column which was eluted with CH_2Cl_2 / MeOH (10/0 to 9/1) to give title compound (43 mg, 47 %).
MS ES$^+$: 535 $(M+H)^+$
^{1}HNMR ($DMSOd_6$, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (m, 5H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.08 (t, 1H) ; 7.32 (m, 3H) ; 7.62 (m, 3H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

4-(ethyl(2-amino-1,3-thiazole-5-yl)acetate)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.
Amidine J of scheme. 2 (4.5 g, 13 mmol) in acetic acid (45 ml) was reacted with ethyl (2-amino-1,3-thiazole-5-yl)acetate (2.54 g, 13.65 mmol) at reflux for 5.5 hour under argon. The mixture was concentrated, and the residue was purified over silicagel chromatography, eluant CH_2Cl_2 / MeOH, 95/5 to 90/10 to give title compound (4.5 g, 63 %).

^{1}HNMR (DMSOd_6) : 1.22 (t, 3H) ; 1.96 (t, 2H) ; 2.37 (m, 4H) ; 2.35 (t, 2H) ; 3.58 (m, 4H) ; 3.91 (s, 2H) ; 3.95 (s, 3H) ; 4.13 (q, 2H) ; 4.20 (t, 2H) ; 7.25 (s, 1H) ; 7.36 (s, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H).

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.

4-(ethyl(2-amino-1,3-thiazole-5-yl)acetate)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (4.38 g, 8 mmol) in ethanol (44 ml) was treated with sodium hydroxyde (2N, 10 ml) at 50°C for 4 hours. The mixture was cooled to room temperature and the pH adjusted to 3.5 with 2N HCl. The residue was dissolved in CH_2Cl_2 / MeOH, 60/40, DIEA (3 g, 24 mmoles) was added, the mixture was stirred for 10 minutes, filtered, and the solution was concentrated to give an oily residue. This residue was dissolved in ethanol, and the solvent was partially evaporated. A cristalin solid was recovered, suspended in ethanol, washed with ether and dried under vacuum to give title compound (3.7 g, 100 %).

^{1}HNMR (DMSOd_6, TFA) : 2.28 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.70 (t, 2H) ; 3.92 (s, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.30 (t, 2H) ; 7.32 (s, 1H) ; 7.60 (s, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 161. Preparation of compound 338 in Table 14

An analogous reaction to that described in example 36 but starting with 3-chloro-4-fluoroaniline (30 mg, 0.2 mmol) yielded the title compound (24 mg, 24 %).

MS ES$^+$: 587 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.34 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (m, 5H) ; 4.03 (d, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.65 (s, 1H) ; 7.85 (s, 1H) ; 7.97 (d, 1H) ; 9.09 (s, 1H).

Example 162. Preparation of compound 339 in Table 14

An analogous reaction to that described in example 36 but starting with 4-chloroaniline (26 mg, 0.2 mmol) yielded title compound (73 mg, 76 %).

MS ES$^+$: 569 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.89 (m, 5H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.39 (d, 2H) ; 7.64 (s, 1H) ; 7.65 (d, 2H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 163. Preparation of compound 340 in Table 14

An analogous reaction to that described in example 36 but starting with 3,4-difluoroaniline (26 mg, 0.2 mmol) yielded title compound (75 mg, 77 %).

MS ES$^+$: 571(M+H)$^+$

^{1}HNMR (DMSOd$_6$, TFA) 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.72 (t, 2H) ; 3.99 (m, 5H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.31 (s, 1H) ; 7.32 (m, 1H) ; 7.41 (q, 1H) ; 7.65 (s, 1H) ; 7.81 (m, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 164. Preparation of compound 341 in Table 14

An analogous reaction to that described in example 36 but starting with 3-methoxyaniline (25 mg, 0.2 mmol) yielded title compound (40 mg, 42 %).

MS ES$^+$: 565 (M+H)$^+$

^{1}HNMR (DMSOd$_6$, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.70 (t, 2H) ; 3.74 (s, 3H) ; 3.97 (s, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.31 (t, 2H) ; 6.68 (d, 1H) ; 7.15 (d, 1H) ; 7.23 (t, 1H) ; 7.29 (s, 1H) ; 7.33 (s, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 165. Preparation of compound 342 in Table 14

An analogous reaction to that described in example 36 but starting with 2-chloroaniline (26 mg, 0.2 mmol) yielded title compound (15 mg, 16 %).

MS ES$^+$: 569 (M+H)$^+$

^{1}HNMR (DMSOd$_6$, TFA) : 2.30 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.05 (m, 4H) ; 4.31 (t, 2H) ; 7.22 (t, 1H) ; 7.30 (s, 1H) ; 7.35 (t, 1H) ; 7.51 (d, 1H) ; 7.65 (s, 1H) ; 7.75 (d, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 166. Preparation of compound 343 in Table 14

An analogous reaction to that described in example 36 but starting with 4-methoxyaniline (26 mg, 0.21 mmol) yielded title compound (55 mg, 57 %).

MS ES$^+$: 565.6 (M+H)$^+$

^{1}HNMR (DMSOd$_6$, TFA) : 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.73 (t, 2H) ; 3.80 (s, 3H) ; 3.97 (s, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 6.93 (d, 2H) ; 7.09 (s, 1H) ; 7.33 (s, 1H) ; 7.56 (d, 2H) ; 7.66 (s, 1H) ; 7.94 (s, 1H) ; 9.12 (s, 1H).

Example 167. Preparation of compound 344 in Table 14

An analogous reaction to that described in example 36 but starting with 4-methylaniline (23 mg, 0.21 mmol) yielded title compound (51 mg, 54 %).

MS ES$^+$: 549.7 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.29 (s, 3H) ; 2.31 (t, 2H) ; 3.19 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 3.99 (s, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.16 (d, 2H) ; 7.33 (s, 1H) ; 7.54 (d, 2H) ; 7.67 (s, 1H) ; 7.94 (s, 1H) ; 9.12 (s, 1H).

Example 168. Preparation of compound 345 in Table 14

An analogous reaction to that described in example 36 but starting with 2-methylaniline (23 mg, 0.21 mmol) yielded title compound (42 mg, 45 %).

MS ES$^+$: 549.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.24 (s, 3H) ; 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.12 (t, 1H) ; 7.19 (t, 1H) ; 7.24 (d, 1H) ; 7.31 (s, 1H) ; 7.43 (t, 1H) ; 7.66 (s, 1H) ; 7.92 (s, 1H) ; 9.08 (s, 1H).

Example 169. Preparation of compound 346 in Table 14

An analogous reaction to that described in example 36 but starting with 2-aminopyridine (20 mg, 0.21 mmol) yielded title compound (12 mg, 13 %).

MS ES$^+$: 536.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (m, 5H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.34 (s, 1H) ; 7.37 (t, 1H) ; 7.68 (s, 1H) ; 7.93 (d, 1H) ; 7.94 (s, 1H) ; 8.10 (t, 1H) ; 8.42 (d, 1H) ; 9.10 (s, 1H).

Example 170. Preparation of compound 347 in Table 14

An analogous reaction to that described in example 36 but starting with 2-aminobenzylalcohol (26 mg, 0.21 mmol) yielded title compound (24 mg, 24 %).

MS ES$^+$: 565.7 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.97 (t, 2H) ; 2.41 (m, 6H) ; 3.59 (m, 4H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.21 (t, 2H) ; 4.50 (d, 2H) ; 5.27 (t, 1H) ; 7.18 (t, 1H) ; 7.25 (d, 1H) ; 7.26 (s, 1H) ; 7.42 (m, 2H) ; 7.52 (d, 1H) ; 8.67 (s, 1H) ; 9.59 (s, 1H).

Example 171. Preparation of compound 348 in Table 14

An analogous reaction to that described in example 36 but starting with 2-amino-3-methyl-1-butanol (22 mg, 0.21 mmol) yielded title compound (25 mg, 27 %).

MS ES$^+$: 545.7 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 0.87 (d, 3H) ; 0.89 (d, 3H) ; 1.86 (m, 1H) ; 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.44 (2s, 2H) ; 3.57 (d, 2H) ; 3.63 (q, 1H) ; 3.70 (t, 2H) ; 3.80 (d, 2H) ; 4.01 (t, 3H) ; 4.07 (d, 2H) ; 4.31 (t, 2H) ; 7.32 (s, 1H) ; 7.58 (s, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 172. Preparation of compound 349 in Table 14

An analogous reaction to that described in example 36 but starting with 2-anilinoethanol (29 mg, 0.21 mmol) yielded title compound (11 mg, 11 %).

MS ES$^+$: 579.7 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.38 (t, 2H) ; 3.40 (m, 2H) ; 3.50 (t, 2H) ; 3.54 (d, 2H) ; 3.67 (m, 2H) ; 3.75 (t, 2H) ; 3.98 (s, 3H) ; 4.07 (d, 2H) ; 4.31 (t, 2H) ; 7.30 (s, 1H) ; 7.40 (s, 1H) ; 7.45 (m, 2H) ; 7.52 (m, 3H) ; 7.89 (s, 1H) ; 9.08 (s, 1H).

Example 173. Preparation of compound 350 in Table 14

An analogous reaction to that described in example 36 but starting with 3-chloro-4-methylamine (30 mg, 0.21 mmol) yielded title compound (3 mg, 3 %).

MS ES$^+$: 583.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.32 (m, 5H) ; 3.20 (t, 2H) ; 3.40 (t, 2H) ; 3.60 (d, 2H) ; 3.72 (t, 2H) ; 4.01 (s, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 7.32 (m, 2H) ; 7.42 (d, 1H) ; 7.68 (s, 1H) ; 7.87 (s, 1H) ; 7.95 (s, 1H) ; 9.13 (s, 1H).

Example 174. Preparation of compound 351 in Table 14

An analogous reaction to that described in example 36 but starting with 3-nitroaniline (29 mg, 0.21 mmol) yielded title compound (20 mg, 21 %).

MS ES$^+$: 580.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.33 (t, 2H) ; 3.20 (t, 2H) ; 3.39 (t, 2H) ; 3.60 (d, 2H) ; 3.73 (t, 2H) ; 4.02 (s, 3H) ; 4.06 (d, 2H) ; ';4.09 (s, 2H) ; 4.34 (t, 2H) ; 7.34 (s, 1H) ; 7.67 (d, 1H) ; 7.70 (s, 1H) ; 7.95 (s, 1H) ; 7.98 (m, 2H) ; 8.74 (s, 1H) ; 9.15 (s, 1H).

Example 175. Preparation of compound 352 in Table 14

An analogous reaction to that described in example 36 but starting with aminoacetonitrile (19 mg, 0.21 mmol) yielded title compound (28 mg, 31 %).

MS ES$^+$: 498.6 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA): 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 3.84 (s, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.21 (s, 2H) ; 4.31 (t, 2H) ; 7.31 (s, 1H) ; 7.60 (s, 1H) ; 9.10 (s, 1H).

Example 176. Preparation of compound 353 in Table 14

An analogous reaction to that described in example 36 but starting with 2-methyl-5-nitroaniline (32 mg, 0.21 mmol) yielded title compound (11 mg, 11 %).

MS ES$^+$: 594.6 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA): 2.32 (t, 2H) ; 2.44 (s, 3H) ; 3.19 (t, 2H) ; 3.40 (t, 2H) ; 3.59 (d, 2H) ; 3.73 (t, 2H) ; 4.03 (s, 3H) ; 4.07 (d, 2H) ; 4.16 (s, 2H) ; 4.34 (t, 2H) ; 7.34 (s, 1H) ; 7.57 (d, 1H) ; 7.71 (s, 1H) ; 7.95 (s, 1H) ; 8.01 (d, 1H) ; 8.58 (s, 1H) ; 9.13 (s, 1H).

Example 177. Preparation of compound 354 in Table 14

An analogous reaction to that described in example 36 but starting with 2-amino-5-chloropyridine (27 mg, 0.21 mmol) yielded title compound (13 mg, 13 %).

MS ES$^+$: 570.6 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.07 (s, 2H) ; 4.31 (t, 2H) ; 7.02 (d, 1H) ; 7.36 (s, 1H) ; 7.64 (s, 1H) ; 7.92 (s, 1H) ; 7.98 (dd, 1H) ; 8.21 (d, 1H) ; 9.1 (s, 1H).

Example 178. Preparation of compound 355 in Table 14

An analogous reaction to that described in example 36 but starting with 4-trifluoromethylaniline (34 mg, 0.21 mmol) yielded title compound (26 mg, 25 %);

MS ES$^+$: 603.7 $(M+H)^+$

^{1}H NMR (DMSOd$_6$, TFA): 2.30 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.72 (t, 2H) ; 3.99 (s, 3H) ; 4.05 (m, 4H) ; 4.31 (t, 2H) ; 7.31 (s, 1H) ; 7.66 (s, 1H) ; 7.70 (d, 2H) ; 7.84 (d, 2H) ; 7.92 (s, 1H) ; 9.10 (s, 1H).

Example 179. Preparation of compound 356 in Table 14

An analogous reaction to that described in example 36 but starting with 3-chloroaniline (27 mg, 0.21 mmol) yielded title compound (47 mg, 48 %).

MS ES$^+$: 569.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2 H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.04 (d, 2H) ; 4.31 (t, 2H) ; 7.14 (d, 1H) ; 7.30 (s, 1H) ; 7.37 (t, 1H) ; 7.47 (d, 1H) ; 7.65 (s,1H) ; 7.87 (s, 1H) ; 7.92 (s, 1H) ; 9.10 (s, 1H).

Example 180. Preparation of compound 357 in Table 14

An analogous reaction to that described in example 36 but starting with 2-methoxyaniline (26 mg, 0.21 mmol) yielded title compound (44 mg, 46 %).

MS ES$^+$: 565.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.33 (t, 2H) ; 3.20 (t, 2H) ; 3.40 (t, 2H) ; 3.60 (d, 2H) ; 3.73 (t, 2H) ; 3.91 (s, 3H) ; 4.03 (s, 3H) ; 4.08 (d, 2H) ; 4.11 (s, 2H) ; 4.34 (t, 2H) ; 6.96 (t, 1H) ; 7.12 (m, 2H) ; 7.34 (s, 1H) ; 7.66 (s, 1H) ; 7.95 (s, 1H) ; 8.01 (d, 1H) ; 9.12 (s, 1H).

Example 181. Preparation of compound 358 in Table 14

An analogous reaction to that described in example 36 but starting with 2-fluoroaniline (23 mg, 0.21 mmol) yielded title compound (43 mg, 46 %).

MS ES$^+$: 553.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (s, 3H) ; 4.05 (d, 2H) ; 4.08 (s, 2H) ; 4.31 (t, 2H) ; 7.19 (m, 2H) ; 7.28 (m, 1H) ; 7.31 (s, 1H) ; 7.64 (s, 1H) ; 7.93 (m, 2H) ; 9.06 (, 1H).

Example 182. Preparation of compound 359 in Table 14

An analogous reaction to that described in example 36 but starting with thiphene-2-methylamine (24 mg, 0.21 mmol) yielded title compound (50 mg, 53 %).

MS ES$^+$: 555.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 3.80 (s, 2H) ; 4.01 (s, 3H) ; 4.06 (d, 2H) ; 4.33 (t, 2H) ; 4.52 (s, 2H), 6.98 (dd, 1H) ; 7.02 (dd, 1H) ; 7.32 (s, 1H) ; 7.41 (dd, 1H) ; 7.60 (sq, 1H) ; 7.93 (s, 1H) ; 9.11 (s, 1H).

Example 183. Preparation of compound 360 in Table 14

An analogous reaction to that described in example 36 but starting with 2-amino-1-phenylethanol (29 mg, 0.21 mmol) yielded title compound (32 mg, 33 %).

MS ES$^+$: 579.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.18 (m, 3H) ; 3.36 (m, 3H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.74 (s, 2H) ; 3.99 (s, 3H) ; 4.05 (d, 2H) ; 4.30 (t, 2H) ; 4.66 (m, 1H) ; 7.3 (m, 6H) ; 7.53 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 184. Preparation of compound 361 in Table 14

An analogous reaction to that described in example 36 but starting with 3-(1-hydroxyethyl)aniline (29 mg, 0.21 mmol) yielded title compound (50 mg, 50 %).

MS ES$^+$: 579.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 1.34 (d, 3H) ; 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.00 (s, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 4.72 (q, 1H) ; 7.07 (d, 1H) ; 7.29 (t, 1H) ; 7.33 (s, 1H) ; 7.53 (d, 1H) ; 7.67 (s, 2H) ; 7.93 (s, 1H) ; 9.12 (s, 1H).

Example 185. Preparation of compound 362 in Table 14

An analogous reaction to that described in example 36 but starting with neopentylamine (18 mg, 0.21 mmol) yielded title compound (57 mg, 64 %).

MS ES$^+$: 529.7 $(M+H)^+$.

^{1}H NMR (DMSOd_6, TFA) : 0.89 (s, 9H) ; 2.33 (t, 2H) ; 2.97 (s, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.59 (d, 2H) ; 3.80 (s, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.32 (t, 2H) ; 7.33 (s, 1H) ; 7.60 (s, 1H) ; 7.93 (s, 1H) ; 9.11 (s, 1H).

Example 186. Preparation of compound 363 in Table 14

An analogous reaction to that described in example 36 but starting with 3-fluoro-4-methoxyaniline (30 mg, 0.21 mmol) yielded title compound (64 mg, 65 %).

MS ES$^+$: 583.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 3.82 (s, 3H) ; 3.96 (s, 2H) ; 4.00 (s, 3H) ; 4.04 (d, 2H) ; 4.31 (t, 2H) ; 7.15 (t, 1H) ; 7.30 (d, 1H) ; 7.31 (s, 1H) ; 7.61 (s, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.10 (s, 1H).

Example 187. Preparation of compound 364 in Table 14

An analogous reaction to that described in example 36 but starting with 2-methyl-4-fluoroaniline (26 mg, 0.21 mmol) yielded title compound (60 mg, 62 %).

MS ES$^+$: 567.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (s, 3H) ; 4.01 (s, 2H) ; 4.04 (d, 2H) ; 4.31 (t, 2H) ; 7.02 (t, 1H) ; 7.10 (d, 1H) ; 7.31 (s, 1H) ; 7.41 (q, 1H) ; 7.66 (s, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 188. Preparation of compound 365 in Table 14

An analogous reaction to that described in example 36 but starting with 2,5-difluoroaniline (27 mg, 0.21 mmol) yielded title compound (14 mg, 14 %).

MS ES$^+$: 571.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.01 (s, 3H) ; 4.06 (d, 2H) ; 4.12 (s, 2H) ; 4.33 (t, 2H) ; 7.00 (m, 1H) ; 7.33 (m, 2H) ; 7.65 (s, 1H) ; 7.95 (m, 2H) ; 9.11 (s, 1H).

Example 189. Preparation of compound 366 in Table 14

An analogous reaction to that described in example 36 but starting with 2-fluoro-4-chloroaniline (31 mg, 0.21 mmol) yielded title compound (12 mg, 12 %).

MS ES$^+$: 587.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (m, 4H) ; 4.31 (t, 2H) ; 7.29 (d, 1H) ; 7.52 (dd, 1H) ; 7.64 (s, 1H) ; 7.97 (d, 1H) ; 9.09 (s, 1H).

Example 190. Preparation of compound 367 in Table 14

An analogous reaction to that described in example 36 but starting with 2-fluoro-4-methylaniline (26 mg, 0.21 mmol) yielded title compound (20 mg, 20 %).

MS ES$^+$: 567.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (s, 3H) ; 2.32 (t, 2H) ; 3.20 (t, 2H) ; 3.39 (t, 2H) ; 3.59 (d, 2H) ; 3.73 (t, 2H) ; 4.03 (s, 3H) ; 4.07 (d, 2H) ; 4.09 (s, 2H) ; 4.34 (t, 2H) ; 7.02 (m, 1H) ; 7.18 (dd, 1H) ; 7.34 (s, 1H) ; 7.67 (s, 1H) ; 7.77 (d, 1H) ; 7.95 (s, 1H) ; 9.12 (s, 1H).

Example 191. Preparation of compound 368 in Table 14

An analogous reaction to that described in example 36 but starting with 3-methylaniline (23 mg, 0.21 mmol) yielded title compound (45 mg, 48 %).

MS ES$^+$: 549.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (m, 5H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.00 (s, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 6.93 (d, 1H) ; 7.24 (t, 1H) ; 7.33 (s, 1H) ; 7.43 (d, 1H) ; 7.51 (s, 1H) ; 7.67 (s, 1H) ; 7.94 (s, 1H) ; 9.12 (s, 1H).

Example 192. Preparation of compound 369 in Table 14

An analogous reaction to that described in example 36 but starting with 2-(methylthio)aniline (29 mg, 0.21 mmol) yielded title compound (13 mg, 13 %).

MS ES$^+$: 581.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.46 (s, 3H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.59 (d, 2H) ; 3.72 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (s, 2H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 7.22 (t, 1H) ; 7.27 (t, 1H) ; 7.34 (s, 1H) ; 7.39 (d, 1H) ; 7.45 (d, 1H) ; 7.68 (s, 1H) ; 7.93 (s, 1H) ; 9.10 (s, 1H).

Example 193. Preparation of compound 370 in Table 14

An analogous reaction to that described in example 36 but starting with 5-aminoindole (28 mg, 0.21 mmol) yielded title compound (33 mg, 34 %).

MS ES$^+$: 574.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.36 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 3.97 (s, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.31 (t, 2H) ; 7.32 (m, 6H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.10 (s, 1H).

Example 194. Preparation of compound 371 in Table 14

An analogous reaction to that described in example 36 but starting with 2,4-difluoroaniline (27 mg, 0.21 mmol) yielded title compound (28 mg, 29 %).

MS ES$^+$: 571.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.59 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.08 (s, 2H) ; 4.34 (t, 2H) ; 7.12 (t, 1H) ; 7.34 (s, 1H) ; 7.36 (m, 1H) ; 7.89 (m, 1H) ; 7.95 (s, 1H) ; 9.12 (s, 1H).

Example 195. Preparation of compound 372 in Table 14

An analogous reaction to that described in example 36 but starting with 2-fluoro-4-methylaniline (26 mg, 0.21 mmol) yielded title compound (35 mg, 37 %).

MS ES$^+$: 567.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.33 (s, 5H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (s, 3H) ; 4.07 (s, 2H) ; 4.08 (d, 2H) ; 4.33 (t, 2H) ; 7.04 (d, 1H) ; 7.12 (d, 1H) ; 7.34 (s, 1H) ; 7.66 (s, 1H) ; 7.78 (t, 1H) ; 7.94 (s, 1H) ; 9.12 (s, 1H).

Example 196. Preparation of compound 373 in Table 14

An analogous reaction to that described in example 36 but starting with 3-cyanoaniline (25 mg, 0.21 mmol) yielded title compound (21 mg, 22 %).

MS ES$^+$: 560.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (s, 3H) ; 4.06 (s, 2H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 7.34 (s, 1H) ; 7.6 (m, 2H) ; 7.69 (s, 1H) ; 7.85 (m, 1H) ; 7.95 (s, 1H) ; 8.18 (s, 1H) ; 9.13 (s, 1H).

Example 197. Preparation of compound 374 in Table 14

An analogous reaction to that described in example 36 but starting with 2-methyl-5-fluoroaniline (26 mg, 0.21 mmol) yielded title compound (15 mg, 16 %).

MS ES$^+$: 567.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.27 (s, 3H) ; 2.32 (t, 2H) ; 3.20 (t, 2H) ; 3.39 (t, 2H) ; 3.59 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.09 (s, 2H) ; 4.33 (t, 2H) ; 6.96 (t, 1H) ; 7.29 (t, 1H) ; 7.34 (s, 1H) ; 7.48 (d, 1H) ; 7.69 (s, 1H) ; 7.95 (s, 1H) ; 9.12 (s, 1H).

Example 198. Preparation of compound 375 in Table 14

An analogous reaction to that described in example 36 but starting with 2-methyl-5-chloroaniline (30 mg, 0.21 mmol) yielded title compound (20 mg, 21 %).

MS ES$^+$: 583.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA) : 2.26 (s, 3H) ; 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.71 (t, 2H) ; 4.01 (s, 3H) ; 4.05 (d, 2H) ; 4.07 (s, 2H) ; 4.32 (t, 2H) ; 7.16 (dd, 1H) ; 7.27 (d, 1H) ; 7.31 (s, 1H) ; 7.65 (d, 1H) ; 7.65 (s, 1H) ; 7.93 (s, 1H) ; 9.10 (s, 1H).

Example 199. Preparation of compound 376 in Table 15

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-((1-methyl-piperidine-4-yl)methoxy)quinazoline (89 mg, 0.2 mmol) in DMF (1.5 ml), was reacted with aniline (22 mg, 0.24 mmol) in presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (99 mg, 0.26 mmol) and DIEA (50 mg, 0.4 mmol) at 60°C over night. After cooling to room temperature the reaction mixture was diluted with dichloromethane, and purified by silicagel chromatography, eluting successively with CH_2Cl_2, CH_2Cl_2 / MeOH 90/10, and CH_2Cl_2 / MeOH sat. NH_3 90/10 to give title compound (50 mg, 42 %).

MS ES^+: 519.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.58 (m, 2H) ; 2.02 (m, 2H) ; 2.13 (m, 1H) ; 2.80 (s, 3H) ; 3.03 (t, 2H) ; 3.52 (d, 2H) ; 3.98 (s, 2H) ; 3.98 (s, 3H) ; 4.10 (d, 2H) ; 7.06 (t, 1H) ; 7.29 (s, 1H) ; 7.33 (t, 2H) ; 7.60 (d, 2H) ; 7.61 (s, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

The NMR spectrum of example 75 in presence of acid shows the existence of 2 forms in a ratio of approximately 9 : 1. Signals due to the minor form are seen at 1.95 (m) 3.23 (m) 3.32 (m) 4.28 (d) 9.38 (m). All other examples, up to example 101, similarly display 2 forms, in subsequent examples, only the major form is being described.

4-benzyloxy-3-methoxybenzonitrile.

4-benzyloxy-3-methoxybenzaldehyde (4.84 g, 20 mmol) in acetic acid (25 ml) and sodium acetate (3.3 g, 40 mmol) was reacted with hydroxylamine hydrochloride (2.8 g, 40 mmol) at reflux for 6 hours. The mixture was cooled, diluted with water, extracted with methylene chloride, dried over $MgSO_4$, concentrated to give title compound (4.8 g, 100 %).

^{1}HNMR ($DMSOd_6$): 3.83 (s, 3H) ; 5.20 (s, 2H) ; 7.21 (d, 1H) ; 7.40 (m, 7H).

2-nitro-4-benzyloxy-5-methoxybenzonitrile

4-benzyloxy-3-methoxybenzonitrile (4.78 g, 20 mmol) in acetic acid (10 ml) was slowly added to nitric acid (25 ml) at 20°C to 30°C. The mixture was stirred at room temperature for 6 hours, basified (pH 10-11) with cooling (KOH 10N), extracted with methylene chloride, dried over $MgSO_4$ evaporated. The solid was recristallysed in hot EtOAc, a yellow solid of title compound was obtained (3.62 g, 64 %).

MS ES^+: 285 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 3.97 (s, 3H) ; 5.33 (s, 2H) ; 7.40 (m, 5H) ; 7.71 (s, 1H) ; 8.01 (s, 1H).

2-nitro-4-hydroxy-5-methoxybenzonitrile

2-nitro-4-benzyloxy-5-methoxybenzonitrile (3 g, 10.6 mmol) was treated with trifluoroacetic acid (30 ml) at reflux for 0.5 hour. The solvent was evaporated, the residue triturated with ether to give a yellow solid of title compound (1.27 g, 62 %).

^{1}HNMR ($DMSOd_6$) : 3.95 (s, 3H) ; 7.63 (s, 1H) ; 7.70 (s, 1H).

2-nitro-4-((1-tert-butyloxycarbonylpiperidin-4-yl)methoxy)-5-methoxybenzonitrile

2-nitro-4-hydroxy-5-methoxybenzonitrile (388 mg, 2 mmol) in DMF (5 ml) and acetonitrile (5 ml) was reacted with 4-(4-tolylsulphonyloxymethyl)-1-tert-butyloxycarbonyl-piperidine (738. mg, 2 mmol) and K_2CO_3 (414 mg, 3 mmol) at 110°C for 3.5 hours. The mixture was diluted with water, extracted with ethylacetate, washed HCl (2N), dried over $MgSO_4$, evaporated to give title compound (630 mg, 80 %).

^{1}HNMR ($CDCl_3$): 1.31 (m, 2H) ; 1.47 (s, 9H) ; 1.85 (m, 2H) ; 2.07 (m, 1H) ; 2.77 (m, 2H) ; 3.96 (d, 2H) ; 3.99 (s, 3H) ; 4.19 (m, 2H) ; 7.19 (s, 1H) ; 7.75 (s, 1H).

2-nitro-4-(1-piperidin-4-ylmethoxy)-5-methoxybenzonitrile.

2-nitro-4-((1-tert-butyloxycarbonylpiperidin-4-yl)methoxy)-5-methoxybenzonitrile (1.17 g, 3 mmol) in CH_2Cl_2 (12 ml) was treated with TFA (2.4 ml) for 1 hour at room temperature. The solvent was evaporated, the residue was taken up in a mixture of CH_2Cl_2 and concentrated sodium bicarbonate, extracted with CH_2Cl_2. The organic phase was dried over MgSO4, concentrated to give title compound as a solid (770 mg, 88 %).

^{1}HNMR ($CDCl_3$): 1.33 (m, 2H) ; 1.86 (d, 2H) ; 2.03 (m, 1H) ; 2.71 (t, 2H) ; 3.15 (d, 2H) ; 3.96 (d, 2H) ; 3.99 (s, 3H) ; 7.18 (s, 1H) ; 7.76 (s, 1H).

2-nitro-4-(1-methylpiperidin-4-ylmethoxy)-5-methoxybenzonitrile.

2-nitro-4-(1-piperidin-4-ylmethoxy)-5-methoxybenzonitrile (771 mg, 2.65 mmol) in CH_2Cl_2 (8 ml) and MeOH (4 ml) was reacted for 0.5 hour with formaldehyde (13.3 M, 300 µl, 4 mmol), acetic acid (191 mg, 3.18 mmol) and $NaBH(OAc)_3$ (674 mg, 3.18 mmol) slowly added over 15 minutes. The solution was evaporated, the oily residue was taken up in a mixture of Na_2CO_3 and ethylacetate, extracted with ethylacetate. The organic phase was dried over $MgSO_4$, evaporated to give title compound as a yellow solid (698 mg, 86 %).

^{1}HNMR ($CDCl_3$) : 4.7 (m, 2H) ; 1.88 (d, 2H) ; 1.90 (m, 1H) ; 2.0 (m, 2H) ; 2.3 (s, 3H) ; 2.91 (d, 2H) ; 2.95 (d, 2H) ; 2.99 (s, 3H) ; 7.18 (s, 1H) ; 7.76 (s, 1H).

2-amino-4-(1-methylpiperidin-4-ylmethoxy)-5-methoxybenzonitrile

2-nitro-4-(1-methylpiperidin-4-ylmethoxy)-5-methoxybenzonitrile (1.1 g, 3.6 mmol) in THF (20 ml) in presence of benzyltrimethylammonium chloride (334 mg, 1.8 mmol) was treated by a slow addition of $Na_2S_2O_4$ (3.1 g, 18 mmol) in water (20 ml). After 0.5h , HCl (6N, 20ml)

was added to the mixture, which was stirred at 60°C for 5 h. The mixture was cooled to room temperature, extracted with ethylacetate. The aqueous phase was made basic with Na_2CO_3 (solid), and extracted with ethylacetate. The organic phase was dried over $MgSO_4$, concentrated, to give a yellow solid (748 mg, 75 %) of title compound.

^{1}HNMR ($DMSOd_6$): 1.29 (m, 2H) ; 1.70 (m, 3H) ; 1.85 (t, 2H) ; 2.14 (s, 3H) ; 2.76 (d, 2H) ; 3.64 (s, 3H) ; 3.75 (d, 2H) ; 5.57 (s, 2H) ; 6.40 (s, 1H) ; 6.87 (s, 1H).

N'-(2-cyano-4-methoxy-5-(1-methylpiperidin-4-ylmethoxy)phenyl)-N,N-dimethylimidoformamide.

2-amino-4-(1-methylpiperidin-4-ylmethoxy)-5-methoxy-benzonitrile (710 mg, 2.58 mmol) was reacted with DMF DMA (414 mg, 3.5 mmol) in toluene (15 ml) at reflux for 5 hours. The solution was concentrated, the oily residue triturated with ether to give a yellow solid of title compound (680 mg, 80 %).

^{1}HNMR ($DMSOd_6$): 1.28 (m, 2H) ; 1.72 (m, 3H) ; 1.85 (t, 2H) ; 2.14 (s, 3H) ; 2.76 (d, 2H) ; 2.95 (s, 3H) ; 3.05 (s, 3H) ; 3.72 (s, 3H) ; 3.86 (d, 2H) ; 6.71 (s, 1H) ; 7.07 (s, 1H) ; 7.89 (s, 1H).

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline.

N'-(2-cyano-4-methoxy-5-(1-methylpiperidin-4-ylmethoxy)phenyl)-N,N-diemethylimidoformamide (627 mg, 1.9 mmol) was reacted with methyl-2-amino-1,3-thiazol-5-acetate (360 mg, 2.1 mmol) in acetic acid (6.3 ml) at reflux for 4.5 hour under nitrogen. The mixture was concentrated, and the oily residue purified by silicagel chromatography, Eluant : CH_2Cl_2 / MeOH 90/10 and CH_2Cl_2 / MeOH sat. NH_3 90/10 to give title compound (552 mg, 63 %).

^{1}HNMR ($DMSOd_6$): 1.35 (m, 2H) ; 1.76 (m, 3H) ; 1.87 (t, 2H) ; 2.16 (d, 2H) ; 2.78 (d, 2H) ; 3.67 (s, 3H) ; 3.93 (s, 2H) ; 3.96 (s, 3H) ; 4.01 (d, 2H) ; 7.24 (s, 1H) ; 7.36 (s, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H).

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (137 mg, 0.3 mmol) in ethanol (1.4 ml) was treated with NaOH (2N, 3.75 ml, 7.5 mmol) at room temperature for 0.5 hour. HCl (2N) was added to adjust the pH to 3. The solution was evaporated, the solid solubilized in CH_2Cl_2 (6 ml) MeOH (4 ml) DIEA

(excess) was added. The insoluble was filtered, the filtrate was concentrated, ethanol was added, the solid filtered, washed with ether, to give title compound (102 mg, 77 %).

MS ES$^+$: 444.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.61 (m, 2H) ; 2.03 (d, 2H) ; 2.16 (m, 1H) ; 2.80 (s, 3H) ; 3.03 (t, 2H) ; 3.5 (d, 2H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.10 (d, 2H) ; 7.32 (s, 1H) ; 7.59 (s, 1H) ; 7.89 (s, 1H) ; 9.07 (s, 1H).

Example 200. Preparation of compound 377 in Table 15

An analogous reaction to that described in example 75 but starting with 3-chloro-4-fluoroaniline (44 mg, 0.3 mmol) yielded compound 76 in table 3 (63 mg, 60 %)

MS ES$^+$: 571 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.64 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.8 (s, 3H) ; 3.04 (t, 2H) ; 3.51 (d, 2H) ; 3.99 (s, 3H) ; 4.0 (s, 2H) ; 4.11 (d, 2H) ; 7.34 (s, 1H) ; 7.39 (t, 1H) ; 7.5 (m, 1H) ; 7.65 (s, 1H) ; 7.91 (dd, 1H) ; 9.09 (s, 1H).

Example 201. Preparation of compound 378 in Table 15

An analogous reaction to that described in example 75 but starting with 2-aminopyridine (40 mg, 0.42 mmol) yielded compound 77 in table 3 (100 mg, 53 %)

MS ES$^+$: 520 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.65 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.78 (s, 3H) ; 3.02 (t, 2H) ; 3.48 (d, 2H) ; 3.99 (s, 3H) ; 4.1 (d, 2H) ; 4.14 (s, 2H) ; 7.32 (m, 1H) ; 7.39 (s, 1H) ; 7.66 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (d, 1H) ; 8.16 (t, 1H) ; 8.4 (d, 1H) ; 9.079 (s, 1H).

Example 202. Preparation of compound 379 in Table 15

An analogous reaction to that described in example 75 but starting with 3,4-difluoroaniline (54 mg, 0.42 mmol) yielded compound 78 in table 3 (120 mg, 72 %)

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.63 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.79 (s, 3H) ; 3.03 (t, 2H) ; 3.49 (d, 2H) ; 3.99 (s, 3H) ; 4.0 (s, 2H) ; 4.10 (d, 2H) ; 7.35 (s, 1H) ; 7.39 (m, 2H) ; 7.64 (s, 1H) ; 7.82 (dd, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 203. Preparation of compound 380 in Table 15

An analogous reaction to that described in example 75 but starting with 2-chloroaniline (54 mg, 0.42 mmol) yielded compound 79 in table 3 (29 mg, 16 %)

MS ES$^+$: 553 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.62 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 1H) ; 2.81 (s, 3H) ; 3.04 (t, 2H) ; 3.51 (d, 2H) ; 4.0 (s, 3H) ; 4.08 (s, 2H) ; 4.11 (d, 2H) ; 7.24 (t, 1H) ; 7.31 (s, 1H) ; 7.34 (dd, 1H) ; 7.53 (d, 1H) ; 7.66 (s, 1H) ; 7.75 (d, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 204. Preparation of compound 381 in Table 15

An analogous reaction to that described in example 75 but starting with 4-methylaniline (45 mg, 0.42 mmol) yielded compound 80 in table 3 (155 mg, 85 %)

MS ES$^+$: 533 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.65 (m, 2H) ; 2.02 (m, 2H) ; 2.16 (m, 1H) ; 2.27 (s, 3H) ; 2.8 (s, 3H) ; 3.05 (t, 2H) ; 3.50 (d, 2H) ; 3.97 (s, 2H) ; 3.99 (s, 3H) ; 4.11 (d, 2H) ; 7.14 (d, 2H) ; 7.34 (s, 1H) ; 7.52 (d, 2H) ; 7.63 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 205. Preparation of compound 382 in Table 15

An analogous reaction to that described in example 75 but starting with 2-methylaniline (45 mg, 0.42 mmol) yielded compound 81 in table 3 (126 mg, 69 %)

MS ES$^+$: 533 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.62 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.24 (s, 3H) ; 2.8 (s, 3H) ; 3.04 (t, 2H) ; 3.51 (d, 2H) ; 3.99 (s, 3H) ; 4.02 (s, 2H) ; 4.10 (d, 2H) ; 7.11 (t, 1H) ; 7.19 (t, 1H) ; 7.24 (d, 1H) ; 7.33 (s, 1H) ; 7.43 (d, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.07 (s, 1H).

Example 206. Preparation of compound 383 in Table 15

An analogous reaction to that described in example 75 but starting with 4-chloroaniline (54 mg, 0.42 mmol) yielded compound 82 in table 3 (128 mg, 68 %)

MS ES$^+$: 553 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.65 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.79 (s, 3H) ; 3.04 (t, 2H) ; 3.50 (d, 2H) ; 3.99 (s, 3H) ; 4.0 (s, 2H) ; 4.1 (d, 2H) ; 7.36 (s, 1H) ; 7.38 (d, 2H) ; 7.64 (s, 1H) ; 7.68 (d, 2H) ; 7.9 (s, 1H) ; 9.08 (s, 1H).

Example 207. Preparation of compound 384 in Table 15

An analogous reaction to that described in example 75 but starting with 4-fluoroaniline (47 mg, 0.42 mmol) yielded compound 83 in table 3 (136 mg, 84 %)

MS ES$^+$: 537 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.62 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.79 (s, 3H) ; 3.03 (t, 2H) ; 3.50 (d, 2H) ; 3.97 (s, 2H) ; 3.98 (s, 3H) ; 4.1 (d, 2H) ; 7.16 (t, 2H) ; 7.34 (s, 1H) ; 7.63 (s, 1H) ; 7.65 (m, 2H) ; 7.9 (s, 1H) ; 9.07 (s, 1H).

Example 208. Preparation of compound 385 in Table 15

An analogous reaction to that described in example 75 but starting with 2-amino-6-methylpyrimidine (45 mg, 0.42 mmol) yielded compound 84 in table 3 (91 mg, 57 %)

MS ES$^+$: 534 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.61 (m, 2H) ; 2.05 (m, 2H) ; 2.15 (m, 1H) ; 2.50 (s, 3H) ; 2.8 (s, 3H) ; 3.03 (t, 2H) ; 3.52 (d, 2H) ; 4.02 (s, 3H) ; 4.1 (s, 2H) ; 4.11 (d, 2H) ; 7.15 (m, 1H) ; 7.33 (s, 1H) ; 7.65 (s, 1H) ; 7.8 (m, 2H) ; 7.91 (s, 1H) ; 9.07 (s, 1H).

Example 209. Preparation of compound 386 in Table 15

An analogous reaction to that described in example 75 but starting with 3-methoxyaniline (52 mg, 0.42 mmol) yielded compound 85 in table 3 (125 mg, 67 %)

MS ES$^+$: 549 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.63 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.8 (s, 3H) ; 3.04 (t, 2H) ; 3.52 (d, 2H) ; 3.75 (s, 3H) ; 3.98 (s, 2H) ; 3.99 (s, 3H) ; 4.11 (d, 2H) ; 6.68 (m, 1H) ; 7.17 (d, 1H) ; 7.24 (t, 1H) ; 7.33 (s, 1H) ; 7.35 (d, 1H) ; 7.64 (s, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 210. Preparation of compound 387 in Table 15

An analogous reaction to that described in example 75 but starting with 2-amino-5-chloropyridine (54 mg, 0.42 mmol) yielded compound 86 in table 3 (22 mg, 11 %)

MS ES$^+$: 554$(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.61 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 1H) ; 2.8 (s, 3H) ; 3.03 (t, 2H) ; 3.5 (d, 2H) ; 3.98 (s, 3H) ; 4.07 (s, 2H) ; 4.11 (d, 2H) ; 7.30 (s, 1H) ; 7.63 (s, 1H) ; 7.9 (s, 1H) ; 7.93 (dd, 1H) ; 8.12 (d, 1H) ; 8.41 (d, 1H).

Example 211 Preparation of compound 388 in Table 15

An analogous reaction to that described in example 75 but starting with 3-chloroaniline (54 mg, 0.42 mmol) yielded compound 87 in Table 2 (130 mg, 69 %).

MS ES$^+$: 553 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.62 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.78 (s, 3H) ; 3.02 (t, 2H) ; 3.49 (d, 2H) ; 3.97 (s, 3H) ; 3.99 (s, 2H) ; 4.08 (d, 2H) ; 7.13 (d, 1H) ; 7.3 (s, 1H) ; 7.38 (t, 1H) ; 7.64 (s, 1H) ; 7.86 (s, 1H) ; 7.90 (s, 1H) ; 9.07 (s, 1H).

Example 212. Preparation of compound 389 in Table 15

An analogous reaction to that described in example 75 but starting with 2-fluoroaniline (47 mg, 0.42 mmol) yielded compound 88 in Table 3 (116 mg, 63 %).

MS ES$^+$: 537 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.64 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.79 (s, 3H) ; 3.03 (t, 2H) ; 3.50 (d, 2H) ; 3.99 (s, 3H) ; 4.07 (s, 2H) ; 4.10 (d, 2H) ; 7.19 (m, 2H) ; 7.25 (m, 1H) ; 7.35 (s, 1H) ; 7.63 (s, 1H) ; 7.90 (s, 1H) ; 7.91 (m, 1H) ; 9.07 (s, 1H).

Example 213. Preparation of compound 390 in Table 15

Analogous reaction to that described in example 75 but starting with 3-fluoro-4-methoxyaniline (59 mg, 0.42 mmol) yielded compound 89 in Table 3 (151 mg, 85 %).

MS ES$^+$: 567 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.62 (m, 2H) ; 2.01 (m, 2H) ; 2.15 (m, 1H) ; 2.79 (s, 3H) ; 3.03 (t, 2H) ; 3.51 (d, 2H) ; 3.81 (s, 3H) ; 3.96 (s, 2H) ; 3.98 (s, 3H) ; 4.10 (d, 2H) ; 7.14 (t, 1H) ; 7.28 (d, 1H) ; 7.34 (s, 1H) ; 7.59 (dd, 1H) ; 7.6 (s, 1H) ; 7.90 (s, 1H) ; 9.07 (s, 1H).

Example 214. Preparation of compound 391 in Table 15

An analogous reaction to that described in example 75 but starting with 2-methyl-4-fluoroaniline (53 mg, 0.42 mmol) yielded compound 90 in Table 3 (151 mg, 81 %).

MS ES$^+$: 551 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.62 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.33 (s, 3H) ; 2.79 (s, 3H) ; 2.93 (t, 2H) ; 3.48 (d, 2H) ; 3.97 (s, 3H) ; 3.99 (s, 2H) , 4.09 (d, 2H) ; 7.01 (dt, 1H) ; 7.1 (dd, 1H) ; 7.37 (s, 1H) ; 7.39 (m, 1H) ; 7.64 (s, 1H) ; 7.89 (s, 1H) ; 9.05 (s, 1H).

Example 215. Preparation of compound 392 in Table 15

An analogous reaction to that described in example 75 but starting with 2-amino-4-methylpyridine (45 mg, 0.42 mmol) yielded compound 91 in Table 3 (119 mg, 66 %).
MS ES$^+$: 534 $(M+H)^+$
^{1}HNMR (DMSOd$_6$, TFA): 1.66 (m, 2H) ; 2.05 (m, 2H) ; 2.15 (m, 1H) ; 2.77 (s, 3H) ; 3.03 (t, 2H) ; 3.48 (d, 2H) ; 3.97 (s, 3H) ; 4.09 (d, 2H) ; 4.21 (s, 2H) ; 7.35 (m, 1H) ; 7.45 (s, 1H) ; 7.69 (s, 1H) ; 7.70 (s, 1H) ; 7.90 (s, 1H) ; 8.31 (d, 1H) ; 9.06 (s, 1H).

Example 216. Preparation of compound 393 in Table 15

An analogous reaction to that described in example 75 but starting with 2,5-difluoroaniline (54 mg, 0.42 mmol) yielded compound 92 in Table 3 (42 mg, 22 %).
MS ES$^+$: 555 $(M+H)^+$
^{1}HNMR (DMSOd$_6$, TFA): 1.60 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.81 (s, 3H) ; 3.04 (t, 2H) ; 3.52 (d, 2H) ; 3.99 (s, 3H) ; 4.10 (s, 2H) ; 4.11 (d, 2H) ; 7.02 (m, 2H) ; 7.32 (s, 1H) ; 7.34 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.92 (m, 1H) ; 9.08 (s, 1H).

Example 217. Preparation of compound 394 in Table 15

An analogous reaction to that described in example 75 but starting with 2-fluoro-4-chloroaniline (61 mg, 0.42 mmol) yielded compound 93 in Table 3 (97 mg, 50 %).
MS ES$^+$: 571 $(M+H)^+$
^{1}HNMR (DMSOd$_6$, TFA): 1.63 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.77 (s, 3H) ; 3.03 (t, 2H) ; 3.48 (d, 2H) ; 3.98 (s, 3H) ; 4.07 (s, 2H) ; 4.09 (d, 2H) ; 7.26 (d, 1H) ; 7.38 (s, 1H) ; 7.5 (dd, 1H) ; 7.62 (s, 1H) ; 7.89 (s, 1H) ; 7.96 (t, 1H) ; 9.06 (s, 1H).

Example 218. Preparation of compound 395 in Table 15

An analogous reaction to that described in example 75 but starting with 2-fluoro-5-methylaniline (53 mg, 0.42 mmol) yielded compound 94 in Table 3 (119 mg, 63 %).
MS ES$^+$: 551 $(M+H)^+$
^{1}HNMR (DMSOd$_6$, TFA): 1.63 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 1H) ; 2.28 (s, 3H) ; 2.77 (s, 3H) ; 3.03 (t, 2H) ; 3.49 (d, 2H) ; 3.98 (s, 3H) ; 4.05 (s, 2H) ; 4.09 (d, 2H) ; 6.98 (m, 1H) ; 7.15 (dd, 1H) ; 7.38 (s, 1H) ; 7.62 (s, 1H) ; 7.72 (m, 1H) ; 7.89 (s, 1H) ; 9.06 (s, 1H).

Example 219. Preparation of compound 396 in Table 15

An analogous reaction to that described in example 75 but starting with 3-methylaniline (45 mg, 0.42 mmol) yielded compound 95 in Table 3 (144g, 79 %).

MS ES$^+$: 533 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.64 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.3 (s, 3H) ; 2.79 (s, 3H) ; 3.04 (t, 2H) ; 3.51 (d, 2H) ; 3.98 (s, 2H) ; 3.99 (3H) ; 4.10 (d, 2H) ; 6.90 (d, 1H) ; 7.21 (t, 1H) ; 7.36 (s, 1H) ; 7.42 (d, 1H) ; 7.49 (s, 1H) ; 7.63 (s, 1H) ; 7.9 (s, 1H) ; 9.07 (s, 1H).

Example 220. Preparation of compound 397 in Table 15

An analogous reaction to that described in example 75 but starting with 2,4-difluoroaniline (54 mg, 0.42 mmol) yielded compound 96 in Table 3 (121 mg, 74 %).

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.63 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 1H) ; 2.78 (s, 3H) ; 3.03 (t, 2H) ; 3.5 (d, 2H) ; 3.98 (s, 3H) ; 4.04 (s, 2H) ; 4.1 (d, 2H) ; 7.08 (m, 1H) ; 7.33 (m, 1H) ; 7.36 (s, 1H) ; 7.63 (s, 1H) ; 7.86 (m, 1H) ; 7.90 (s, 1H) ; 9.07 (s, 1H).

Example 221. Preparation of compound 398 in Table 15

An analogous reaction to that described in example 75 but starting with 2-fluoro-4-methylaniline (53 mg, 0.42 mmol) yielded compound 97 in Table 3 (147 mg, 79 %).

MS ES$^+$: 551 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.63 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.3 (s, 3H) ; 2.79 (s, 3H) ; 3.04 (t, 2H) ; 3.51 (d, 2H) ; 3.99 (s, 3H) ; 4.04 (s, 2H) ; 4.1 (d, 2H) ; 6.99 (d, 1H) ; 7.10 (d, 1H) ; 7.35 (s, 1H) ; 7.62 (s, 1H) ; 7.75 (t, 1H) ; 7.90 (s, 1H) ; 9.07 (s, 1H).

Example 222. Preparation of compound 399 in Table 15

An analogous reaction to that described in example 75 but starting with 3-cyanoaniline (50 mg, 0.42 mmol) yielded compound 98 in Table 3 (118 mg, 71 %).

MS ES$^+$: 544 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.66 (m, 2H) ; 2.07 (m, 2H) ; 2.17 (m, 1H) ; 2.81 (s, 3H) ; 3.06 (t, 2H) ; 3.53 (d, 2H) ; 4.0 (s, 3H) ; 4.05 (s, 2H) ; 4.11 (d, 2H) ; 7.36 (s, 1H) ; 7.54 (m, 2H) ; 7.65 (s, 1H) ; 7.86 (dd, 1H) ; 7.92 (s, 1H) ; 8.18 (s, 1H) ; 9.09 (s, 1H).

Example 223. Preparation of compound 400 in Table 15

An analogous reaction to that described in example 75 but starting with 2-methyl-5-fluoroaniline (53 mg, 0.42 mmol) yielded compound 99 in Table 3 (107 mg, 57 %).

MS ES^+: 551 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.65 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.24 (s, 3H) ; 2.76 (s, 3H) ; 3.02 (t, 2H) ; 3.47 (d, 2H) ; 3.98 (s, 3H) ; 4.07 (s, 2H) ; 4.08 (d, 2H) ; 6.92 (m, 1H) ; 7.25 (t, 1H) ; 7.4 (s, 1H) ; 7.43 (m, 1H) ; 7.64 (s, 1H) ; 7.88 (s, 1H) ; 9.04 (s, 1H).

Example 224. Preparation of compound 401 in Table 15

An analogous reaction to that described in example 75 but starting with 3,5-difluoroaniline (54 mg, 0.42 mmol) yielded compound 100 in Table 3 (83 mg, 44 %).

MS ES^+: 555 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.66 (m, 2H) ; 2.02 (m, 2H) ; 2.16 (m, 1H) ; 2.76 (s, 3H) ; 3.03 (t, 2H) ; 3.45 (d, 2H) ; 3.97 (s, 3H) ; 4.03 (s, 2H) ; 4.08 (d, 2H) ; 6.90 (dd, 1H) ; 7.38 (m, 2H) ; 7.39 (s, 1H) ; 7.87 (s, 1H) ; 9.05 (s, 1H).

Example 225. Preparation of compound 402 in Table 15

An analogous reaction to that described in example 75 but starting with 3-fluoroaniline (47 mg, 0.42 mmol) yielded compound 101 in Table 3 (142 mg, 77 %).

MS ES^+ : 537 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.62 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 1H) ; 2.78 (s, 3H) ; 3.02 (t, 2H) ; 3.49 (d, 2H) ; 3.98 (s, 3H) ; 4.0 (s, 2H) ; 4.1 (d, 2H) ; 6.9 (s, 1H) ; 7.35 (s, 1H) ; 7.36 (m, 2H) ; 7.62 (m, 1H) ; 7.64 (s, 1H) ; 7.9 (s, 1H) ; 9.08 (s, 1H).

Example 226. Preparation of compound 403 in Table 16

4-((2-amino-1,3-thiazol-5-yl)acetic acid)-6-methoxy-7-(3-N-methylpiperazinylpropoxy)quinazoline (142 mg, 0.3 mmol) in NMP (1.5 ml) was reacted with aniline (42 µl, 0.45 mmol) in presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N', tetramethyluronium hexafluorophosphate (173 mg, 0.45 mmol) and diisopropylethylamine (105 µl, 0.6 mmol) at 65°C under nitrogen over night. After cooling to room temperature, the reaction mixture was diluted with dichloromethane and purified by silicagel chromatography, eluant CH_2Cl_2, CH_2Cl_2 / MeOH, 9/1, CH_2Cl_2 / MeOH sat. NH_3, 9/1 to give title compound (24 mg, 15 %).

MS ES$^+$: 548.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.2 (m, 8H) ; 3.45 (t, 2H) ; 3.99 (s, 5H) ; 4.30 (t, 2H) ; 7.08 (t, 1H) ; 7.31 (s, 1H) ; 7.33 (, 2H) ; 7.62 (d, 2H) ; 7.64 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

2-nitro-4-(3-N-methylpiperazinylpropoxy)-5-methoxybenzonitrile

2-nitro-4-hydroxy-5-methoxybenzonitrile (45 g, 25 mmol) in CH_2Cl_2 (125 ml) was reacted with ditertiobutylazodicarboxylate (6.9 g, 30 mmol) triphenylphosphine (7.86 g, 30 mmol) at room temperature for 2 hours. A solution of ether (2.3N HCl, 55 ml) was added. The solid was recovered, washed with CH_2Cl_2, ether. The solid was dissolved in MeOH, treated with MeOH / NH_3, the solvent were evaporated, and the residue purified by silicagel chromatography eluant : CH_2Cl_2 / AcOEt 50/50, CH_2Cl_2 / MeOH 90/10, to give title compound (8.2 g, 98 %).

MS ES$^+$: 335.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.29 (t, 2H) ; 3.95 (s, 3H) ; 3.2-4 (m, 8H) ; 3.38 (t, 2H) ; 3.98 (s, 3H) ; 4.32 (t, 2H) ; 7.70 (s, 1H) ; 7.89 (s, 1H).

2-amino-4-(3-N-methylpiperazinylpropoxy)-5-methoxy-benzonitrile.

2-nitro-4-(3-N-methylpiperazinylpropoxy)-5-methoxybenzonitrile (1.67 g, 5 mmol), benzyltrimethylammonium chloride (0.46 g, 2.5 mmol) in methyle chloride (40 ml) was treated with sodium hydrosulfite (4.35 g, 5 mmol) in water (40 ml) at room temperature for 1 hour. HCl (6N, 28 ml) was added to the mixture which was heated at 60°C for 2.5 hours. The mixture was cooled, extracted with ethylacetate. The aqueous phase was treated with Na_2CO_3 (solid), extracted with ethylacetate. The organic phase was dried over $MgSO_4$, concentrated to give title compound (0.93 g, 61 %).

MS ES$^+$: 305.7 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.18 (t, 2H) ; 2.93 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.39 (t, 2H) ; 3.66 (s, 3H) ; 4.05 (t, 2H) ; 6.54 (s, 1H) ; 7.00 (s, 1H).

N'-(2-cyano-4-methoxy-5-(3-N-methylpiperazinylpropoxy)phenyl)-N,N-dimethylimidoformamide.

2-amino-4-(3-N-methylpiperazinylporpoxy)-5-methoxybenzonitrile (16.4 g, 54 mmol) was reacted with dimethylformamide dimethyl acetal (12 ml, 90 mmol) in toluene (400 ml) at reflux for 4 hours. The solvent was evaporated to give title compound (19.4 g, 100 %).

MS ES$^+$: 360.7 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.28 (t, 2H) ; 2.96 (s, 3H) ; 3.26 (s, 3H) ; 3.35 (s, 3H) ; 3.40 (t, 2H) ; 3.1-4 (m, 8H) ; 3.88 (s, 3H) ; 4.21 (t, 2H) ; 7.32 (s, 1H) ; 7.53 (s, 1H) ; 8.56 (s, 1H).

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6-methoxy-4-((3-N-methylpiperazinylpropoxy)quinazoline

N'-(2-cyano-4-methoxy-5-(3-N-piperazinylpropoxy)phenyl)-N,N-dimethylimidoformamide (9.7 g, 27 mmol) in acetic acid (100 ml) was reacted with methyl (2-amino-1,3-thiazole-5-yl)acetate (5.2 g, 30 mmol) at reflux for 4 hours. The solvent was evaporated and the residue purified by silicagel chromatography, Eluant : CH_2Cl_2 / MeOH 99/1 to 97/3 to give title compound (9.15 g, 70 %).

MS ES$^+$: 487.6$(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 2.97 (s, 3H) ; 3.2-4.2 (m, 8H) ; 3.48 (t, 2H) ; 3.97 (s, 2H) ; 4.00 (s, 3H) ; 4.33 (t, 2H) ; 7.36 (s, 1H) ; 7.61 (s, 1H) ; 7.93 (s, 1H) ; 9.10 (s, 1H).

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-(N-methylpiperazinylpropoxy) quinazoline

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6-methoxy-7-(3-(N-methylpiperazinylpropoxy) quinazoline (8.25 g, 17 mmol) in ethanol (80 ml) was treated with sodium hydroxyde (2N, 42.5 ml, 85 mmol) at room temperature for 1 hour. Hydrochloride acid (2N) was added to the solution (pH 3). The solution was evaporated, the residue dissolved in ethanol and N-ethyl diisopropyl amine (8.9 ml, 51 mmol). Ether was added to the solution, the solid was recovered, dried to give title compound (7.44 g, 93 %).

MS ES$^+$: 473.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.1 (m, 8H) ; 3.45 (t, 2H) ; 3.89 (s, 2H) ; 3.97 (s, 3H) ; 4.29 (t, 2H) ; 7.30 (s, 1H) ; 7.56 (s, 1H) ; 7.90 (s, 1H) ; 9.06 (s, 1H).

Example 227. Preparation of compound 404 in Table 16

An analogous reaction to that described in example 103 but starting with 3,4-difluoroaniline (77 mg, 0.6 mmol) yielded title compound (105 mg, 60 %).

MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 5H) ; 4.30 (t, 2H) ; 7.32 (s, 1H) ; 7.32 (m, 1H) ; 7.40 (q, 1H) ; 7.65 (s, 1H) ; 7.81 (m, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 228. Preparation of compound 405 in Table 16

An analogous reaction to that described in example 103 but starting with 2-aminopyridine (56 mg, 0.6 mmol) yielded title compound (53 mg, 36 %).

MS ES$^+$: 549.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.41 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (s, 2H) ; 4.32 (t, 2H) ; 7.21 (m, 1H) ; 7.34 (s, 1H) ; 7.64 (s, 1H) ; 7.91 (m, 2H) ; 8.03 (d, 1H) ; 8.37 (m, 1H) ; 9.98 (s, 1H).

Example 229. Preparation of compound 406 in Table 16

An analogous reaction to that described in example 103 but starting with 3-chloro-4-fluoroaniline (87 mg, 0.6 mmol) yielded title compound (134 mg, 74 %).

MS ES$^+$: 600.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.43 (t, 2H) ; 3.1-4.1 (m, 8H) ; 3.99 (s, 5H) ; 4.32 (t, 2H) ; 7.33 (s, 1H) ; 7.38 (t, 1H) ; 7.50 (m, 1H) ; 7.64 (s, 1H) ; 7.90 (s, 1H) ; 7.96 (m, 1H) ; 9.09 (s, 1H).

Example 230. Preparation of compound 407 in Table 16

An analogous reaction to that described in example 103 but starting with 3-chloroaniline (77 mg, 0.6 mmol) yielded title compound (46 mg, 26 %).

MS ES$^+$: 582.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.2-4.1 (m, 8H) ; 3.45 (t, 2H) ; 3.99 (s, 3H) ; 4.07 (s, 2H) ; 4.30 (t, 2H) ; 7.22 (t, 1H) ; 7.31 (s, 1H) ; 7.35 (t, 1H) ; 7.53 (d, 1H) ; 7.65 (s, 1H) ; 7.74 (d, 1H) ; 7.92 (s, 1H) ; 9.08 (s, 1H).

Example 231. Preparation of compound 408 in Table 16

An analogous reaction to that described in example 103 but starting with 4-methylaniline (64 mg, 0.6 mmol) yielded title compound (105 mg, 62 %).

MS ES$^+$: 562.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.26 (s, 3H) ; 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.43 (t, 2H) ; 3.95 (s, 2H) ; 3.98 (s, 3H) ; 4.30 (t, 2H) ; 7.12 (d, 2H) ; 7.31 (s, 1H) ; 7.50 (d, 2H) ; 7.63 (s, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 232. Preparation of compound 409 in Table 16

An analogous reaction to that described in example 103 but starting with 2-methylaniline (64 mg, 0.6 mmol) yielded title compound (127 mg, 75 %).

MS ES+ : 562.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.24 (s, 3H) ; 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.2-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (s, 2H) ; 4.31 (t, 2H) ; 7.12 (t, 1H) ; 7.19 (t, 1H) ; 7.24 (d, 1H) ; 7.33 (s, 1H) ; 7.44 (d, 1H) ; 7.66 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 233. Preparation of compound 410 in Table 16

An analogous reaction to that described in example 103 but starting with 4-chloroaniline (77 mg, 0.6 mmol) yielded title compound (101 mg, 58 %).

MS ES^+: 582.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 4.00 (s, 5H) ; 4.31 (t, 2H) ; 7.33 (s, 1H) ; 7.40 (d, 2H) ; 7.65 (s, 1H) ; 7.66 (d, 2H) ; 7.92 (s, 1H) ; 9.10 (s, 1H).

Example 234. Preparation of compound 411 in Table 16

An analogous reaction to that described in example 103 but starting with 4-fluoroaniline (67 mg, 0.6 mmol) yielded title compound (97 mg, 57 %).

MS ES^+: 566.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.97 (s, 2H) ; 3.99 (s, 3H) ; 4.30 (t, 2H) ; 7.17 (t, 2H) ; 7.34 (s 1H) ; 7.64 (m, 3H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 235. Preparation of compound 412 in Table 16

An analogous reaction to that described in example 103 but starting with 2-amino-6-methylpyridine (65 mg, 0.6 mmol) yielded title compound (70 mg, 42 %).

MS ES^+ : 563.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.30 (t, 2H) ; 2.46 (s, 3H) ; 2.94 (s, 3H) ; 3.10-4.10 (m, 8H) ; 3.43 (t, 2H) ; 3.98 (s, 3H) ; 4.06 (s, 2H) ; 4.30 (t, 2H) ; 7.08 (d, 1H) ; 7.32 (s, 1H) ; 7.63 (s, 1H) ; 7.79 (t, 1H) ; 7.88 (d, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 236. Preparation of compound 413 in Table 16

An analogous reaction to that described in example 103 but starting with 2-methoxyaniline (74 mg, 0.6 mmol) yielded title compound (99 mg, 57 %).

MS ES$^+$: 578.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.43 (t, 2H) ; 3.74 (s, 3H) ; 3.97 (s, 2H) ; 3.99 (s, 3H) ; 4.30 (t, 2H) ; 6.67 (d, 1H) ; 7.15 (d, 1H) ; 7.24 (t, 1H) ; 7.33 (s, 2H) ; 7.64 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 237. Preparation of compound 414 in Table 16

An analogous reaction to that described in example 103 but starting with 2-amino-5-chloropyridine (77 mg, 0.6 mmol) yielded title compound (23 mg, 13 %).

MS ES$^+$: 583.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.10-4.10 (m, 8H) ; 3.45 (t, 2H) ; 3.98 (s, 3H) ; 4.06 (s, 2H) ; 4.30 (t, 2H) ; 7.31 (s, 1H) ; 7.63 (s, 1H) ; 7.90 (s, 1H) ; 7.91 (dd, 1H) ; 8.11 (d, 1H) ; 8.40 (d, 1H) ; 9.09 (s, 1H).

Example 238. Preparation of compound 415 in Table 16

An analogous reaction to that described in example 103 but starting with 3-chloroaniline (77 mg, 0.6 mmol) yielded title compound (96 mg, 55 %).

MS ES$^+$: 582.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.2 (m, 8H) ; 3.45 (t, 2H) ; 3.98 (s, 5H) ; 4.28 (t, 2H) ; 7.12 (d, 1H) ; 7.31 (s, 1H) ; 7.34 (t, 1H) ; 7.46 (d, 1H) ; 7.62 (s, 1H) ; 7.85 (s, 1H) ; 7.91 (s, 1H) ; 9.07 (s, 1H).

Example 239. Preparation of compound 416 in Table 16

An analogous reaction to that described in example 103 but starting with 2-fluoroaniline (67 mg, 0.6 mmol) yielded title compound (68 mg, 40 %).

MS ES$^+$: 596.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.28 (t, 2H) ; 2.91 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.40 (t, 2H) ; 3.95 (s, 3H) ; 4.03 (s, 2H) ; 4.26 (t, 2H) ; 7.13 (m, 2H) ; 7.25 (m, 2H) ; 7.28 (s, 1H) ; 7.60 (s, 1H) ; 7.87 (s, 1H) ; 9.05 (s, 1H).

Example 240. Preparation of compound 417 in Table 16

An analogous reaction to that described in example 103 but starting with 3-cyanoaniline (71 mg, 0.6 mmol) yielded title compound (101 mg, 63 %).

MS ES$^+$: 573.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.45 (t, 2H) ; 4.00 (s, 3H) ; 4.04 (s, 2H) ; 4.31 (t, 2H) ; 7.33 (s, 1H) ; 7.56 (s, 1H) ; 7.57 (m, 1H) ; 7.66 (s, 1H) ; 7.82 (m, 1H) ; 7.92 (s, 1H) ; 8.15 (s, 1H) ; 9.10 (s, 1H).

Example 241. Preparation of compound 418 in Table 16

An analogous reaction to that described in example 103 but starting with 2-fluoro-4-methylaniline (75 mg, 0.6 mmol) yielded title compound (109 mg, 63 %).

MS ES$^+$: 580.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.29 (m, 5H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.98 (s, 3H) ; 4.03 (s, 2H) ; 4.30 (t, 2H) ; 6.98 (d, 1H) ; 7.09 (d, 1H) ; 7.32 (s, 1H) ; 7.63 (s, 1H) ; 7.74 (t, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 242. Preparation of compound 419 in Table 16

An analogous reaction to that described in example 103 but starting with 3-fluoro-4-methoxyaniline (85 mg, 0.6 mmol) yielded title compound (121 mg, 68 %).

MS ES$^+$: 596.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.81 (s, 3H) ; 3.95 (s, 2H) ; 3.99 (s, 3H) ; 4.30 (t, 2H) ; 7.13 (t, 1H) ; 7.27 (m, 1H) ; 7.31 (s, 1H) ; 7.60 (m, 1H) ; 7.64 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 243. Preparation of compound 420 in Table 16

An analogous reaction to that described in example 103 but starting with 2-methyl-4-fluoroaniline (75 mg, 0.6 mmol) yielded title compound (130 mg, 75 %).

MS ES$^+$: 580.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.23 (s, 3H) ; 2.29 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.30 (t, 2H) ; 7.01 (m, 1H) ; 7.09 (dd, 1H) ; 7.32 (s, 1H) ; 7.40 (m, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 244. Preparation of compound 421 in Table 16

An analogous reaction to that described in example 103 but starting with 2-amino-4-methylpyridine (65 mg, 0.6 mmol) yielded title compound (87 mg, 52 %).

MS ES$^+$: 563.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.29 (t, 2H) ; 2.45 (s, 3H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.15 (s, 2H) ; 4.30 (t, 2H) ; 7.24 (d, 1H) ; 7.37 (s, 1H) ; 7.67 (s, 1H) ; 7.72 (s, 1H) ; 7.92 (s, 1H) ; 8.29 (d, 1H) ; 9.08 (s, 1H);

Example 245. Preparation of compound 422 in Table 16

An analogous reaction to that described in example 103 but starting with 2,5-difluoroaniline (77 mg, 0.6 mmol) yielded title compound (56 mg, 32 %).

MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.43 (t, 2H) ; 3.98 (s, 3H) ; 4.10 (s, 2H) ; 4.30 (t, 2H) ; 7.0 (m, 1H) ; 7.32 (s, 1H) ; 7.33 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (m, 2H) ; 9.09 (s, 1H).

Example 246. Preparation of compound 423 in Table 16

An analogous reaction to that described in example 103 but starting with 2-fluoro-4-chloroaniline (87 mg, 0.6 mmol) yielded title compound (69 mg, 38 %).

MS ES$^+$: 600.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.32 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.2 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.07 (s, 2H) ; 4.30 (t, 2H) ; 7.20 (dd, 1H) ; 7.33 (s, 1H) ; 7.51 (dd, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (t, 1H) ; 9.09 (s, 1H).

Example 247. Preparation of compound 424 in Table 16

An analogous reaction to that described in example 103 but starting with 2-fluoro-5-methylaniline (75 mg, 0.6 mmol) yielded title compound (81 mg, 46 %).

MS ES$^+$: 580.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.27 (s, 3H) ; 2.32 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.05 (s, 2H) ; 4.30 (t, 2H) ; 6.97 (m, 1H) ; 7.13 (dd, 1H) ; 7.34 (s, 1H) ; 7.63 (s, 1H) ; 7.74 (d, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 248. Preparation of compound 425 in Table 16

An analogous reaction to that described in example 103 but starting with 3-methylaniline (64 mg, 0.6 mmol) yielded title compound (116 mg, 69 %).

MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.28 (s, 3H) ; 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.45 (t, 2H) ; 3.96 (s, 2H) ; 3.98 (s, 3H) ; 4.30 (t, 2H) ; 6.88 (d, 1H) ; 7.19 (t, 1H) ; 7.30 (s, 1H) ; 7.39 (d, 1H) ; 7.47 (s, 1H) ; 7.62 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 249. Preparation of compound 426 in Table 16

An analogous reaction to that described in example 103 but starting with 2,4-difluoroaniline (77 mg, 0.6 mmol) yielded title compound (84 mg, 48 %).

MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.99 (s, 3H) ; 4.05 (s, 2H) ; 4.30 (t, 2H) ; 7.07 (t, 1H) ; 7.32 (m, 2H) ; 7.64 (s, 1H) ; 7.86 (m, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 250. Preparation of compound 427 in Table 16

An analogous reaction to that described in example 103 but starting with 2-methyl-5-fluoroaniline (75 mg, 0.6 mmol) yielded title compound (98 mg, 57 %).

MS ES$^+$: 580.6$(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.23 (s, 3H) ; 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.43 (t, 2H) ; 3.98 (s, 3H) ; 4.05 (s, 2H) ; 4.30 (t, 2H) ; 6.91 (m, 1H) ; 7.25 (t, 1H) ; 7.32 (s, 1H) ; 7.44 (dd, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 251. Preparation of compound 428 in Table 16

An analogous reaction to that described in example 103 but starting with 3,5-difluoroaniline (77 mg, 0.6 mmol) yielded title compound (54 mg, 31 %).

MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.45 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (s, 2H) ; 4.31 (t, 2H) ; 6.92 (m, 1H) ; 7.33 (s, 1H) ; 7.35 (m, 2H) ; 7.66 (s, 1H) ; 7.92 (s, 1H) ; 9.10 (s, 1H).

Example 252. Preparation of compound 429 in Table 16

An analogous reaction to that described in example 103 but starting with 3-fluoroaniline (67 mg, 0.6 mmol) yielded title compound (120 mg, 70 %).

MS ES$^+$: 566.6 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA) : 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.2 (m, 8H) ; 3.44 (t, 2H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.30 (t, 2H) ; 6.90 (s, 1H) ; 7.34 (s, 1H) ; 7.36 (m, 2H) ; 7.61 (m, 1H) ; 7.64 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 253. Preparation of compound 430 in Table 17

N-(3-chlorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide (141 mg, 0.22 mmol) in acetonitrile (2 ml) was reacted with pyrrolidine (3.3 mmol) in presence of potassium iodide (100 mg, 0.6 mmol) at 80°C for 15 h / 30 hours. When the reaction was completed (tlc) DMF (2 ml), silicagel (2 g) was added, the mixture evaporated, and the residue was purified by silica gel chromatography, eluant : CH_2Cl_2 / MeOH 95/5, CH_2Cl_2 / MeOH sat. NH_3 90/10 to give title compound (81 mg, 29 %).

MS ES$^+$: 553.4, 554.4 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA): 1.90 (m, 2H) ; 2.06 (m, 2H) ; 2.26 (t, 2H) ; 3.09 (m, 2H) ; 3.36 (t, 2H) ; 3.67 (m, 2H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.29 (t, 2H) ; 7.14 (d, 1H) ; 7.30 (s, 1H) ; 7.37 (t, 1H) ; 7.47 (d, 1H) ; 7.65 (s, 1H) ; 7.85 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

3-methoxy-4-benzyloxybenzonitrile

3-methoxy-4-benzyloxybenzoldehyde (4.87 g, 20 mmol) in acetic acid (25 ml) was treated with hydroxylamine HCl (2.8 g, 40 mmol), sodium acetate (3.3 g, 40 mmol) at reflux for 6 hours. The mixture was cooled, extracted with water and methylenechloride, dried over $MgSO_4$, evaporated, to give title compound (4.8 g, 100 %).

^{1}HNMR (DMSOd$_6$, TFA): 3.72 (s, 3H) ; 5.15 (s, 2H) ; 7.18 (d, 1H) ; 7.39 (m, 7H).

2-nitro-4-benzyloxy-5-methoxybenzonitrile.

3-methoxy-4-benzyloxybenzonitrile (4.78 g, 20 mmol) in acetic acid (10 ml) was slowly added to nitric acid (d = 1.42, 25 ml) at 20-30° with cooling in an ice bath. The mixture was then stirred at room temperature for 6 hours. The reaction mixture was treated with potassium hydroxyde (10N) at 0°C. The basic mixture (pH 10) was extracted with CH_2Cl_2, the organic phase was dried over $MgSO_4$, concentrated to give title compound (3.62 g, 64 %).

MS ES$^+$: 285 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 3.97 (s, 3H) ; 5.33 (s, 2H) ; 7.42 (m, 5H) ; 7.70 (s, 1H) ; 8.03 (s, 1H).

2-amino-4-benzyloxy-5-methoxybenzonitrile.

2-nitro-4-benzyloxy-5-methoxybenzonitrile (40 g, 125 mmol) tetrabutylammonium chloride (21 g, 75 mmol) in methylenechloride (500 ml) was treated with $Na_2S_2O_4$ (180 g, 87.9 mmol) in H_2O (700 ml), sodium hydrosulfite was added over 45 minutes, and the mixture was stirred for 2 hours at room temperature. Sodium hydroxyde was added (pH 8.2) the mixture was extracted with methylene chloride. The organic phase was made acidic with HCl-ether (2.3N, 250 ml), the solid was recovered, suspended in methanol (250 ml) and treated with a saturated solution of sodium bicarbonate (pH 8.1). The solid was recovered, washed with water, ether to give title compound (30.7 g, 97 %).

^{1}HNMR (DMSOd_6) : 3.65 (s, 3H) ; 5.04 (s, 2H) ; 5.61 (s, 2H) ; 6.51 (s, 1H) ; 6.91 (s, 1H) ; 7.40 (m, 5H).

N'-(2-cyano-4-methoxy-5-benzyloxyphenyl)-N,N-dimethylimidoformamide.

2-amino-4-benzyloxy-5-methoxy benzonitrile (102 g, 400 mmol) in toluene (1.5 l) was reacted with DMF-DMA (110 ml, 780 mmol) at reflux for 5 hours. The solvent was evaporated, the residue triturated with ether to give title compound as yellow solid.

^{1}HNMR (DMSOd_6) : 2.96 (s, 3H) ; 3.06 (s, 3H) ; 3.73 (s, 3H) ; 5.15 (s, 2H) ; 6.87 (s, 1H) ; 7.11 (s, 1H) ; 7.40 (m, 5H) ; 7.89 (s, 1H).

N'-(2-cyano-4-methoxy-5-hydroxyphenyl)-N,N-dimethylimidoformamide.

N'-(2-cyano-4-methoxy-5-benzyloxyphenyl)-N,N-dimethylimidoformamide (15.45 g, 50 mmol) in TFA (200 ml) was irradiated in a microwave oven at 75°C for 45 minutes. The solvent was evaporated, the residue dissolved in dichloromethane washed with sodium bicarbonate, dried over magnesiumsulfate, evaporated to give a pale yellow solid (10.26 g, 94 %).

^{1}HNMR (DMSOd_6, TFA) : 3.24 (s, 3H) ; 3.34 (s, 3H) ; 3.87 (s, 3H) ; 7.02 (s, 1H) ; 7.49 (s, 1H) ; 8.56 (s, 1H).

N'-(2-cyano-4-methoxy-5-(3-chloropropoxyphenyl)-N,N-dimethylimidoformamide.

N'-(2-cyano-4-methoxy-5-hydroxyphenyl)-N,N-dimethylimidoformamide (439 mg, 2 mmol) in acetonitrile (5 ml) was reacted with 1-bromo-3-chloropropane (0.22 ml, 2.2 mmol) and cesium carbonate (1.95 g, 5.98 mmol) at 85°C for 0.5 hour. The reaction mixture was evaporated, taken up in methylene chloride water, extracted with CH_2Cl_2, dried over $MgSO_4$, evaporated to give title compound as a pale yellow solid (450 mg, 76 %).

MS ES$^+$: 296.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.26 (t, 2H) ; 3.26 (s, 3H) ; 3.37 (s, 3H) ; 3.81 (t, 2H) ; 3.87 (s, 3H) ; 4.23 (t, 2H) ; 7.34 (s, 1H) ; 7.53 (s, 1H) ; 8.56 (s, 1H).

g) N-(3-chlorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-ylamino)1,3-thiazol-5-yl)acetamide.

N'-(2-cyano-4-methoxy-5-(3-chloropropoxyphenyl)-N,N-dimethylimidoformamide (296 mg, 1 mmol) and 2-(2-amino-1,3-thiazol-5-yl)-N-(3-chlorophenyl)acetamide (268 mg, 1 mmol) in AcOH (1.5 ml, was irradiated in a microwave oven at 120°C for 40 minutes. The mixture was cooled, the solid was filtered to give title compound (445 mg, 72 %).

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.84 (t, 2H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.32 (t, 2H) ; 7.13 (d, 1H) ; 7.29 (s, 1H) ; 7.36 (t, 1H) ; 7.46 (d, 1H) ; 7.63 (s, 1H) ; 7.85 (s, 1H) ; 7.88 (s, 1H) ; 9.07 (s, 1H).

Example 254. Preparation of compound 431 in Table 17

An analogous reaction to that described in example 130 but starting with N-(3,4-difluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide (52 mg, 0.1 mmol) and pyrrolidine (150 µl, 1.8 mmol) yielded title compound (26 mg, 47 %).

^{1}HNMR (DMSOd_6, TFA): 1.91 (m, 2H) ; 2.07 (m, 2H) ; 2.28 (t, 2H) ; 3.10 (m, 2H) ; 3.37 (t, 2H) ; 3.67 (m, 2H) ; 3.99 (s, 5H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.33 (m, 1H) ; 7.40 (q, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Starting material N-(3,4-difluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxy quinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide was obtained by an analogous reaction to that described in example 130 but starting with 2-(2-amino-1,3-thiazol-5-yl)-N-(3,4-difluorophenyl)acetamide (540 mg, 2 mmol) to give title compound (980 mg, 78 %).

MS ES$^+$: 520.4, 522.4$(M+H)^+$

1HNMR (DMSOd6) : 1.26 (t, 2H) ; 3.82 (t, 2H) ; 3.88 (s, 2H) ; 3.97 (s, 3H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.32 (m, 1H) ; 7.36 (s, 1H) ; 7.39 (t, 1H) ; 7.80 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 255. Preparation of compound 432 in Table 17

An analogous reaction to that described in example 130 but starting with N-(3,5-difluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide (138 mg, 0.22 mmol) and dimethylamine (3.6 M in CH_2Cl_2, 3 ml, 3.6 mmol) yielded title compound (47 mg, 40 %).

MS ES^+: 529.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.25 (t, 2H) ; 3.28 (t, 2H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.28 (t, 2H) ; 6.93 (m, 1H) ; 7.30 (s, 1H) ; 7.34 (m, 2H) ; 7.65 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Starting material N-(3,5-difluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide was obtained by an analogous reaction to that described in example 130 but starting with 2-(2-amino-1,3-thiazole-5-yl)-N-(3,5-difluorophenyl)acetamide (810 mg, 3 mmol) to give title compound (630 mg, 40 %).

MS ES^+: 520.4, 522.4 $(M+H)^+$

1HNMR (DMSOd6) : 2.26 (t, 2H) ; 3.84 (t, 2H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.30 (t, 2H) ; 6.94 (m, 1H) ; 7.30 (s, 1H) ; 7.35 (m, 2H) ; 7.40 (s, 1H) ; 8.14 (s, 1H) ; 8.69 (s, 1H) ; 10.64 (s, 1H).

Example 256. Preparation of compound 433 in Table 17

An analogous reaction to that described in example 130 but starting with N-(3-chloro-4-fluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide (123 mg, 0.22 mmol) and 2-amino-2-methyl-1-propanol (89.1 mg, 3.3 mmol) yielded title compound (6 mg, 5 %).

MS ES^+: 589.4 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.24 (s, 6H) ; 2.22 (t, 2H) ; 3.10 (t, 2H) ; 3.45 (s, 2H) ; 3.98 (s, 3H) ; 4.31 (t, 2H) ; 7.29 (s, 1H) ; 7.38 (t, 1H) ; 7.50 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (s, 1H) ; 9.09 (s, 1H).

Starting material N-(3-chloro-4-fluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide was obtained by an analogous reaction to that described in example 130 but starting with 2-(2-amino-1,3-thiazole-5-yl)-N-(3-chloro-4-fluorophenyl)acetamide (2.29 g, 8.0 mmol) to give title compound (3.62 g, 84 %).

MS ES^+ : 536.3, 538.3 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 2.26 (t, 2H) ; 3.82 (t, 2H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.29 (t, 2H) ; 7.28 (s, 1H) ; 7.38 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (m, 1H) ; 7.93 (m, 1H) ; 8.12 (s, 1H) ; 8.67 (s, 1H) ; 10.47 (s, 1H).

Example 257. Preparation of compound 434 in Table 17

An analogous reaction to that described in example 130, but starting with N-(3-fluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide (116 mg, 0.22 mmol) and 2-amino-2-methyl-1-propanol (89 mg, 3.3 mmol) yielded title compound (40 mg, 33 %).

MS ES$^+$: 555.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.22 (t, 2H) ; 3.09 (t, 2H) ; 3.16 (s, 2H) ; 3.97 (s, 3H) ; 4.30 (t, 2H) ; 6.86 (t, 1H) ; 7.28 (s, 1H) ; 7.33 (m, 2H) ; 7.58 (m, 1H) ; 7.62 (s, 1H) ; 7.91 (s, 1H) ; 9.07 (s, 1H).

Starting material N-(3-fluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide was obtained by an analogous reaction to that described in example 130 but starting with 2-(2-amino-1,3-thiazole-5-yl)-N-(3-fluorophenyl)acetamide (2.01 g, 8 mmol) to give title compound (3.08 g, 77 %).

MS ES$^+$: 502.4, 504.4 $(M+H)^+$

^{1}HNMR (DMSOd_6): 2.28 (t, 2H) ; 3.84 (t, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.31 (t, 2H) ; 6.91 (t, 1H) ; 7.30 (s, 1H) ; 7.35 (m, 2H) ; 7.39 (s, 1H) ; 7.63 (d, 1H) ; 8.14 (s, 1H) ; 8.69 (s, 1H) ; 10.48 (s, 1H).

Example 258. Preparation of compound 435 in Table 17

An analogous reaction to that described in example 131 but starting with 4-hydroxyperidine (405 mg, 4.0 mmol) yielded compound 135 in Table 17 (82 mg, 70 %).

MS ES$^+$: 585.5 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.43 (m, 2H) ; 1.73 (m, 2H) ; 1.95 (m, 2H) ; 2.03 (t, 2H) ; 2.44 (t, 2H) ; 2.74 (m, 2H) ; 3.38 (m, 1H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.53 (d, 1H) ; 7.26 (s, 1H) ; 7.31 (m, 1H) ; 7.39 (s, 1H) ; 7.42 (ddd, 1H) ; 7.83 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.50 (s, 1H).

Example 259. Preparation of compound 436 in Table 17

An analogous reaction to that described in example 131 but starting with N,N-dimethylenediamine (0.44 ml, 4.0 mmol) yielded compound 136 in Table 17 (40 mg, 35 %).

MS ES$^+$: 572.5 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.95 (m, 2H) ; 2.14 (s, 6H) ; 2.33 (t, 2H) ; 2.63 (t, 2H) ; 2.73 (t, 2H) ; 3.89 (s, 2H) ; 3.97 (s, 3H) ; 4.22 (t, 2H) ; 7.26 (s, 1H) ; 7.34 (m, 1H) ; 7.38 (s, 1H) ; 7.41 (ddd, 1H) ; 7.82 (m, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.50 (s, 1H).

Example 260. Preparation of compound 437 in Table 17

An analogous reaction to that described in example 131 but starting with piperidine (0.4 ml, 3.0 mmol) yielded compound 137 in Table 17 (67 mg, 59 %).

MS ES$^+$: 569.5 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.40 (m, 2H) ; 1.52 (m, 4H) ; 1.95 (m, 2H) ; 2.42 (m, 4H) ; 2.48 (t, 2H) ; 3.89 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 7.25 (s, 1H) ; 7.33 (m, 1H) ; 7.39 (s, 1H) ; 7.41 (ddd, 1H) ; 7.82 (m, 1H) ; 8.11 (s, 1H) ; 8.68 (s, 1H) ; 10.51 (s, 1H).

Example 261. Preparation of compound 438 in Table 17

An analogous reaction to that described in example 131 but starting with 2-methylaminoethanol (248 mg, 3.3 mmol) yielded compound 138 in Table 17 (23 mg, 19 %).

MS ES$^+$: 559 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.95 (m, 2H) ; 2.23 (s, 3H) ; 2.47 (m, 2H) ; 3.32 (m, 2H) ; 3.49 (m, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.21 (t, 2H) ; 4.37 (m, 1H) ; 7.27 (s, 1H) ; 7.34 (m, 1H) ; 7.38 (s, 1H) ; 7.40 (dd, 1H) ; 7.82 (ddd, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.50 (s, 1H).

Example 262. Preparation of compound 439 in Table 17

An analogous reaction to that described in example 131 but starting with 1,2-diamino-2-methylpropane (291 mg, 3.3 mmol) yielded compound 139 in Table 17 (16 mg, 13 %).

MS ES$^+$: 572 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.10 (s, 6H) ; 1.96 (m, 2H) ; 2.48 (s, 2H) ; 2.75 (t, 2H) ; 3.89 (s, 2H) ; 3.97 (s, 3H) ; 4.26 (t, 2H) ; 7.27 (s, 1H) ; 7.34 (m, 1H) ; 7.37 (s, 1H) ; 7.42 (dd, 1H) ; 7.83 (ddd, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H) ; 10.50 (s, 1H).

Example 263. Preparation of compound 440 in Table 17

An analogous reaction to that described in example 131 but starting with cyclohexylamine (327 mg, 3.3 mmol) yielded compound 140 in Table 17 (70 mg, 55 %).

MS ES^+: 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.12 (m, 1H) ; 1.27 (m, 4H) ; 1.63 (brd, 1H) ; 1.78 (m, 2H) ; 2.04 (m, 2H) ; 2.16 (m, 2H) ; 3.03 (m, 1H) ; 3.16 (t, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.29 (t, 2H) ; 7.31 (s, 1H) ; 7.34 (m, 1H) ; 7.40 (s, 1H) ; 7.42 (dd, 1H) ; 7.82 (ddd, 1H) ; 8.16 (bra, 1H) ; 8.70 (s, 1H) ; 10.51 (s, 1H).

Example 264. Preparation of compound 441 in Table 17

An analogous reaction to that described in example 131 but starting with N,N,N'-trimethylethylenediamine (337 mg, 3.3 mmol) yielded compound 141 in Table 17 (63 mg, 49 %).

MS ES^+: 587 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.33 (m, 2H) ; 2.88 (s, 6H) ; 2.93 (s, 3H) ; 3.38 (m, 2H) ; 3.56 (m, 4H) ; 3.98 (s, 5H) ; 4.30 (t, 2H) ; 7.29 (m, 1H) ; 7.33 (s, 1H) ; 7.35 (dd, 1H) ; 7.63 (s, 1H) ; 7.80 (ddd, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 265. Preparation of compound 442 in Table 17

An analogous reaction to that described in example 131 but starting with (R)-(-)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 142 in Table 17 (90 mg, 70 %).

MS ES^+: 585 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.79 (m, 1H) ; 1.91 (m, 1H) ; 2.03 (m, 1H) ; 2.11 (m, 1H) ; 2.29 (m, 2H) ; 3.21 (m, 2H) ; 3.62 (m, 4H) ; 3.77 (m, 1H) ; 3.98 (s, 5H) ; 4.29 (t, 2H) ; 7.30 (s, 1H) ; 7.32 (m, 1H) ; 7.39 (dd, 1H) ; 7.64 (s, 1H) ; 7.80 (ddd, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 266. Preparation of compound 443 in Table 17

An analogous reaction to that described in example 131 but starting with (S)-(+)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 143 in Table 17 (82 mg, 63 %).

MS ES^+: 585 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.76 (m, 1H) ; 1.88 (m, 1H) ; 2.01 (m, 1H) ; 2.10 (m, 1H) ; 2.26 (m, 2H) ; 3.21 (m, 2H) ; 3.59 (m, 4H) ; 3.74 (dd, 1H) ; 3.95 (s, 5H) ; 4.27 (t, 2H) ; 7.27 (s, 1H) ; 7.28 (m, 1H) ; 7.34 (dd, 1H) ; 7.60 (s, 1H) ; 7.77 (ddd, 1H) ; 7.88 (s, 1H) ; 9.05 (s, 1H).

Example 267. Preparation of compound 444 in Table 17

An analogous reaction to that described in example 131 but starting with 3-pyrrolidinol (288 mg, 3.3 mmol) yielded compound 144 in Table 17 (15 mg, 12 %).

MS ES$^+$: 571 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.85-2.04 (m, 2H) ; 2.28 (m, 2H) ; 3.03-3.54 (m, 4H) ; 3.75 (m, 2H) ; 3.99 (s, 5H) ; 4.28 (m, 2H) ; 4.40-4.52 (m, 1H) ; 7.29 (s, 1H) ; 7.33 (m, 1H) ; 7.39 (dd, 1H) ; 7.64 (s, 1H) ; 7.81 (ddd, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 268. Preparation of compound 445 in Table 17

An analogous reaction to that described in example 131 but starting with 1-(2-aminoethyl)pyrrolidine (377 mg, 3.3 mmol) yielded compound 145 in Table 17 (20 mg, 15 %).

MS ES$^+$: 598 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.92 (m, 2H) ; 2.06 (m, 2H) ; 2.24 (m, 2H) ; 3.11 (m, 2H) ; 3.23 (t, 2H) ; 3.42 (m, 2H) ; 3.49 (m, 2H) ; 3.52 (m, 2H) ; 4.00 (s, 5H) ; 4.32 (t, 2H) ; 7.32 (s, 1H) ; 7.33 (m, 1H) ; 7.39 (dd, 1H) ; 7.65 (s, 1H) ; 7.81 (ddd, 1H) ; 7.92 (s, 1H) ; 9.10 (s, 1H).

Example 269. Preparation of compound 446 in Table 17

An analogous reaction to that described in example 131 but starting with 1-acetylpiperazine (423 mg, 3.3 mmol) yielded compound 146 in Table 17 (100 mg, 74 %).

MS ES$^+$: 612 $(M+H)^+$

^{1}HNMR (DMSOd_6): 2.00 (s, 5H) ; 2.35 (m, 2H) ; 2.42 (m, 2H) ; 3.92-3.06 (m, 1H) ; 3.45 (m, 4H) ; 3.56 (t, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.23 (t, 2H) ; 7.28 (s, 1H) ; 7.34 (m, 1H) ; 7.40 (s, 1H) ; 7.42 (dd, 1H) ; 7.83 (ddd, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H).

Example 270. Preparation of compound 447 in Table 17

An analogous reaction to that described in example 131 but starting with 1-(2-morpholinoethyl)-piperazine (658 mg, 3.3 mmol) yielded compound 147 in Table 17 (44 mg, 29 %).

MS ES$^+$: 683 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.98 (m, 2H) ; 2.30-2.70 (m, 18H) ; 3.58 (m, 4H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.21 (t, 2H) ; 7.26 (s, 1H) ; 7.33 (m, 1H) ; 7.40 (s, 1H) ; 7.41 (dd, 1H) ; 7.82 (ddd, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.54 (s, 1H).

Example 271. Preparation of compound 448 in Table 17

An analogous reaction to that described in example 131 but starting with 2-piperidineethanol (426 mg, 3.3 mmol) yielded compound 148 in Table 17 (19 mg, 14 %).

MS ES$^+$: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.45-1.92 (m, 7H) ; 2.00-2.15 (m, 1H) ; 2.20-2.40 (m, 2H) ; 3.10-3.70 (m, 7H) ; 3.99 (s, 5H) ; 4.30 (m, 2H) ; 7.30 (s, 1H) ; 7.34 (m, 1H) ; 7.40 (dd, 1H) ; 7.64 (s, 1H) ; 7.81 (ddd, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 272. Preparation of compound 449 in Table 17

An analogous reaction to that described in example 131 but starting with 1-(2-hydroxyethyl)piperazine (430 mg, 3.3 mmol) yielded compound 149 in Table 17 (90 mg, 66 %).

MS ES$^+$: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H) ; 2.35-2.47 (m, 12H) ; 3.49 (q, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 1H) ; 4.37 (t, 1H) ; 7.25 (s, 1H) ; 7.33 (m, 1H) ; 7.39 (s, 1H) ; 7.41 (dd, 1H) ; 7.81 (ddd, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.50 (s, 1H) ; 12.03 (brs, 1H).

Example 273. Preparation of compound 450 in Table 17

An analogous reaction to that described in example 131 but starting with cyclopentylamine (281 mg, 3.3 mmol) yielded compound 150 in Table 17 (43 mg, 34 %).

MS ES$^+$: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.53 (m, 4H) ; 1.69 (m, 2H) ; 1.93 (m, 2H) ; 2.10 (m, 2H) ; 3.00 (m, 2H) ; 3.38 (m, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.28 (t, 2H) ; 7.30 (s, 1H) ; 7.32 (m, 1H) ; 7.42 (dd, 1H) ; 7.81 (ddd, 1H) ; 8.15 (brs, 1H) ; 8.70 (s, 1H) ; 10.51 (s, 1H).

Example 274. Preparation of compound 451 in Table 17

An analogous reaction to that described in example 131 but starting with 4-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 151 IN Table 17 (53 mg, 39 %).

MS ES$^+$: 613 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.14 (m, 2H) ; 1.36 (m, 3H) ; 1.63 (brd, 2H) ; 1.87 (m, 2H) ; 1.95 (m, 2H) ; 2.45 (m, 1H) ; 2.86 (m, 2H) ; 3.44 (m, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.32 (t, 1H) ; 7.26 (s, 1H) ; 7.31 (m, 1H) ; 7.40 (s, 1H) ; 7.42 (dd, 1H) ; 7.82 (ddd, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.50 (s, 1H) ; 12.02 (brs, 1H).

Example 275. Preparation of compound 452 in Table 17

An analogous reaction to that described in example 131 but starting with L-alanine-T-butylester hydrochloride (599 mg, 3.3 mmol) and treating the crude reaction mixture with a 1:1 solution of CH_2Cl_2-TFA (4 ml) yielded compound 152 in Table 17 (75 mg, 60 %).

MS ES$^+$: (573 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.48 (d, 3H) ; 2.24 (m, 2H) ; 3.22 (m, 2H) ; 3.97 (s, 5H) ; 4.15 (q, 1H) ; 4.30 (m, 2H) ; 7.30 (s, 1H) ; 7.34 (m, 1H) ; 7.40 (dd, 1H) ; 7.64 (s, 1H) ; 7.81 (ddd, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H) ; 10.60 (s, 1H).

Example 276. Preparation of compound 453 in Table 17

An analogous reaction to that described in example 131 but starting with 3-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 153 in Table 17 (84 mg, 65 %).

MS ES$^+$: 585 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.07 (m, 1H) ; 1.41 (m, 1H) ; 1.62 (m, 1H) ; 1.76 (m, 2H) ; 1.87 (m, 1H) ; 1.95 (m, 2H) ; 2.47 (m, 2H) ; 2.68 (m, 1H) ; 2.85 (m, 1H) ; 3.48 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.20 (t, 2H) ; 4.59 (d, 1H) ; 7.26 (s, 1H) ; 7.31 (m, 1H) ; 7.39 (s, 1H) ; 7.42 (dd, 1H) ; 7.81 (ddd, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.50 (s, 1H) ; 12.02 (brs, 1H).

Example 277. Preparation of compound 454 in Table 17

An analogous reaction to that described in example 131 but starting with 4-hydroxymethylpiperidine (380 mg, 3.3 mmol) yielded compound 154 in Table 17 (42 mg, 32 %).

MS ES^+: 599 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.13 (m, 2H) ; 1.33 (m, 1H) ; 1.62 (brd, 2H) ; 1.90 (m, 2H) ; 1.95 (m, 2H) ; 2.44 (m, 2H) ; 2.88 (m, 2H) ; 3.22 (t, 2H) ; 3.86 (s, 2H) ; 3.93 (s, 3H) ; 4.17 (t, 2H) ; 4.38 (t, 1H) ; 7.22 (s, 1H) ; 7.31 (m, 1H) ; 7.36 (s, 1H) ; 7.38 (dd, 1H) ; 7.80 (ddd, 1H) ; 8. 09 (brs, 1H) ; 8.65 (s, 1H) ; 10.46 (s, 1H) ; 12.00 (brs, 1H).

Example 278. Preparation of compound 455 in Table 17

An analogous reaction to that described in example 130 but starting with 1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 155 in Table 17 (52 mg, 42 %).

MS ES^+: 573 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H) ; 1.95 (m, 2H) ; 2.48 (m, 2H) ; 2.72 (t, 2H) ; 3.68 (m, 1H) ; 3.89 (s, 2H) ; 3.97 (s, 3H) ; 4.23 (t, 2H) ; 4.46 (m, 1H) ; 7.26 (s, 1H) ; 7.32 (m, 1H) ; 7.38 (s, 1H) ; 7.41 (dd, 1H) ; 7.81 (ddd, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.49 (s, 1H).

Example 279. Preparation of compound 456 in Table 17

An analogous reaction to that described in example 130 but starting with L-alamine-t-butylester hydrochloride (599 mg, 3.3 mmol) and treating the crude reaction mixture with CH_2Cl_2-TFA (1/1, 4 ml) yielded compound 156 in Table 17 (106 mg, 84 %).

MS ES^+: 571 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.40 (d, 3H) ; 2.25 (m, 2H) ; 3.20 (m, 2H) ; 3.98 (s, 3H) ; 4.00 (s, 2H) ; 4.14 (m, 1H) ; 4.31 (t, 2H) ; 7.13 (dd, 1H) ; 7.32 (s, 1H) ; 7.35 (t, 1H) ; 7.47 (dd, 1H) ; 7.63 (s, 1H) ; 7.86 (t, 1H) ; 7.90 (s, 1H) ; 8.30 (m, 1H) ; 9.08 (s, 1H) ; 10.60 (s, 1H).

Example 280. Preparation of compound 457 in Table 17

An analogous reaction to that described in example 130 but starting with2-methylaminoethanol (248 mg, 3.3 mmol) yielded compound 157 in Table 17 (86 mg, 70 %).

MS ES^+: 557 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.93 (m, 2H) ; 2.20 (s, 3H) ; 2.43 (t, 2H) ; 2.48 (m, 1H) ; 2.55 (m, 1H) ; 3.47 (dd, 2H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.19 (t, 2H) ; 4.34 (t, 1H) ; 7.13 (brd, 1H) ; 7.25 (s, 1H) ; 7.35 (t, 1H) ; 7.38 (s, 1H) ; 7.47 (s, 1H) ; 7.84 (s, 1H) ; 8.11 (dd, 1H) ; 8.66 (s, 1H) ; 10.44 (s, 1H) ; 12.00 (dd, 1H).

Example 281. Preparation of compound 458 in Table 17

An analogous reaction to that described in example 130 but starting with 1,2-diamino-2-methylpropane (291 mg, 3.3 mmol) yielded compound 158 in Table 17 (21 mg, 17 %).

MS ES$^+$: 570 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.39 (s, 1H) ; 2.28 (m, 2H) ; 3.23 (m, 4H) ; 3.98 (s, 3H) ; 4.00 (s, 2H) ; 4.32 (m, 2H) ; 7.14 (ddd, 1H) ; 7.31 (s, 1H) ; 7.36 (t, 1H) ; 7.47 (ddd, 1H) ; 7.64 (s, 1H) ; 7.86 (t, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 282. Preparation of compound 459 in Table 17

An analogous reaction to that described in example 130 but starting with cyclohexylamine (327 mg, 3.3 mmol) yielded compound 159 in Table 17 -85 mg, 66 %).

MS ES$^+$: 581 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.13 (m, 1H) ; 1.26 (m, 4H) ; 1.62 (brd, 1H) ; 1.77 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 2H) ; 3.07 (m, 1H) ; 3.14 (t, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.29 (t, 2H) ; 7.13 (brd, 1H) ; 7.29 (s, 1H) ; 7.36 (t, 1H) ; 7.39 (s, 1H) ; 7.46 (dd, 1H) ; 8.16 (dd, 1H) ; 8.26 (brs, 1H) ; 8.69 (s, 1H) ; 10.45 (s, 1H).

Example 283. Preparation of compound 460 in Table 17

An analogous reaction to that described in example 130 but starting with N,N-dimethylethylenediamine (291 mg, 3.3 mmol) yielded compound 160 in Table 17 (41 mg, 32 %).

MS ES$^+$: 570 $(M+H)^+$

^{1}HNMR (DMSOd_6): 2.00 (m, 1H) ; 2.17 (s, 6H) ; 2.38 (t, 2H) ; 2.72 (t, 2H) ; 2.81 (t, 2H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.24 (t, 2H) ; 7.14 (dd, 1H) ; 7.27 (s, 1H) ; 7.37 (t, 1H) ; 7.40 (s, 1H) ; 7.49 (dd, 1H) ; 7.86 (t, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H) ; 10.50 (s, 1H).

Example 284. Preparation of compound 461 in Table 17

An analogous reaction to that described in example 130 but starting with N,N,N'-trimethylethylenediamine (337 mg, 3.3 mmol) yielded compound 161 in Table 17 (11 mg, 8 %).

MS ES^+: 584 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.91 (m, 2H) ; 2.12 (s, 6H) ; 2.20 (s, 3H) ; 2.33 (m, 3H) ; 2.42 (m, 3H) ; 3.76 (s, 2H) ; 3.91 (s, 3H) ; 4.12 (t, 2H) ; 6.98 (s, 1H) ; 7.11 (dd, 1H) ; 7.16 (s, 4H) ; 7.35 (t, 1H) ; 7.52 (dd, 1H) ; 7.83 (s, 1H) ; 7.88 (t, 1H) ; 8.37 (s, 1H) ; 10.56 (s, 1H).

Example 285. Preparation of compound 462 in Table 17

An analogous reaction to that described in example 130 but starting with (R)-(-)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 162 in Table 17 (76 mg, 59 %).

MS ES^+: 583 $((M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.77 (m, 1H) ; 1.89 (m, 1H) ; 2.02 (m, 1H) ; 2.4 (m, 1H) ; 2.29 (m, 2H) ; 3.21 (m, 2H) ; 3.62 (m, 4H) ; 3.76 (m, 1H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.29 (t, 2H) ; 7.13 (dd, 1H) ; 7.29 (s, 1H) ; 7.35 (t, 1H) ; 7.46 (dd, 1H) ; 7.63 (s, 1H) ; 7.85 (t, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 286. Preparation of compound 463 in Table 17

An analogous reaction to that described in example 130 but starting with (S)-(+)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 163 in Table 17 (72 mg, 56 %).

MS ES^+: 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.78 (m, 1H) ; 1.90 (m, 1H) ; 2.03 (m, 1H) ; 2.13 (m, 1H) ; 2.30 (m, 2H) ; 3.23 (m, 2H) ; 3.62 (m, 4H) ; 3.77 (m, 1H) ; 3.98 (s, 3H) ; 4.00 (s, 2H) ; 4.30 (t, 2H) ; 7.14 (dd, 1H) ; 7.30 (s, 1H) ; 7.36 (t, 1H) ; 7.46 (dd, 1H) ; 7.64 (s, 1H) ; 7.85 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 287. Preparation of compound 464 in Table 17

An analogous reaction to that described in example 130 but starting with 4-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 164 in Table 17 (63 mg, 49 %).

MS ES^+: 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.41 (m, 2H) ; 1.73 (m, 2H) ; 1.96 (m, 2H) ; 2.04 (m, 2H) ; 2.74 (m, 2H) ; 2.50 (m, 2H) ; 3.43 (s, 1H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.54 (d, 1H) ; 7.14 (d,

1H) ; 7.26 (s, 1H) ; 7.37 (t, 1H) ; 7.40 (s, 1H) ; 7.49 (d, 1H) ; 7.86 (t, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.46 (s, 1H).

Example 288. Preparation of compound 465 in Table 17

An analogous reaction to that described in example 130 but starting with 3-pyrrolidinol (288 mg, 3.3 mmol) yielded compound 165 in Table 17 (57 mg, 45 %).

MS ES$^+$: 569 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.56 (m, 1H) ; 1.99 (m, 4H) ; 2.36 (m, 1H) ; 2.56 (m, 4H) ; 2.74 (m, 1H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.21 (t, 2H) ; 4.70 (d, 1H) ; 7.14 (dd, 1H) ; 7.26 (s, 1H) ; 7.37 (t, 1H) ; 7.40 (s, 1H) ; 7.49 (dd, 1H) ; 7.86 (t, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.47 (s, 1H) ; 12.03 (brs, 1H).

Example 289. Preparation of compound 466 in Table 17

An analogous reaction to that described in example 130 but starting with 1-(2-aminoethyl)pyrrolidine (377 mg, 3.3 mmol) yielded compound 166 in Table 17 (39 mg, 29 %).

MS ES$^+$: 596 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.91 (m, 2H) ; 2.06 (m, 2H) ; 2.24 (m, 2H) ; 3.11 (m, 2H) ; 3.23 (t, 2H) ; 3.42 (m, 2H) ; 3.48 (m, 2H) ; 3.67 (m, 2H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ;4.31 (t, 2H) ; 7.14 (d, 1H) ; 7.31 (s, 1H) ; 7.35 (t, 1H) ; 7.47 (d, 1H) ; 7.64 (s, 1H) ; 7.85 (t, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 290. Preparation of compound 467 in Table 17

An analogous reaction to that described in example 130 but starting with 4-hydroxymethylpiperidine (380 mg, 3.3 mmol) yielded compound 167 in Table 17 (64 mg, 49 %).

MS ES$^+$: 597 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H) ; 1.35 (m, 1H) ; 1.65 (brd, 2H) ; 1.88 (m, 2H) ; 1.97 (m, 2H) ; 2.47 (m, 2H) ; 2.90 (brd, 2H) ; 3.25 (t, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.41 (t, 1H) ; 7.14 (d, 1H) ; 7.25 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (s, 1H) ; 7.86 (s, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.46 (s, 1H) ; 12.03 (s, 1H).

Example 291. Preparation of compound 468 in Table 17

An analogous reaction to that described in example 130 but starting with 1-(2-hydroxyethyl)piperazine (430 mg, 3.3 mmol) yielded compound 168 in Table 17 (63 mg, 47 %).

MS ES$^+$: 612 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H) ; 2.41 (m, 12H) ; 3.50 (q, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.37 (t, 1H) ; 7.14 (dd, 1H) ; 7.25 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (d, 1H) ; 7.86 (t, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.46 (s, 1H) ; 12.04 (s, 1H).

Example 292. Preparation of compound 469 in Table 17

An analogous reaction to that described in example 130 but starting with cyclopentylamine 281 mg, 3.3 mmol) yielded compound 169 in Table 17 (77 mg, 61 %).

MS ES$^+$: 567 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.58 (m, 4H) ;1.73 (m, 2H) ; 2.00 (m, 2H) ; 2.17 (m, 2H) ; 3.12 (t, 2H) ; 3.56 (m, 1H) ; 3.92 (s, 3H) ; 3.99 (s, 3H) ; 4.31 (t, 2H) ; 7.15 (d, 1H) ; 7.31 (s, 1H) ; 7.37 (t, 1H) ; 7.41 (s, 1H) ; 7.48 (d, 1H) ; 7.86 (s, 1H) ; 8.16 (brs, 1H) ; 8.71 's, 1H) ; 10.47 (s, 1H) ; 12.03 (brs, 1H).

Example 293. Preparation of compound 470 in Table 17

An analogous reaction to that described in example 130 but starting with 4-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 170 in Table 17 (78 mg, 58 %).

MS ES$^+$: 611 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.16 (m, 2H) ; 1.36 (m, 3H) ; 1.63 (d, 2H) ; 1.88 (t, 2H) ; 1.96 (m, 2H) ; 2.44 (t, 2H) ; 2.87 (d, 2H) ; 3.44 (m, 2H) ; 3.9 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.33 (t, 1H) ; 7.14 (d, 1H) ; 7.25 (s, 1H) ; 7.37 (t, 1H) ; 7.40 (s, 1H) ; 7.49 (d, 1H) ; 7.86 (t, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.46 (s, 1H) ; 12.04 (s, 1H).

Example 294. Preparation of compound 471 in Table 17

An analogous reaction to that described in example 130 but starting with 3-hydroxypiperidine (339 mg, 3.3 mmol) yielded compound 171 in Table 17 (117 mg, 91 %).

MS ES$^+$: 583 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.07 (m, 1H) ; 1.41 (m, 1H) ; 1.62 (m, 1H) ; 1.70-1.90 (m, 3H) ; 1.95 (m, 2H) ; 2.46 (m, 2H) ; 2.67 (m, 1H) ; 2.83 (brd, 1H) ; 3.47 (m, 1H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.20 (t, 2H) ; 4.57 (d, 1H) ; 7.13 (ddd, 1H) ; 7.24 (s, 1H) ; 7.36 (t, 1H) ; 7.38 (s, 1H) ; 7.47 (d, 1H) ; 7.84 (t, 1H) ; 8.11 (brs, 1H) ; 8.67 (s, 1H) ; 10.46 (s, 1H) ; 12.00 (brs, 1H).

Example 295. Preparation of compound 472 in Table 17

An analogous reaction to that described in example 130 but starting with (S)-1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 172 in Table 17 (55 mg, 45 %).

MS ES$^+$: 557 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.06 (d, 3H) ; 1.96 (m, 2H) ; 2.48 (m, 2H) ; 2.73 (t, 2H) ; 3.70 (m, 1H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.24 (t, 2H) ; 4.48 (brs, 1H) ; 7.14 (d, 1H) ; 7.27 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.49 (d, 1H) ; 7.86 (t, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.46 (s, 1H).

Example 296. Preparation of compound 473 in Table 17

An analogous reaction to that described in example 130 but starting with (R)-1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 172 in Table 17 (84 mg, 68 %).

MS ES$^+$: 557 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.04 (d, 3H) ; 1.93 (m, 2H) ; 2.45 (m, 2H) ; 2.70 (t, 2H) ; 3.67 (m, 1H) ; 3.88 (s, 2H) ; 3.95 (s, 3H) ; 4.21 (t, 2H) ; 4.46 (brs, 1H) ; 7.12 (d, 1H) ; 7.24 (s, 1H) ; 7.35 (t, 1H) ; 7.37 (s, 1H) ; 7.47 (d, 1H) ; 7.84 (t, 1H) ; 8.09 (s, 1H) ; 8.65 (s, 1H) ; 10.45 (s, 1H).

Example 297. Preparation of compound 474 in Table 17

An analogous reaction to that described in example 130 but starting with tert-butyl-1-piperazinecarboxylate (615 mg, 3.3 mmol) and treating the crude reaction mixture with hydrochloric acid in 1,4 dioxane (4.0 M , 2 ml) yielded compound 174 (3 HCl) in Table 17 (89 mg, 61 %.

MS ES$^+$: 568 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.34 (m, 2H) ; 3.25-3.68 (m, 10H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.33 (t, 2H) ; 7.14 (dd, 1H) ; 7.35 (s, 1H) ; 7.37 (t, 1H) ; 7.49 (d, 1H) ; 7.65 (s, 1H) ; 7.86 (t, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H) ; 10.66 (s, 1H).

Example 298. Preparation of compound 475 in Table 17

An analogous reaction to that described in example 130 but starting with 2-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 175 in Table 17 (29 mg, 22 %).

MS ES$^+$: 611 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.30 (m, 2H) ; 1.48 (m, 4H) ; 1.60 (m ,2H) ; 1.76 (m, 1H) ; 1.93 (m, 2H) ; 2.26 (m, 1H) ; 2.48 (m, 1H) ; 2.79 (m, 2H) ; 3.46 (m, 2H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.18 (t, 2H) ; 4.40 (brs, 1H) ; 7.13 (d, 1H) ; 7.24 (s, 1H) ; 7.35 (t, 1H) ; 7.38 (s, 1H) ; 7.47 (d, 1H) ; 7.84 (s, 1H) ; 8.11 (brs, 1H) ; 8.67 (s, 1H) ; 10.44 (s, 1H).

Example 299. Preparation of compound 476 in Table 17

An analogous reaction to that described in example 130 but starting with 2-amino-2-methyl-1-propanol (294 mg, 3.3 mmol) yielded compound 176 in Table 17 (49 mg, 39 %).

MS ES$^+$: 571 $(M+H)^+$

1HNMR (DMSOd6, TFA) : 1.25 (s, 6H) ; 2.22 (m, 2H) ; 3.10 (m, 2H) ; 3.46 (s, 2H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.32 (t, 2H) ; 7.15 (d, 1H) ; 7.30 (s, 1H) ; 7.37 (t, 1H) ; 7.47 (d, 1H) ; 7.65 (s, 1H) ; 7.86 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 4H) ; 10.56 (s, 1H).

Example 300. Preparation of compound 477 in Table 17

An analogous reaction to that described in example 130 but starting with 1-(2-dimethylaminoethylpiperazine (519 mg, 3.3 mmol) yielded compound 177 in Table 17 (19 mg, 15 %).

MS ES$^+$: 639 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.96 (m, 2H) ; 2.13 (s, 6H) ; 2.30-2.52 (m, 14H) ; 3.89 (s, 2H) ; 3.95 (s, 3H) ; 4.18 (t, 2H) ; 7.13 (d, 1H) ; 7.23 (s, 1H) ; 7.35 (t, 1H) ; 7.38 (s, 1H) ; 7.84 (t, 1H) ; 8.10 (s, 1H) ; 8.67 (s, 1H) ; 10.45 (s, 1H).

Example 301. Preparation of compound 478 in Table 17

An analogous reaction to that described in example 130 but starting with a solution of dimethylamine in chloroform (3,6M, 3 ml, 3.6 mmol) yielded compound 178 in Table 17 (44 mg, 34 %).

MS ES$^+$: 527 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.95 (m, 2H) ; 2.17 (s, 6H) ; 2.41 (t, 2H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.18 (t, 2H) ; 7.12 (d, 1H) ; 7.23 (s, 1H) ; 7.35 (t, 1H) ; 7.38 (s, 1H) ; 7.47 (d, 1H) ; 7.84 (t, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.45 (s, 1H).

Example 302. Preparation of compound 479 in Table 17

An analogous reaction to that described in example 130 but starting with aminomethylcyclopropane (234 mg, 3.3 mmol) yielded compound 179 in Table 17 (88 mg, 65 %).

MS ES$^+$: 553 $(M+H)^+$

^{1}HNMR (DMSOd_6): 0.18 (m, 2H) ; 0.46 (m, 2H) ; 0.94 (m, 1H) ; 2.01 (m, 2H) ; 2.51 (d, 2H) ; 2.79 (t, 2H) ; 3.94 (s, 2H) ; 4.01 (s, 3H) ; 4.28 (t, 2H) ; 7.18 (d, 1H) ; 7.31 (s, 1H) ; 7.41 (t, 1H) ; 7.43 (s, 1H) ; 7.53 (d, 1H) ; 7.90 (s, 1H) ; 8.16 (s, 1H) ; 8.72 (s, 1H) ; 10.53 (s, 1H).

Example 303. Preparation of compound 480 in Table 17

An analogous reaction to that described in example 130 but starting with piperidine (344 mg, 4.0 mmol) yielded compound 180 in Table 17 (52 mg, 40 %).

MS ES- : 565 $(M-H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.43 (m, 1H) ; 1.69 (m, 3H) ; 1.87 (d, 2H) ; 2.30 (m, 2H) ; 2.96 (t, 2H) ; 3.27 (t, 2H) ; 3.55 (d, 2H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.31 (t, 2H) ; 7.15 (d, 1H) ; 7.31 (s, 1H) ; 7.37 (t, 1H) ; 7.47 (d, 1H) ; 7.65 (s, 1H) ; 7.86 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H) ; 10.56 (s, 1H).

Example 304. Preparation of compound 481 in Table 17

An analogous reaction to that described in example 132 but starting with 1-(2-dimethylaminomethyl)piperazine (281 mg, 3.3 mmol) yielded compound 181 in Table 17 (81 mg, 64 %).

MS ES$^+$: 641 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.33 (m, 2H) ; 2.80-3.70 (m, 14H) ; 2.84 (s, 6H) ; 3.98 (s, 3H) ; 4.01 (s, 2H) ; 4.30 (brt, 1H) ; 6.90 (m, 1H) ; 7.32 (s, 2H) ; 7.35 (dd, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 305. Preparation of compound 482 in Table 17

An analogous reaction to that described in example 132 but starting with (S)-(+)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 182 in Table 17 (58 mg, 45 %).
MS ES$^+$: 585 $(M+H)^+$
^{1}HNMR ($DMSOd_6$, TFA) : 1.79 (m, 1H) ; 1.90 (m, 1H) ; 2.02 (m, 1H) ; 2.13 (m, 1H) ; 2.30 (m, 2H) ; 3.33 (m, 2H) ; 3.62 (m, 4H) ; 3.77 (dd, 1H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.30 (brt, 2H) ; 6.91 (t, 1H) ; 7.30 (s, 1H) ; 7.35 (dd, 2H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 306. Preparation of compound 483 in Table 17

An analogous reaction to that described in example 132 but starting with 4-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 183 in Table 17 (28 mg, 22 %).
MS ES$^+$: 585 $(M+H)^+$
^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H) ; 1.73 (m, 2H) ; 1.96 (m, 2H) ; 2.03 (m, 2H) ; 2.45 (m, 2H) ; 2.74 (m, 2H) ; 3.45 (m, 1H) ; 3.92 (s, 2H) ; 3.97 (s, 3H) ; 3.97 (t, 2H) ; 4.54 (d, 1H) ; 6.95 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.14 (brs, 1H) ;8.68 (s, 1H) ; 10.65 (s, 1H) ; 12.04 (brs, 1H).

Example 307. Preparation of compound 484 in Table 17

An analogous reaction to that described in example 132 but starting with 3-pyrrolidinol (288 mg, 3.3 mmol) yielded compound 184 in Table 17 (30 mg, 23 %).
MS ES$^+$: 571 $(M+H)^+$
^{1}HNMR ($DMSOd_6$) : 1.57 (m, 1H) ; 1.97 'm, 4H) ; 2.37 (m, 1H) ; 2.58 (m, 4H) ; 2.74 (m, 1H) ; 3.92 (s, 2H) ; 3.98 (s 3H) ; 4.22 (brt, 2H) ; 4.72 (brs, 1H) ; 6.95 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.65 (s, 1H) ; 12.04 (brs, 1H).

Example 308. Preparation of compound 485 in Table 17

An analogous reaction to that described in example 132 but starting with 1-(2-aminoethyl)pyrrolidine (377 mg, 3.3 mmol) yielded compound 185 in Table 17 (25 mg, 19 %).
MS ES$^+$: 598 $(M+H)^+$
^{1}HNMR ($DMSOd_6$, TFA) : 1.91 (m, 2H) ; 2.06 (m, 2H) ; 2.24 (m, 2H) ; 3.11 (m, 2H) ; 3.23 (t, 2H) ; 3.41 (lm, 2H) ; 3.49 (m, 2H) ; 3.67 (m, 2H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.31 (t, 2H) ; 6.89 (t, 1H) ; 7.32 (s, 1H) ; 7.34 (d, 2H) ; 7.64 (s, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 309. Preparation of compound 486 in Table 17

An analogous reaction to that described in example 132 but starting with 4-hydroxymethylpyperidine (380 mg, 3.3 mmol) yielded compound 186 in Table 17 (62 mg, 47 %).

MS ES$^+$: 599 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H) ; 1.34 (m, 1H) ; 1.65 (d, 2H) ; 1.88 (t, 2H) ; 1.96 (m, 2H) ; 2.45 (t, 2H) ; 2.90 (d, 2H) ; 3.25 (t, 2H) ; 3.92 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.41 (t, 1H) ; 6.94 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.64 (s, 1H) ; 12.07 (brs, 1H).

Example 310. Preparation of compound 487 in Table 17

An analogous reaction to that described in example 132 but starting with 2-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 187 in Table 17 (61 mg, 45 %).

MS ES$^+$: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.47-1.90 (m, 7H) ; 2.09 (m, 1H) ; 2.27 (m, 2H) ; 3.08-3.70 (m, 7H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.30 (m, 2H) ; 6.84 (m, 1H) ; 7.29 (d, 1H) ; 7.34 (dd, 1H) ; 7.62 (s, 1H) ; 7.92 (s, 1H) ; 9.08 (s, 1H).

Example 311. Preparation of compound 488 in Table 17

An analogous reaction to that described in example 132 but starting with 1-(2-hydroxyethyl)piperazine (430 mg, 3.3 mmol) yielded compound 188 in Table 17 (124 mg, 92 %).

MS ES$^+$: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.96 (m, 2H) ; 2.40 (m, 12H) ; 2.70 (m, 1H) ; 3.48 (m, 2H) ; 3.90 (s, 2H) ; 3.95 (s, 3H) ; 4.18 (t, 2H) ; 4.35 (brt, 1H) ; 6.43 (m, 1H) ; 7.23 (s, 1H) ; 7.34 (dd, 2H) ; 7.38 (s, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H) ; 10.63 (s, 1H).

Example 312. Preparation of compound 489 in Table 17

An analogous reaction to that described in example 132 but starting with 4-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 189 in Table 17 (54 mg, 40 %).

MS ES^+: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H) ; 1.36 (m, 3H) ; 1.63 (brd, 2H) ; 1.88 (m, 2H) ; 1.96 (m, 2H) ; 2.44 (m, 2H) ; 2.87 (brd, 2H) ; 3.44 (m, 2H) ; 3.92 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.33 (t, 1H) ; 6.95 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.64 (s, 1H) ; 12.04 (brs, 1H).

Example 313. Preparation of compound 490 in Table 17

An analogous reaction to that described in example 132 but starting with 3-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound in Table 17 (53 mg, 41 %).

MS ES^+: 559 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.09 (m, 1H) ; 1.43 (m, 1H) ; 1.64 (m, 1H) ; 1.79 (m, 2H) ; 1.87 (m, 1H) ; 1.96 (m, 2H) ; 2.47 (m, 2H) ; 2.69 (m, 2H) ; 2.85 (m, 2H) ; 3.49 (m, 1H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.21 (t, 2H) ; 4.60 (d, 1H) ; 6.95 (t, 1H) ; 7.26 (s, 1H) ; 7.36 (d, 2H) ; 7.40 (s, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.65 (s, 1H) ; 12.04 (brs, 1H).

Example 314. Preparation of compound 491 in Table 17

An analogous reaction to that described in example 132 but starting with N,N,N'-trimethylethylenediamine (337 mg, 3.3 mmol) yielded compound 191 in Table 17 (54 mg, 42 %).

MS ES^+: 586 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.32 (m, 1H) ; 2.34 (m, 1H) ; 2.88 (s, 6H) ; 2.93 (s, 3H) ; 3.39 (m, 2H) ; 3.56 (m, 4H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.30 (t, 2H) ; 6.91 (m, 1H) ; 7.33 (s, 1H) ; 7.35 (dd, 2H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 315. Preparation of compound 492 in Table 17

An analogous reaction to that described in example 132 but starting with piperidine (281 mg, 3.3 mmol) yielded compound 192 in Table 17 (81 mg, 64 %).

MS ES^+: 569 $(M+H)^+$

^{1}HNMR (DMSOd$_6$) : 1.38 (m, 2H) ; 1.50 (m, 4H) ; 2.34 (brs, 4H) ; 2.41 (t, 2H) ; 3.90 (s, 2H) ; 3.96 (s, 3H) ; 4.19 (t, 2H) ; 6.93 (t, 1H) ; 7.24 (s, 1H) ; 7.34 (d, 2H) ; 7.38 (s, 1H) ; 8.11 (brs, 1H) ; 8.67 (s, 1H) ; 10.63 (s, 1H) ; 11.98 (brs, 1H).

Example 316. Preparation of compound 493 in Table 17

An analogous reaction to that described in example 132 but starting with pyrrolidine (235 mg, 3.3 mmol) yielded compound 193 in Table 17 (66 mg, 54 %).

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA): 1.90 (m, 2H) ; 2.06 (m, 2H) ; 2.28 (m, 2H) ; 3.09 (m, 2H) ; 3.36 (m, 2H) ; 3.68 (m, 2H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.29 (t, 2H) ; 6.93 (m, 1H) ; 7.30 (s, 1H) ; 7.34 (dd, 2H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 317. Preparation of compound 494 in Table 17

An analogous reaction to that described in example 132 but starting with 2-amino-2-methyl-1-propanol (294 mg, 3.3 mmol) yielded compound 194 in Table 17 (28 mg, 22 %).

MS ES$^+$: 573 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA): 1.24 (s, 6H) ; 2.23 (m, 2H) ; 3.10 (t, 2H) ; 3.45 (s, 2H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.31 (t, 2H) ; 6.91 (m, 1H) ; 7.30 (s, 1H) ; 7.34 (dd, 2H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 318. Preparation of compound 495 in Table 17

An analogous reaction to that described in example 132 but starting with 2-methylaminoethanol (248 mg, 3.3 mmol) yielded compound 195 in Table 17 (33 mg, 27 %).

MS ES$^+$: 559 $(M+H)^+$

^{1}HNMR (DMSOd$_6$) : 1.95 (m, 2H) ; 2.24 (s, 3H) ; 2.48 (m, 2H) ; 2.45 (m, 2H) ; 3.49 (m, 2H) ; 3.93 (s, 2H) ; 3.98 (s, 3H) ; 4.21 (t, 2H) ; 4.38 (m, 1H) ; 6.95 (m, 1H) ; 7.27 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.65 (s, 1H) ; 12.04 (brs, 1H).

Example 319. Preparation of compound 496 in Table 17

An analogous reaction to that described in example 132 but starting with N,N-dimethylethylenediamine (291 mg, 3.3 mmol) yielded compound 196 in Table 17 (22 mg, 17 %).

MS ES$^+$: 572 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.23 (m, 2H) ; 2.89 (s, 6H) ; 3.22 (m, 2H) ; 3.41 (s, 4H) ; 3.96 (s, 3H) ; 4.01 (s, 2H) ; 4.31 (t, 2H) ; 6.92 (m, 1H) ; 7.31 (s, 1H) ; 7.35 (dd, 2H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 320. Preparation of compound 497 in Table 17

An analogous reaction to that described in example 132 but starting with (S(-(+)-1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 197 in Table 17 (32 Mg, 26 %).

MS ES$^+$: 559 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.15 (d, 3H) ; 2.24 (m, 2H) ; 2.83 (dd, 1H) ; 3.06 (dd, 1H) ; 3.15 (t, 2H) ; 3.95 (m, 1H) ; 3.99 (s, 3H) ; 4.01 (s, 3H) ; 4.29 (t, 1H) ; 6.92 (m, 1H) ; 7.28 (s, 1H) ; 7.34 (dd, 2H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 321. Preparation of compound 498 in Table 17

An analogous reaction to that described in example 132 but starting with (R)-(-)-1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 198 in Table 17 (40 mg, 32 %).

MS ES$^+$: 559 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.15 (d, 3H) ; 2.24 (m, 2H) ; 2.83 (dd, 1H) ; 3.06 (dd, 1H) ; 3.15 (t, 2H) ; 3.95 (m, 1H) ; 3.99 (s, 3H) ; 4.01 (s, 3H) ; 4.29 (t, 1H) ; 6.90 (m, 1H) ; 7.28 (s, 1H) ; 7.34 (dd, 2H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 322. Preparation of compound 499 in Table 17

An analogous reaction to that described in example 132 but starting with tert-butyl-1-piperazine carboxylate (615 mg, 3.3 mmol) and treating the crude reaction mixture with hydrochloric acid in 1,4-dioxane (4M, 2 ml) yielded compound 199 in Table 17 (66 mg, 45 %, 3 HCl).

MS ES$^+$: 570 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.35 (m, 2H) ; 3.20-3.94 (m, 10H) ; 3.99 (s, 3H) ; 4.03 (s, 2H) ; 4.33 (t, 2H) ; 6.93 (m, 1H) ; 7.36 (s, 1H) ; 7.37 (dd, 2H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 323. Preparation of compound 500 in Table 17

An analogous reaction to that described in example 132 but starting with N-allylpiperazine (416 mg, 3.3 mmol) yielded compound 200 in Table 17 (33 mg, 25 %).

MS ES$^+$: 610 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 1.96 (m, 2H) ; 2.30-2.50 (m, 10H) ; 2.93 (d, 2H) ; 3.92 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 5.12 (d, 1H) ; 5.18 (d, 1H) ; 5.82 (m, 1H) ; 6.95 (m, 1H) ; 7.25 (s, 1H) ; 7.35 (dd, 2H) ; 7.40 (s, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.64 (s, 1H) ; 11.99 (brs, 1H).

Example 324. Preparation of compound 501 in Table 17

An analogous reaction to that described in example 132 but starting with (R)-(-)-2-pyrrolidinemethanol (334 mg, 3.3 mol) yielded compound 201 in Table 17 (51 mg, 40 %).

MS ES$^+$: 585 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.57 (m, 1H) ; 1.67 (m, 2H) ; 1.82 (m, 1H) ; 1.96 (m, 2H) ; 2.18 (q, 1H) ; 2.45 (m, 3H) ; 2.98 (m, 1H) ; 3.10 (m, 1H) ; 3.20 (m, 1H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.22 (t, 2H) ; 4.35 (brs, 1H) ; 6.95 (m, 1H) ; 7.27 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H) ; 10.66 (s, 1H) ; 12.00 (brs, 1H).

Example 325. Preparation of compound 502 in Table 17

An analogous reaction to that described in example 132 but starting with cyclopentylamine (281 mg, 3.3 mmol) yielded compound 202 in Table 17 (28 mg, 22 %).

MS ES$^+$: 569 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.31 (m, 2H) ; 1.47 (m, 2H) ; 1.62 (m, 2H) ; 1.73 (m, 2H) ; 1.93 (m, 2H) ; 2.70 (t, 2H) ; 3.03 (m, 1H) ; 3.92 (s, 2H) ; 3.97 (s, 3H) ; 4.23 (t, 2H) ; 6.94 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (dd, 2H) ; 7.39 (s, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.66 (s, 1H).

Example 326. Preparation of compound 503 in Table 17

An analogous reaction to that described in example 133 but starting with 2-methylaminoethanol (248 mg, 3.3 mmol) yielded compound 203 in Table 17 (31 mg, 24 %).

MS ES$^+$: 575 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (m, 2H) ; 2.88 (s, 3H) ; 3.16-3.45 (m, 4H) ; 3.77 (t, 2H) ; 3.99 (s, 5H) ; 4.29 (t, 2H) ; 7.30 (s, 1H) ; 7.38 (t, 1H) ; 7.50 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (dd, 1H) ; 9.09 (s, 1H).

Example 327. Preparation of compound 504 in Table 17

An analogous reaction to that described in example 133 but starting with N,N,N'-trimethylethylenediamine (337 mg, 3.3 mmol) yielded compound 204 in Table 17 (28 mg, 21 %).

MS ES$^+$: 602 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (m, 2H) ; 2.89 (s, 6H) ; 2.93 (s, 3H) ; 3.38 (m, 2H) ; 3.56 (brs, 4H) ; 3.99 (s, 5H) ; 4.30 (t, 2H) ; 7.35 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (dd, 1H) ; 9.09 (s, 1H).

Example 328. Preparation of compound 505 in Table 17

An analogous reaction to that described in example 133 but starting with N-allylpyperazine (416 mg, 3.3 mmol) yielded compound 205 in Table 17 (42 mg, 30 %).

MS ES$^+$: 626 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.33 (m, 2H) ; 3.20-3.80 (m, 10H) ; 3.91 (d, 2H) ; 3.99 (s, 5H) ; 4.32 (t, 2H) ; 5.60 (m, 2H) ; 5.94 (m, 1H) ; 7.33 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (dd, 1H) ; 9.09 (s, 1H).

Example 329. Preparation of compound 506 in Table 17

An analogous reaction to that described in example 133 but starting with 4-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 206 in Table 17 (32 mg, 25 %).

MS ES$^+$: 601 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 1.41 (m, 2H) ; 1.73 (m, 2H) ; 1.96 (m, 2H) ; 2.03 (m, 2H) ; 2.45 (m, 2H) ; 2.74 (m, 2H) ; 3.46 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.21 (t, 2H) ; 4.55 (brs, 1H) ; 7.26 (s, 1H) ; 7.40 (s, 1H) ; 7.41 (t, 1H) ; 7.51 (m, 1H) ; 7.97 (dd, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.49 (s, 1H) ; 12.03 (brs, 1H).

Example 330. Preparation of compound 507 in Table 17

An analogous reaction to that described in example 133 but starting with 3-pyrrolidinol (288 mg, 3.3 mmol) yielded compound 207 in Table 17 (24 mg, 19 %).

MS ES^+: 587 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.57 (m, 1H) ; 1.98 (m, 3H) ; 2.30-2.81 (m, 6H) ; 3.38 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.22 (t, 2H) ; 4.74 (brs, 1H) ; 7.27 (s, 1H) ; 7.39 (s, 1H) ; 7.40 (t, 1H) ; 7.50 (m, 1H) ; 7.96 (dd, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.49 (s, 1H) ; 12.05 (brs, 1H).

Example 331. Preparation of compound 508 in Table 17

An analogous reaction to that described in example 133 but starting with 1-(2-aminoethyl)pyrrolidine (377 mg, 3.3 mmol) yielded compound 208 in Table 17 (18 mg, 13 %).

MS ES^+: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.91 (m, 2H) ; 2.06 (m, 2H) ; 2.23 (m, 2H) ; 3.11 (m, 2H) ; 3.22 (t, 2H) ; 3.41 (m, 2H) ; 3.47 (m, 2H) ; 3.67 (m, 2H) ; 3.98 (s, 5H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.36 (t, 1H) ; 7.49 (m, 1H) ; 7.63 (s, 1H) ; 7.91 (s, 1H). 7.95 (dd, 1H) ; 9.09 (s, 1H).

Example 332. Preparation of compound 509 in Table 17

An analogous reaction to that described in example 133 but starting with N-acetylpiperazine (423 mg, 3.3 mmol) yielded compound 209 in Table 17 (113 mg, 82 %).

MS ES^+: 628 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.98 (m, 2H) ; 2.00 (s, 3H) ; 2.36 (t, 2H) ; 2.42 (t, 2H) ; 2.92 (t, 0.5H) ; 2.99 (t, 0.5H) ; 3.45 (m, 4H) ; 3.55 (t, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.23 (t, 2H) ; 7.27 (s, 1H) ; 7.40 (s, 1H) ; 7.41 (t, 1H) ; 7.52 (m, 1H) ; 7.97 (dd, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H) ; 10.51 (s, 1H).

Example 333. Preparation of compound 510 in Table 17

An analogous reaction to that described in example 133 but starting with 2-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 210 in Table 17 (34 mg, 24 %).

MS ES^+: 629 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.48-1.90 (m, 7H) ; 2.08 (m, 1H) ; 2.27 (m, 2H) ; 3.09-3.69 (m, 7H) ; 3.99 (s, 5H) ; 4.30 (m, 2H) ; 7.30 (d, 1H) ; 7.38 (t, 1H) ; 7.50 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (dd, 1H) ; 9.09 (s, 1H).

Example 334. Preparation of compound 511 in Table 17

An analogous reaction to that described in example 133 but starting with 2-(2-hydroxyethyl)piperazine (430 mg, 3.3 mmol) yielded compound 211 in Table 17 (80 mg, 58 %).

MS ES$^+$: 630 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.96 (m, 2H) ; 2.42 (m, 12H) ; 3.49 (dd, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.37 (t, 1H) ; 7.25 (s, 1H) ; 7.39 (s, 1H) ; 7.40 (t, 1H) ; 7.51 (m, 1H) ; 7.97 (dd, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.42 (s, 1H) ; 12.02 (brs, 1H).

Example 335. Preparation of compound 512 in Table 17

An analogous reaction to that described in example 133 but starting with cyclopentylamine (281 mg, 3.3 mmol) yielded compound 212 in Table 17 (12 mg, 9 %).

MS ES$^+$: 585 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.59 (m, 4H) ; 1.73 (m, 2H) ; 2.00 (m, 2H) ; 2.21 (m, 2H) ; 3.13 (t, 2H) ; 3.56 (m, 1H) ; 3.99 (s, 5H) ; 4.31 (t, 2H) ; 7.29 (s, 1H) ; 7.37 (t, 1H) ; 7.49 (m, 1H) ; 7.64 (s, 1H) ; 7.92 (s, 1H) ; 7.96 (dd, 1H) ; 9.09 (s, 1H).

Example 336. Preparation of compound 513 in Table 17

An analogous reaction to that described in example 133 but starting with 4-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 213 in Table 17 (54 mg, 39 %).

MS ES$^+$: 629 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 1.15 (m, 2H) ; 1.36 (m, 3H) ; 1.63 (d, 2H) ; 1.88 (t, 2H) ; 1.96 (m, 2H) ; 2.44 (t, 2H) ; 2.87 (d, 2H) ; 3.44 (m, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.33 (t, 1H) ; 7.25 (s, 1H) ; 7.40 (s, 1H) ; 7.41 (t, 1H) ; 7.51 (m, 1H) ; 7.97 (dd, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.03 (brs, 1H).

Example 337. Preparation of compound 514 in Table 17

An analogous reaction to that described in example 133 but starting with 3-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 214 in Table 17 (96 mg, 73 %).

MS ES^+:601 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 1.09 (m, 1H) ; 1.43 (m, 1H) ; 1.63 (m, 1H) ; 1.78 (m, 2H) ; 1.87 (m, 1H) ; 1.96 (m, 2H) ; 2.47 (m, 2H) ; 2.68 (m, 1H) ; 2.84 (brd, 1H) ; 3.50 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.20 (t, 2H) ; 4.59 (d, 1H) ; 7.26 (s, 1H) ; 7.40 (s, 1H) ; 7.41 (t, 1H) ; 7.51 (m, 1H) ; 7.97 (dd, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.03 (brs, 1H).

Example 338. Preparation of compound 515 in Table 17

An analogous reaction to that described in example 133 but starting with 4-hydroxymethylpyperidine (380 mg, 3.3 mmol) yielded compound 214 in Table 17 (18 mg, 13 %).

MS ES^+: 615 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H) ; 1.35 (m, 1H) ; 1.65 (d, 2H) ; 1.88 (m, 2H) ; 1.97 (m, 2H) ; 2.46 (m, 2H) ; 2.91 (m, 2H) ; 3.25 (t, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.21 (t, 2H) ; 4.41 (t, 1H) ; 7.26 (s, 1H) ; 7.40 (s, 1H) ; 7.41 (t, 1H) ; 7.50 (m, 1H) ; 7.97 (dd, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.49 (s, 1H) ; 12.03 (brs, 1H).

Example 339. Preparation of compound 516 in Table 17

An analogous reaction to that described in example 133 but starting with 1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 216 in Table 17 (14 mg, 11 %).

MS ES^+: 575 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H) ; 1.96 (m, 2H) ; 2.49 (m, 2H) ; 2.74 (t, 2H) ; 3.71 (m, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.24 (t, 2H) ; 4.50 (brs, 1H) ; 7.27 (s, 1H) ; 7.39 (s, 1H) ; 7.41 (t, 1H) ; 7.51 (m, 1H) ; 7.97 (dd, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.49 (s, 1H).

Example 340. Preparation of compound 517 in Table 17

An analogous reaction to that described in example 133 but starting with tert-butyl-1-piperazinecarboxylate (615 mg, 3.3 mmol) and treating the crude reaction mixture with hydrochloric acid in 1,4-dioxane (4.M, 2 ml) yielded compound 217 in Table 17 (61 mg, 47 %).

MS ES$^+$: 586 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (m, 2H) ; 3.00-3.95 (m, 10 H) ; 3.99 (s, 5H) ; 4.31 (t, 2H) ; 7.32 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (dd, 1H) ; 9.10 (s, 1H).

Example 341. Preparation of compound 518 in Table 17

An analogous reaction to that described in example 133 but starting with 1-(2-morpholinoethyl)piperazine (519 mg, 3.3 mmol) yielded compound 218 in Table 17 (69 mg, 48 %).

MS ES$^+$: 699 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (m, 2H) ; 2.98 (m, 2H) ; 3.10-37.5 (m, 16H) ; 3.86 (m, 4H) ; 3.99 (s, 5H) ; 4.31 (t, 2H) ; 7.33 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.65 (s, 1H) ; 7.92 (s, 1H) ; 7.97 (dd, 1H) ; 9.10 (s, 1H).

Example 342. Preparation of compound 519 in Table 17

An analogous reaction to that described in example 131 but starting with pyrrolidine (235 mg, 3.3 mmol) yielded compound 219 in Table 17 (55 mg, 44 %).

MS ES$^+$: 571 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.90 (m, 2H) ; 2.06 (m, 2H) ; 2.27 (m, 2H) ; 3.09 (m, 2H) ; 3.36 (t, 2H) ; 3.66 (m, 2H) ; 3.98 (s, 5H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.64 (s, 1H) ; 7.90 (s,1H) ; 7.96 (dd, 1H) ; 9.09 (s, 1H).

Example 343. Preparation of compound 520 in Table 17

An analogous reaction to that described in example 134 but starting with 2-methylaminoethanol (248 mg, 3.3 mmol) yielded compound 220 in Table 17 (34 mg, 29 %).

MS ES$^+$: 541 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.30 (m, 2H) ; 3.57 (s, 3H) ; 3.16-3.45 (m, 4H) ; 3.75 (t, 2H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.29 (t, 2H) ; 6.89 (t, 1H) ; 7.29 (s, 1H) ; 7.30-7.40 (m, 2H) ; 7.62 (d, 1H) ; 7.63 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 344. Preparation of compound 521 in Table 17

An analogous reaction to that described in example 134 but starting with 1,2-diamino-2-methylpropane (291 mg, 3.3 mmol) yielded compound 221in Table 17 (10 mg, 8 %).

MS ES$^+$: 554 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.39 (s, 6H) ; 2.27 (m, 2H) ; 3.22 (m, 4H) ; 3.97 (s, 3H) ; 3.98 (s, 2H) ; 4.32 (t, 2H) ; 6.89 (m, 1H) ; 7.29-7.39 (m, 3H) ; 7.62 (d, 1H) ; 7.63 (s, 1H) ; 7.92 (s, 1H) ; 9.08 (s, 1H).

Example 345. Preparation of compound 522 in Table 17

An analogous reaction to that described in example 134 but starting with N,N-dimethylethylenediamine (291 mg, 3.3 mmol) yielded compound 222 in Table 17 (26 mg, 22 %).

MS ES$^+$: 554 $(M+H)^+$

^{1}HNMR (DMSOd_6)) : 1.95 (m, 2H) ; 2.15 (s, 6H) ; 2.33 (t, 2H) ; 2.63 (t, 2H) ; 2.73 (t, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.23 (t, 2H) ; 6.91 (m, 1H) ; 7.26 (s, 1H) ; 7.31-7.42 (m, 2H) ; 7.39 (s, 1H) ; 7.64 (d, 1H) ; 8.11 (s, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H).

Example 346. Preparation of compound 523 in Table 17

An analogous reaction to that described in example 134 but starting with N,N,N'-trimethylethylenediamine (337 mg, 3.3 mmol) yielded compound 223 in Table 17 (37 mg, 30 %).

MS ES$^+$: 568 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.34 (m, 2H) ; 2.88 (s, 6H) ; 2.93 (s, 3H) ; 3.38 (m, 2H) ; 3.55 (m, 4H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.29 (t, 2H) ; 6.89 (m, 1H) ; 7.29-7.41 (m, 2H) ; 7.33 (s, 1H) ; 7.63 (d, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 347. Preparation of compound 524 in Table 17

An analogous reaction to that described in example 134 but starting with N-allylpiperazine (416 mg, 3.3 mmol) yielded compound 224 in Table 17 (77 mg, 59 %).

MS ES$^+$: 592 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.34 (m, 2H) ; 3.00-3.08 (m, 8H) ; 2.86 (d, 2H) ; 3.92 (m, 2H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.31 (t, 2H) ; 5.53-5.66 (m, 2H) ; 5.60-5.87 (m, 1H) ; 6.89 (m, 1H) ; 7.31-7.40 (m, 3H) ; 7.62 (d, 1H) ; 7.63 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 348. Preparation of compound 525 in Table 17

An analogous reaction to that described in example 134 but starting with 4-hydroxypyperidine (334 mg, 3.3 mmol) yielded compound 225 in Table 17 (21 mg, 17 %).

MS ES$^+$: 567 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.59 (m, 1H) ; 1.85 (m, 2H) ; 2.01 (d, 1H) ; 2.28 (m, 2H) ; 3.03 (t, 1H) ; 3.21 (m, 1H) ; 3.28 (m, 2H) ; 3.40 (m, 1H) ; 3.57 (d, 1H) ; 3.68 (m, 1H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.28 (t, 2H) , 6.90 (t, 1H) ; 7.29 (s, 1H) ; 7.30-7.40 (m, 2H) ; 7.63 (d, 1H) ; 7.64 (s,1H) , 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 349. Preparation of compound 526 in Table 17

An analogous reaction to that described in example 134 but starting with 3-pyrrolidinol (288 mg, 3.3 mmol) yielded compound 226 in Table 17 (18 mg, 15 %).

MS ES$^+$: 553 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.84-2.03 (m, 2H) ; 2.27 (m, 2H) ; 3.02-3.79 (m, 6H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.29 (m, 2H) ; 4.41-4.51 (m, 1H) ; 6.91 (m, 1H) ; 7.28 (d, 1H) ; 7.31-7.41 (m, 2H) ; 7.63 (d, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 350. Preparation of compound 527 in Table 17

An analogous reaction to that described in example 134 but starting with 1-(aminoethyl)pyrrolidine (377 mg, 3.3 mmol) yielded compound 227 in Table 17 (34 mg, 27 %).

MS ES$^+$: 580$(M+H)^+$

^{1}HNMR (DMSOd_6): 1.68 (m, 4H) ; 1.97 (m, 2H) ; 2.47 (m, 6H) ; 2.70 (t, 2H) ; 2.77 (t, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.24 (t, 2H) ; 6.91 (m, 1H) ; 7.27 (s, 1H) ; 7.30-7.42 (m, 2H) ; 7.39 (s, 1H) ; 7.64 (d,1H) , 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.49 (s, 1H).

Example 351. Preparation of compound 528 in Table 17

An analogous reaction to that described in example 134 but starting with N-acetylpiperazine (423 mg, 3.3 mmol) yielded compound 228 in Table 17 (93 mg, 71 %).

MS ES$^+$: 594 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.99 (m, 2H) ; 2.00 (s, 3H) ; 2.35 (t, 2H) ; 2.41 (t, 2H) ; 2.49 (m, 2H) ; 3.45 (m, 4H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.23 (t, 2H) ; 6.92 (m, 1H) ; 7.27 (s, 1H) ; 7.32-7.42 (m, 2H) ; 7.40 (s, 1H) ; 7.63 (d, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.48 (s, 1H).

Example 352. Preparation of compound 529 in Table 17

An analogous reaction to that described in example 134 but starting with 1-(2-hydroxyethyl)piperazine (430 mg, 3.3 mmol) yielded compound 229 in Table 17 (91 mg, 69 %).

MS ES$^+$: 596 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H) ; 2.41 (m, 12H) ; 3.50 (q, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.37 (t, 1H) ; 6.91 (t, 1H) ; 7.25 (s, 1H) ; 7.32-7.42 (m, 2H) ; 7.39 (s, 1H) ; 7.65 (d, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.04 (brs, 1H).

Example 353. Preparation of compound 530 in Table 17

An analogous reaction to that described in example 134 but starting cyclopentylamine (281 mg, 3.3 mmol) yielded compound 230 in Table 17 (47 mg, 39 %).

MS ES$^+$: 551 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.39 (m, 2H) ; 1.50 (m, 2H) ; 1.65 (m, 2H) ; 1.80 (m, 2H) ; 2.00 (m, 2H) ; 2.80 (t, 2H) ; 3.16 (m, 1H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.25 (t, 2H) ; 6.98 (t, 1H) ; 7.28 (s, 1H) ; 7.31-7.42 (m, 2H) ; 7.40 (s, 1H) ; 7.64 (d, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H) ; 10.49 (s, 1H).

Example 354. Preparation of compound 531 in Table 17

An analogous reaction to that described in example 134 but starting with 4-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 231 in Table 17 (65 mg, 50 %).

MS ES$^+$: 595 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H) ; 1.36 (m, 3H) ; 1.63 (d, 2H) ; 1.88 (m, 2H) ; 1.96 (m, 2H) ; 2.44 (m, 2H) ; 2.87 (d, 2H) ; 3.44 (m, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.33 (t, 1H) ; 6.91 (t, 1H) ; 7.25 (s, 1H) ; 7.32-7.42 (m, 2H) ; 7.40 (s, 1H) ; 7.63 (d, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.03 (s, 1H).

Example 355. Preparation of compound 532 in Table 17

An analogous reaction to that described in example 134 but starting with 3-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 232 in Table 17 (72 mg, 58 %).

MS ES$^+$: 567 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.09 (m, 1H) ; 1.43 (m, 1H) ; 1.63 (m, 1H) ; 1.78 (m, 2H) ; 1.87 (m, 1H) ; 1.96 (t, 2H) ; 2.47 (m, 2H) ; 2.69 (m, 1H) ; 2.85 (brd, 1H) ; 3.49 (m, 1H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.20 (t, 2H) ; 4.60 (d, 1H) , 6.91 (t, 1H) ; 7.26 (s, 1H) ; 7.31-7.42 (m, 2H) ; 7.40 (s, 1H) ; 7.64 (d, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.02 (brs, 1H).

Example 356. Preparation of compound 533 in Table 17

An analogous reaction to that described in example 134 but starting with 4-hydroxymethylpyperidine (380 mg, 3.3 mmol) yielded compound 233 in Table 17 (56 mg, 44 %).

MS ES$^+$: 581 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.14 (m, 2H) ; 1.34 (m, 1H) ; 1.65 (d, 2H) ; 1.88 (t, 2H) ; 1.97 (m, 2H) ; 2.45 (t, 2H) ; 2.90 (d, 2H) ; 3.25 (t, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.41 (t, 1H) ; 6.93 (t, 1H) ; 7.25 (s, 1H) ; 7.32-7.42 (m, 2H) ; 7.40 (s, 1H) ; 7.63 (d, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.03 (brs, 1H).

Example 357. Preparation of compound 534 in Table 17

An analogous reaction to that described in example 134 but starting with 1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 234 in Table 17 (36 mg, 30 %).

MS ES$^+$: 541 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.06 (d, 3H) ; 1.95 (m, 2H) ; 2.48 (m, 2H) ; 2.72 (t, 2H) ; 3.69 (m, 1H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.23 (t, 2H) ; 4.47 (brs, 1H) ; 6.91 (t, 1H) ; 7.26 (s, 1H) ; 7.32-7.41 (m, 2H) ; 7.39 (s, 1H) ; 7.63 (d, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.48 (s, 1H).

Example 358. Preparation of compound 535 in Table 17

An analogous reaction to that described in example 134 but starting with (R)-(-)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 235 in Table 17 (66 mg, 53 %).

MS ES$^+$: 567 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.57 (m, 1H) ; 1.67 (m, 2H) ; 2.82 (m, 1H) ; 1.96 (m, 2H) ; 2.18 (m, 1H) ; 2.45 (m, 2H) ; 2.98 (m, 1H) ; 3.10 (m, 1H) ; 3.20 (m, 1H) ; 3.41 (m, 1H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.22 (t, 2H) ; 4.35 (brs, 1H) ; 6.91 (t, 1H) ; 7.26 (s, 1H) ; 7.31-7.42 (m, 2H) ; 7.39 (s, 1H) ; 7.64 (d, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.01 (brs, 1H).

Example 359. Preparation of compound 536 in Table 17

An analogous reaction to that described in example 134 but starting with (S)-(+)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 236 in Table 17 (59 mg, 48 %).

MS ES$^+$: 567 $(M+H)^+$

1HNMR (DMSOd6, TFA) : 1.78 (m, 1H) ; 1.90 (m, 1H) ; 2.03 (m, 1H) ; 2.13 (m, 1H) ; 2.31 (m, 2H) ; 3.23 (m, 2H) ; 3.61 (m, 4H) ; 3.77 (q, 1H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.29 (t, 2H) ; 6.89 (t, 1H) ; 7.29 (s, 1H) ; 7.30-7.40 (m, 2H) ; 7.63 (d, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 360. Preparation of compound 537 in Table 17

An analogous reaction to that described in example 134 but starting with t-butyl-1-pyperazinecarboxylate (615 mg, 3.3 mmol) and treating the crude reaction mixture with hydrochloric acid in 1,4-dioxane (4M, 2 ml) yielded compound 237 in Table 17 (35 mg, 27 %).

MS ES$^+$: 552 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.96 (m, 2H) ; 2.33 (brs, 4H) ; 2.42 (t, 2H) ; 2.73 (t, 4H) ; 3.89 (s, 2H) ; 3.95 (s, 3H) ; 4.19 (t, 2H) ; 6.89 (t, 1H) ; 7.24 (s, 1H) ; 7.32-7.42 (m, 2H) ; 7.37 (s, 1H) ; 7.62 (d, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H) ; 10.47 (s, 1H).

Example 361. Preparation of compound 538 in Table 17

An analogous reaction to that described in example 134 but starting with 1-(2-morpholinoethyl)piperazine (519 mg, 3.3 mmol) yielded compound 238 in Table 17 (50 mg, 37 %).

MS ES$^+$: 665 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.33 (m, 2H) ; 2.99 (t, 2H) ; 3.05-3.75 (m, 16H) ; 3.86 (brs, 4H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.29 (t, 2H) ; 6.90 (t, 1H) ; 7.32 (s, 1H) ; 7.41-7.31 (m, 2H) ; 7.62 (d, 1H) ; 7.64 (s, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 362. Preparation of compound 539 in Table 17

An analogous reaction to that described in example 134 but starting with 2-amino-2-methyl-1-propanol (294 mg, 3.3 mmol) yielded compound 239 in Table 17 (40 mg, 33 %).

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 0.96 (s, 6H) ; 1.91 (m, 2H) ; 2.67 (t, 2H) ; 3.19 (s, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.24 (t, 2H) ; 4.53 (brs, 1H) ; 6.91 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (m, 2H) ; 7.38 (s, 1H) ; 7.63 (d, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.48 (s, 1H).

Example 363. Preparation of compound 540 in Table 18

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (125 mg, 0.27 mmol) in DMF (2.5 ml) was reacted with N-ethylaniline (84.3 µl, 0.707 mmol) in presence of O-(7-azabenzotriazol-1-yl) -N,N,N',N'- tetramethyluronium hexafluorophosphate (136 mg, 0.37 mmol) and DIEA (95 µl, 0.54 mmol) at 50°C for 18 hours. The reaction mixture was cooled, sodium bicarbonate (sat., 1 ml) 3 g alumina were added, the mixture was evaporated to dryness, and the residue purified by chromatography over alumina, Eluant CH_2Cl_2, CH_2Cl_2/MeOH 99/1 to 95/5 to give title compound (68 mg, 44 %).

MS ES$^+$: 563.6 $(M+H)^+$

^{1}H NMR ($DMSOd_6$, TFA) : 1.05 (t, 3H) ; 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.65 (m, 6H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.31 (s, 1H) ; 7.38 (s, 1H) ; 7.40 (m, 2H) ; 7.46 (m, 1H) ; 7.53 (m, 2H) ; 7.87 (s, 1H) ; 9.06 (s, 1H).

Example 364. Preparation of compound 541 in Table 18

An analogous reaction to that described in example 240 but starting with 3-chloro-4-fluoro-N-methylaniline (97 mg, 0.35 mmol) yielded title compound (98 mg, 60 %).

MS ES$^+$: 601.5, 603.5 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA) : 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.21 (s, 3H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.7 (m, 4H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.31 (s, 1H) ; 7.41 (s, 1H) ; 7.50 (m, 2H) ; 7.80 (m, 1H) ; 7.87 (s, 1H) ; 9.06 (s, 1H).

N-(tert-butyloxycarbonyl)-3-chloro-4-fluoroaniline

3-chloro-4-fluoroaniline (2 g, 13.7 mmol) in THF (12.5 ml) under argon, was treated with NaHMDS (1 M, 27.5 ml, 27.5 mmol) at room temperature for 15 minutes. Di-tert-butyl dicarbonate in THF (10 ml) was slowly added to the reaction mixture, and the mixture stirred at room temperature for 45 minutes. The solvent was evaporated, diluted HCl (0.1 N) was added, and the mixture extracted with ethylacetate, dried, purified by silica gel chromatography, ether/petroleum ether 10-20 / 90-80 to give title compound (2.77 g, 82 %).

^{1}H NMR ($CDCl_3$) : 1.49 (s, 9H) ; 6.42 (s, 1H) ; 7.01 (t, 1H) ; 7.01 (m, 1H) ; 7.54 (m, 1H).

3-chloro-4-fluoro-N-methylaniline

To a solution of N-(tert-butyloxycarbonyl)-3-chloro-4-fluoroaniline (250 mg, 1.02 mmol) in THF (4 ml) at 0°C was added sodium hydride (60 %, 45 mg, 1.12 mmol), and the mixture was stirred for 20 minutes. Methyl iodide (70 µl, 1.12 mmol) was added to the mixture which was stirred at room temperature for 4 hours. The solvent was evaporated, a saturated solution of sodium chloride was added, and the mixture was extracted with CH_2Cl_2, dried, and purified by silica gel chromatography, ether / petroleum ether, 8/2 to give compound (235 mg). This compound was dissolved in CH_2Cl_2(2 ml) and TFA (2 ml), H_2O (200 µl) was added, the mixture was stirred for 1 hour at room temperature, the solvent was evaporated, to give title compound (256 mg, 89 %).

^{1}HNMR ($CDCl_3$) : 2.98 (s, 3H) ; 7.3 (m, 3H).

Example 365. Preparation of compound 542 in Table 18

An analogous reaction to that described in example 240 but starting with ethyl-2-(3-chloro-4-fluoroaniline)acetate (151 mg, 0.65 mmol) yielded title compound (10 mg, 4.5 %).

MS ES$^+$: 673.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 1.18 (t, 3H) ; 2.30 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.83 (s, 1H) ; 3.97 (s, 3H) ; 4.03 (m, 4H) ; 4.13 (s, 2H) ; 4.29 (t, 2H) ; 4.41 (s, 1H) ; 7.30 (s, 1H) ; 7.44 (s, 1H) ; 7.55 (m, 2H) ; 7.78 (m, 1H) ; 7.87 (s, 1H) ; 9.06 (s, 1H).

Example 366. Preparation of compound 543 in Table 18

An analogous reaction to that described in example 240 but starting with 2-anilinoacetonitrile (371 mg, 2.72 mmol) yielded title compound (110 mg, 18 %).

MS ES$^+$: 574.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.77 (s, 1H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 4.81 (s, 2H) ; 7.31 (s, 1H) ; 7.43 (s, 1H) ; 7.57 (m, 5H) ; 7.88 (s, 1H) ; 9.09 (s, 1H).

Example 367. Preparation of compound 544 in Table 18

An analogous reaction to that described in example 240 but starting with 3-anilinoacetonitrile (335 mg, 2.18 mmol) yielded title compound (100 mg, 18 %).

MS ES$^+$: 588.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.29 (t, 2H) ; 2.75 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (m, 4H) ; 3.95 (t, 2H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.42 (s, 1H) ; 7.48 (m, 3H) ; 7.55 (m, 2H) ; 7.87 (s, 1H) ; 9.08 (s, 1H).

Example 368. Preparation of compound 545 in Table 18

An analogous reaction to that described in example 240 but starting with N-(2-tert-butylethyl)-3-chloro-4-fluoroaniline (346 mg, 1.42 mmol) yielded title compound (147 mg, 30 %).

MS ES$^+$: 687.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 1.08 (s, 9H) ; 2.31 (t, 2H) ; 3.14 (t, 2H) ; 4.3-4.5 (m, 4H) ; 3.55 (d, 2H) ; 3.68 (m, 6H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.30 (s, 1H) ; 7.41 (s, 1H) ; 7.51 (m, 2H) ; 7.78 (m, 1H) ; 7.87 (s, 1H) ; 9.06 (s, 1H).

N-(2-hydroxyethyl)-3-chloro-4-fluoroaniline.

ethyl-2-(3-chloro-4-fluoroanilino)acetate (J. Med. Chem. 1965, 405-407) (2 g, 8.6 mmol) in THF (15 ml) ether (10 ml) was treated with Li Al H4 (460 mg, 12.1 mmol) at 40°C for 4 hours. The mixture was then poured onto ice, treated with NaOH (2N, 10 ml), extracted with ethyl acetate, dried, evaporated to give title compound (1.48 g, 90 %).

^{1}H NMR ($CDCl_3$) : 1.67 (s, 1H) ; 3.24 (t, 2H) ; 3.84 (t, 2H) ; 3.92 (s, 1H) ; 6.47 (m, 1H) ; 6.64 (m, 1H) ; 6.95 (t, 1H).

N-(2-tert-butoxyethyl)-3-chloro-4-fluoroaniline

N-2-hydroxyethyl-3-chloro-4-fluoroaniline (1.48 g, 7.81 mmol) in CH_2Cl_2 (20 ml) was reacted with N,N-diisopropyl O-tert-butyl-isourea (6.25 g, 31.2 mmol) at room temperature over night. The product was purified by silicagel chromatography, Eluant, ether / petroleum ether 5/95, 10/90 to give title compound (1.15 g, 60 %).

^{1}H NMR ($CDCl_3$) : 1.20 (s, 9H) ; 3.18 (t, 2H) ; 3.55 (t, 2H) ; 4.00 (s, 1H) ; 6.44 (m, 1H) ; 6.62 (m, 1H) ; 6.93 (t, 1H).

Example 369. Preparation of compound 546 in Table 18

An analogous reaction to that described in example 240 but starting with N-allylaniline (0.3 ml, 2.18 mmol) yielded title compound (252 mg, 50 %).

MS ES$^+$: 575.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (m, 4H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.28 (m, 4H) ; 5.12 (m, 2H) ; 5.82 (m, 1H) ; 7.30 (s, 1H) ; 7.38 (m, 3H) ; 7.40 (s, 1H) ; 7.51 (m, 2H) ; 7.87 (s, 1H) ; 9.07 (s, 1H).

Example 370. Preparation of compound 547 in Table 18

An analogous reaction to that described in example 240 but starting with N-ethyl-3,4-(methylenedioxy)aniline (320 µl, 2.18 mmol) yielded title compound (351 mg, 66 %).

MS ES$^+$: 607.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 1.04 (t, 3H) ; 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (m, 6H) ; 3.97 (s, 3H) ; 4.09 (d, 2H) ; 4.29 (t, 2H) ; 6.12 (s, 2H) ; 6.83 (d, 1H) ; 7.02 (m, 2H) ; 7.30 (s, 1H) ; 7.42 (s, 1H) ; 7.86 (s, 1H) ; 9.06 (s, 1H).

Example 371. Preparation of compound 548 in Table 18

An analogous reaction to that described in example 240 but starting with ethyl-4-(N-butylamino)benzoate (482 mg, 2.18 mmol) yielded title compound (58 mg, 10 %).

MS ES$^+$: 663.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 0.85 (t, 3H) ; 1.32 (m, 7H) ; 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.70 (m, 6H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 4.35 (s, 2H) ; 7.30 (s, 1H) ; 7.41 (s, 1H) ; 7.54 (d, 2H) ; 7.87 (s, 1H) ; 8.07 (d, 2H) ; 9.07 (s, 1H).

Example 372. Preparation of compound 549 in Table 18

An analogous reaction to that described in example 240 but starting with N-ethyl-m-toluidine (294 mg, 2.18 mmol) yielded title compound (294 mg, 58 %).

MS ES$^+$: 577.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 1.05 (t, 9H) ; 2.31 (t, 2H) ; 2.38 (s, 3H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.67 (m, 6H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.18 (m, 2H) ; 7.28 (d, 1H) ; 7.30 (s, 1H) ; 7.39 (s, 1H) ; 7.42 (d, 1H) ; 7.86 (s, 1H) ; 9.07 (s, 1H).

Example 373. Preparation of compound 550 in Table 18

Compound 245 (120 mg) in CH_2Cl_2 (2 ml) was treated with TFA (3 ml) and H_2O (200 µl) at room temperature for 3 hours. The solvent was evaporated to give title compound (45 mg, 41 %).

MS ES$^+$: 631.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA) : 2.29 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.51 (t, 2H) ; 3.54 (d, 2H) ; 3.70 (m, 6H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.42 (s, 1H) ; 7.54 (m, 2H) ; 7.78 (d, 1H) ; 7.87 (s, 1H) ; 9.06 (s, 1H).

Example 374. Preparation of compound 551 in Table 19

4-((2-amino-4-methyl-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (118 mg, 0.25 mmol) in DMF (1.5 ml) was reacted with aniline (32 mg, 0.35 mmol) in presence of O-(7-azabenzotriazol-1-yl) -N,N,N',N'-tetramethyluronium hexafluorophosphate (142 mg, 0.375 mmol) and DIEA (65 mg, 0.5 mmol) at 65° over night. The mixture was cooled, sodium bicarbonate was added, and the resulting mixture was evaporated. The residue was dissolved in CH_2Cl_2 / MeOH 92/8 and purified by chromatography over alumina, Eluant CH_2Cl_2, CH_2Cl_2 /MeOH 98/2 to 95/5 a second purification over silicagel was performed, Eluant CH_2Cl_2 /MeOH 95/5 to 90/10 to give title compound (86 mg, 62 %).

MS ES$^+$: 549.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.34 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.72 (t, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ;(4.03) ; (d, 2H) ; 4.30 (t, 2H) ; 7.08 (t, 2H) ; 7.29 (s, 1H) ; 7.31 (t, 2H) ; 7.62 (d, 2H) ; 7.85 (s, 1H) ; 9.05 (s, 1H).

4-(ethyl(2-amino-4-methyl-1,3-thiazole-5-yl)acetate)-6-methoxy-7-(3-morpholinopropoxy)quinazoline

N'-(2-cyano-4-methoxy-5-(3-morpholinopropoxy)phenyl)-N,N-dimethylimidoformamide (1.38 g, 4 mmol) in acetic acid was reacted with ethyl-2-amino-4-methyl-1,3-thiazole-5-yl)acetate at reflux for 3.5 hours. The mixture was cooled, evaporated, HCl (1N) was added and the mixture extracted with ethylacetate. Sodium bicarbonate was cautiously added to the aqueous phase, which was extracted with ethylacetate. The organic fractions were dried, evaporated, the residue was purified by chromatography over alumina, Eluant CH_2Cl_2, CH_2Cl_2 /AcOEt 1/1, CH_2Cl_2 /AcOEt/MeOH 50/45/5 to give starting material as a yellow solid. (1.12 g, 52 %).

MS ES$^+$: 502.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 1.24 (t, 3H) ; 2.28 (m, 5H) ; 3.15 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3:92 (s, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.15 (q, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.86 (s, 1H) ; 9.05 (s, 1H).

4-((2-amino-4-methyl-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline

4-(ethyl(2-amino-4-methyl-1,3-thiazole-5-yl)acetate)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (1.1 g, 2.2 mmol) in ethanol (11 ml) was treated with NaOH (2N, 5.5 ml, 11 mmol) at room temperature for 1 hour. The mixture was then acidified with HCl (2N) to pH 3. The solution was evaporated, the solid suspended in CH_2Cl_2 (8 ml) MeOH (6 ml), and DIEA was added (852 mg, 6.6 mmol). The mixture was stirred for 10 minutes, filtered. The filtrate was concentrated, ethanol was added and the solid recovered to give title compound (980 mg, 94 %).

MS ES$^+$: 474.5 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.28 (m, 5H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.70 (t, 2H) ; 3.83 (s, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.86 (s, 1H) ; 9.05 (s, 1H).

Example 375. Preparation of compound 552 in Table 19

An analogous reaction to that described in example 251 but starting with 3-chloro-4-fluoroaniline (51 mg, 0.35 mmol) yielded the title compound (60 mg, 40 %).

MS ES$^+$: 601.5 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.30 (t, 2H) ; 2.33 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; (3.55) (d, 2H) ; 3.69 (t, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.28 (s, 1H) ; 7.39 (t, 1H) ; 7.49 (m, 1H) ; 7.86 (s, 1H) ; 7.96 (m, 1H) ; 9.05 (s, 1H).

Example 376. Preparation of compound 553 in Table 19

An analogous reaction to that described in example 251 but starting with 2-aminopyridine (33 mg, 0.35 mmol) yielded the title compound (45 mg, 32 %).

MS ES$^+$: 550.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.35 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.98 (s, 3H) ; 4.04 (m, 4H) ; 4.30 (t, 2H) ; 7.30 (m, 2H) ; 7.87 (s, 1H) ; 7.95 (d, 1H) ; 8.05 (m, 1H) ; 8.40 (d, 1H) ; 9.04 (s, 1H).

Example 377. Preparation of compound 554 in Table 19

An analogous reaction to that described in example 251 but starting with 3,4 difluoroaniline (50 mg, 0.39 mmol) yielded the title compound (120 mg, 74 %).

MS ES$^+$: 585.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA) : 2.30 (t, 2H) ; 2.33 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.67 (t, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.05 (d, 2H) ; 4.31 (t, 2H) ; 7.28 (s, 1H) ; 7.32 (m, 1H) ; 7.40 (q, 1H) ; 7.80 (m, 1H) ; 7.86 (s, 1H) ; 9.05 (s, 1H).

Compound 378. Preparation of compound 555 in Table 20

N'-(2-cyano-5-((2S)-2-hydroxy-3-piperidinylpropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide (381 mg, 0.96 mmol) in acetic acid (6 ml) was irradiated in a microwave oven in presence of N-(4-fluoro-3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (275 mg, 0.96 mmol) at reflux for 0.5 hour. The solvent was evaporated, and the residue purified by silica gel chromatography, eluant CH_2Cl_2 / MeOH sat. NH_3 95/5 to 93/7 to give title compound (230 mg, 40 %).

MS ES$^+$: 601.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.42 (m, 1H) ; 1.6-1.9 (m, 5H) ; 3.02 (m, 2H) ; 3.28 (m, 2H) ; 3.52 (m, 2H) ; 3.99 (s, 5H) ; 4.19 (d, 2H) ; 4.43 (m, 1H) ; 7.35 (s, 1H) ; 7.40 (t, 1H) ; 7.48 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.95 (m, 1H) ; 9.08 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-piperidinylpropoxy)-4-methoxyphenyl)-N,N,-dimethylimidoformamide.

N'-(2-cyano-5-(2S)-oxiranylmethoxy-4-methoxyphenyl)-N,N-dimethylimidoformamide (850 mg, 3.09 mmol) in chloroform (6 ml) and ethanol (12 ml) was irradiated with piperidine (0.46 ml, 4.6 mmol) in a microwave oven at reflux for 10 minutes. The solvent was evaporated and the residue was purified by silica gel chromatography, eluant CH_2Cl_2 / MeOH 90/10 to give title compound (954 mg, 86 %).

MS ES^+: 361.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.43 (m, 6H) ; 2.4 (m, 6H) ; 2.97 (s, 3H) ; 3.06 (s, 3H) ; 3.75 (s, 3H) ; 3.95 (d, 2H) ; 4.03 (m, 1H) ; 4.83 (s, 1H) ; 6.75 (s, 1H) ; 7.10 (s, 1H) ; 7.90 (s, 1H).

N'-(2-cyano-5-(2S)-oxiranylmethoxy-4-methoxyphenyl)-N,N-dimethylimidoformamide.

N'-(2-cyano-4-methoxy-5-hydroxyphenyl)-N,N-dimethyl-imidoformamide (1 g, 4.57 mmol) in DMF (25 ml) was reacted with (2S) glycidyl toxylate (1.15 g, 5.02 mmol) in presence of cesium carbonate (5.95 g, 18.3 mmol) at 60°C under argon for 2 hours. The solvent was evaporated, water was added, and the mixture was extracted with ethylacetate, dried, concentrated and purified by silica gel chromatography, eluant CH_2Cl_2 / AcOEt 80/20 to 70/30 to give title compound (1.18 g, 94 %).

MS ES^+: 276.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.70 (m, 1H) ; 2.86 (m, 1H) ; 2.95 (s, 3H) ; 3.01 (s, 3H) ; 3.35 (m, 1H) ; 3.75 (s, 3H) ; 3.90 (m, 1H) ; 4.37 (m, 1H) ; 6.75 (s, 1H) ; 7.11 (s, 1H) ; 7.89 (s, 1H).

methyl-(2-tritylamino-1,3-thiazole-5-yl)acetate

Methyl-(2-amino-1,3-thiazole-5-yl)acetate (1 g, 5.8 mmol) in CH_2Cl_2 (15 ml) was reacted with triphenylmethyl chloride (1.73 g, 6.2 mmol) and triethylamine (0.89 ml, 6.4 mmol) at 0°C for 1.5 hour. Water was added to the mixture which was extracted with ethyl acetate, dried, purified by silica gel chromatography to give title compound (2.21 g, 91 %).

^{1}HNMR ($DMSOd_6$): 3.58 (s, 3H) ; 3.59 (s, 2H) ; 6.57 (s, 1H) ; 7.23 (m, 15H) ; 8.40 (s, 1H).

(2-tritylamino-1,3-thiazol-5-yl)acetic acid

Methyl(2-tritylamino-1,3-thiazole-5-yl)acetate (2 g, 4.8 mmol) in THF (10 ml) and ethanol (10 ml) was reacted with sodium hydroxyde (1N, 7.2 ml, 7.2 mmol) at room temperature for 1.5 hour. The solvent was evaporated, HCl (6N) was added, the solid recovered by filtration to give title compound (1.96 g).

^{1}HNMR ($DMSOd_6$): 3.63 (s, 2H) ; 5.70 (s, 1H) ; 7.32 (m, 15H).

N-(4-fluoro-3-chlorophenyl)-2-tritylamino-1,3-thiazole-5-yl)acetamide

(2-tritylamino-1,3-thiazol-5-yl)acetic acid (1.96 g, 4.9 mmol) in DMF (25 ml) was reacted with 3-chloro-4-fluoroaniline (1.07 g, 7.3 mmol) in presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (2.42 g, 6.37 mmol) and DIEA (1.7 ml, 9.8 mmol) at 50°C for 18 hours. DMF was evaporated, the residue taken up in CH_2Cl_2 / EtOAc, washed with a saturated solution of sodium bicarbonate. The solid precipitating in the organic phase was recovered, the organic phase was evaporated, MeOH was added to the residue to give a solid, a second crop of title compound was thus recovered to give together (1.38 g, 53 %).

^{1}HNMR ($DMSOd_6$): 3.56 (s, 2H) ; 6.61 (s, 1H) ; 7.28 (m, 17H) ; 7.88 (m, 1H) ; 8.41 (s, 1H).

N-(4-fluoro-3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide

N-(4-fluoro-3-chlorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide (12.28 g, 23 mmol) was dissolved in TFA (100 ml) and water (10 ml). The mixture was stirred at room temperature for 45 minutes. Water (300 ml) was added to the reaction mixture, a solid was recovered by filtration, washed with water and ether. The solid was dissolved in MeOH, and the solution treated with ammonia (pH 8), MeOH was then partially evaporated, water (300 ml) was added and a precipitate of title compound recovered, dried (5.37 g, 81 %).

^{1}HNMR ($DMSOd_6$): 3.64 (s, 2H) ; 6.76 (m, 3H) ; 7.38 (t, 1H) ; 7.48 (m, 1H) ; 7.92 (m, 1H).

Example 379. Preparation of compound 556 in Table 20

An analogous reaction to that described in example 255 but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-pyrrolidinylpropoxy)-4-methoxyphenyl)-N,N,-dimethylimido-formamide (267 mg, 0.77 mmol) yielded title compound (213 mg, 52 %).

MS ES$^+$: 587.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.68 (m, 4H) ; 2.5 (m, 5H) ; 2.66 (m, 1H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.00 (m, 1H) ; 4.07 (m, 1H) ; 4.20 (m, 1H) ; 4.95 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (s, 1H) ; 7.37 (m, 1H) ; 7.47 (m, 1H) ; 7.95 (m, 1H) ; 8.11 (s, 1H) ; 8.66 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-pyrrolinylpropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide.

An analogous reaction to that described in example 255, but starting with pyrrolidine (1.4 ml, 16 mmol) yielded title compound (2.8 g, 74 %).

MS ES$^+$: 347.6 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 1.67 (m, 4H) ; 1.45 (m, 4H) ; 1.63 (m, 2H) ; 2.95 (s, 3H) ; 3.05 (s, 3H) ; 3.73 (s, 3H) ; 3.95 (m, 2H) ; 4.04 (m, 1H) ; 4.93 (m, 1H) ; 6.73 (s, 1H) ; 7.08 (s, 1H) ; 7.89 (s, 1H).

Example 380. Preparation of compound 557 in Table 20

An analogous reaction to that described in example 255 but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-(4-hydroxypiperidinyl)propoxy)-4-methoxy-phenyl)-N,N-dimethylimidoformamide (195 mg, 0.52 mmol) yielded title compound (88 mg, 30 %).

MS ES$^+$: 617.5, 619.5 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.40 (m, 2H) ; 1.70 (m, 2H) ; 2.13 (m, 2H) ; 2.43 (m, 2H) ; 2.77 (m, 2H) ; 3.43 (m, 1H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.03 (m, 2H) ; 4.19 (m, 1H) ; 4.52 (d, 1H) ; 4.87 (m, 1H) ; 7.27 (s, 1H) ; 7.39 (m, 2H) ; 7.49 (m, 1H) ; 7.99 (m, 1H) ; 8.67 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-(4-hydroxypiperidinyl)propoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide

An analogous reaction to that described in example 255, but starting with 4-hydroxypiperidine (131 mg, 1.27 mmol) yielded title compound (200 mg, 58 %).

MS ES$^+$: 377.6 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.39 (m, 2H) ; 1.68 (m, 2H) ; 2.10 (m, 2H) ; 2.40 (m, 2H) ; 2.75 (m, 2H) ; 2.95 (s, 3H) ; 3.05 (s, 3H) ; 3.21 (s, 3H) ; 3.31 (m, 1H) ; 3.95 (m, 2H) ; 4.00 (m, 1H) ; 4.52 (m, 1H) ; 4.82 (m, 1H) ; 6.73 (s, 1H) ; 7.08 (s, 1H) ; 7.88 (s, 1H).

Example 381. Preparation of compound 558 in Table 20

An analogous reaction to that described in example 255a, but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-(4-tert-butyloxycarbonylpiperazinyl)propoxy)-4-methoxtphenyl)-N,N-dimethylimidoformamide (355 mg, 0.77 mmol) yielded title compound (70 mg, 17 %).

MS ES$^+$: 602.4 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 2.42 (m, 6H) ; 2.73 (d, 4H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.04 (m, 2H) ; 4.19 (m, 1H) ; 4.90 (m, 1H) ; 7.28 (s, 1H) ; 7.37 (m, 2H) ; 7.47 (m, 1H) ; 7.94 (m, 1H) ; 8.11 (s, 1H) ; 8.66 (s, 1H) .

N'-(2-cyano-5-((2S)-2-hydroxy-3-(4-tert-butyloxycarbonylpiperazinyl)propoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide.

An analogous reaction to that described in example 255, but starting with tert-butyloxycarbonylpiperazine (284 mg, 1.53 mmol) yielded title compound (444 mg, 88 %).
MS ES$^+$: 462.6 $(M+H)^+$
^{1}HNMR ($DMSOd_6$): 1.39 (s, 9H) ; 2.40 (m, 6H) ; 2.95 (s, 3H) ; 3.04 (s, 3H) ; 3.30 (m, 4H) ; 3.72 (s, 3H) ; 3.95 (m, 2H) ; 4.02 (m, 1H) ; 4.91 (d, 1H) ; 6.74 (s, 1H) ; 7.09 (s, 1H) ; 7.88 (s, 1H).

Example 382. Preparation of compound 559 in Table 20

An analogous reaction to that described in example 255 , but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-cyclopentylaminopropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide (290 mg, 0.77 mmol) yielded title compound (226 mg, 54 %).
MS ES$^+$: 601.4 $(M+H)^+$
^{1}HNMR ($DMSOd_6$): 1.32 (m, 2H) , 1.48 (m, 2H) ; 1.62 (m, 2H) ; 1.73 (m, 2H) ; 2.63 (m, 1H) ; 2.71 (m, 1H) ; 3.05 (m, 1H) ; 3.89 (s, 2H) ; 3.98 (m, 4H) ; 4.09 (m, 1H) ; 4.17 (m, 1H) ; 5.03 (m, 1H) ; 7.27 (s, 1H) ; 7.40 (m, 2H) ; 7.51 (m, 1H) ; 7.97 (m, 1H) ; 8.12 (s, 1H) ; 8.67 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-cyclopentylaminopropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide.

An analogous reaction to that described in example 255, but starting with cyclopentylamine (2.7 ml, 27 mmol) yielded title compound (1.6 g, 82 %).
MS ES$^+$: 361.6 $(M+H)^+$
^{1}HNMR ($DMSOd_6$): 1.30 (m, 2H) ; 1.48 (m, 2H) ; 1.60 (m, 2H) ; 1.72 (m, 2H) ; 2.56 (m, 1H) ; 2.67 (m, 1H) ; 2.97 (s, 3H) ; 3.01 (m, 1H) ; 3.07 (s, 3H) ; 3.75 (s, 3H) ; 3.89 (m, 1H) ; 4.00 (m, 2H) ; 5.01 (m, 1H) ; 6.75 (s, 1H) ; 7.10 (s, 1H) ; 7.91 (s, 1H).

Example 383. Preparation of compound 560 in Table 20

An analogous reaction to that described in example 255, but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-((2-hydroxy-1,1-dimethylethyl)amino)propoxy-4-methoxyphenyl)-N,N-dimethylimidoformamide (350 mg, 0.77 mmol) yielded title compound (147 mg, 34 %).
MS ES$^+$: 305.4 $(M+H)^+$
^{1}HNMR ($DMSOd_6$): 0.97 (s, 3H) ; 0.98 (s, 3H) ; 2.63 (m, 2H) ; 3.19 (dd, 2H) ; 3.89 (m, 3H) ; 3.98 (s, 3H) ; 4.10 (m, 1H) ; 4.18 (m, 1H) ; 4.56 (m, 1H) ; 7.29 (s, 1H) ; 7.39 (m, 2H) ; 7.50 (m, 1H) ; 7.97 (m, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-((2-hydroxy-1,1-dimethylethyl)amino)propoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide.

An analogous reaction to that described in example 255, but starting with 2-amino-2-methyl-1-propanol (1.8 ml, 18.2 mmol) yielded title compound (1.25 g, 93 %).

^{1}HNMR ($DMSOd_6$): 0.93 (s, 3H) ; 0.94 (s, 3H) ; 2.58 (m, 2H) ; 3.19 (m, 2H) ; 3.73 (s, 3H) ; 3.80 (m, 1H) ; 3.97 (m, 1H) ; 4.03 (m, 1H) ; 4.50 (m, 1H) ; 4.95 (m, 1H) ; 6.75 (s, 1H) ; 7.10 (s, 1H) ; 7.91 (s, 1H).

Example 384. Preparation of compound 561 in Table 20

An analogous reaction to that described in example 255, but starting with N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) and acetic acid (3 ml) yielded title compound (263 mg, 60 %).

MS ES$^+$: 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.37 (m, 2H) ; 1.50 (m, 4H) ; 2.41 (m, 6H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.03 (m, 2H) ; 4.18 (d, 1H) ; 4.88 (m, 1H) ; 7.28 (s, 1H) ; 7.40 (s, 1H) ; 7.40 (m, 2H) ; 7.80 (m, 1H) ; 8.11 (s, 1H) ; 8.66 (s, 1H).

N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 255, but starting with N-(3,4-difluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide (1,75 g, 3.42 mmol) yielded title compound (642 mg, 70 %).

^{1}HNMR ($DMSOd_6$): 3.62 (s, 2H) ; 6.73 (s, 1H) ; 6.74 (s, 2H) ; 7.28 (m, 1H) ; 7.37 (q, 1H) ; 7.77 (m, 1H).

N-(3,4-difluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 255, but starting with 3,4-difluoroaniline (0.97 ml, 9.75 mmol) yielded title compound (1.75 g, 46 %).

MS ES$^+$: 512.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 3.54 (s, 2H) ; 6.58 (s, 1H) ; 7.25 (m, 17H) ; 7.71 (m, 1H) ; 8.39 (s, 1H).

Example 385. Preparation of compound 562 in Table 20

An analogous reaction to that described in example 256 but starting with N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (226 mg, 53 %).

MS ES^+: 571.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.70 (m, 4H) ; 2.52 (m, 5H) ; 2.68 (m, 1H) ; 3.89 (s, 2H) ; 3.98 (s, 3H) ; 4.06 (m, 2H) ; 4.21 (m, 1H) ; 4.95 (m, 1H) ; 7.28 (s, 1H) ; 7.33 (m, 1H) ; 7.39 (s, 1H) ; 7.40 (m, 1H) ; 7.81 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 386. Preparation of compound 563 in Table 20

An analogous reaction to that described in example 257, but starting with N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (220 mg, 49 %).

MS ES^+: 601.5$(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H) ; 1.70 (m, 2H) ; 2.12 (m, 2H) ; 2.40 (m, 2H) ; 2.78 (m, 2H) ; 3.43 (m, 1H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.03 (m, 2H) ; 4.18 (m, 1H) ; 4.51 (d, 1H) ; 4.87 (m, 1H) ; 7.27 (s, 1H) ; 7.32 (m, 1H) ; 7.38 (s, 1H) ; 7.40 (m, 1H) ; 7.80 (m, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H).

Example 387. Preparation of compound 565 in Table 20

An analogous reaction to that described in example 259, but starting with N-(3,4-difluorophenyl)-2-(2(amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (233 mg, 53 %).

MS ES^+: 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.32 (m, 2H) ; 1.47 (m, 2H) ; 1.61 (m, 2H) ; 1.72 (m, 2H) ; 2.63 (m, 1H) ; 2.72 (m, 1H) ; 3.05 (m, 1H) ; 3.89 (s, 2H) ; 3.97 (m, 4H) ; 4.09 (m, 1H) ; 4.16 (m, 1H) ; 5.05 (m, 1H) ; 7.27 (s, 1H) ; 7.34 (m, 1H) ; 7.38 (s, 1H) ; 7.42 (m, 1H) ; 7.82 (m, 1H) ; 8.12 (s, 1H) ; 8.67 (s, 1H).

Example 388. Preparation of compound 566 in Table 20

An analogous reaction to that described in example 256 but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (238 mg, 56 %).

MS ES$^+$: 569.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.70 (s, 1H) ; 2.52 (m, 5H) ; 2.68 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.06 (m, 2H) ; 4.21 (m, 1H) ; 4.97 (m, 1H) ; 7.14 (d, 1H) ; 7.27 (s, 1H) ; 7.37 (m, 2H) ; 7.48 (d, 1H) ; 7.85 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 255, but starting with N-(3-chlorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide (3.62 g, 7.1 mmol) yielded title compound (1.6 g, 84 %).

^{1}HNMR ($DMSOd_6$): 3.63 (s, 2H) ; 6.74 (m, 3H) ; 7.11 (m, 1H) ; 7.33 (t, 1H) ; 7.42 (d, 1H) ; 7.79 (m, 1H).

N-(3-chlrophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 255, but starting with 3-chloroaniline (1.4 ml, 13 mmol) yielded title compound (3.62 g, 71 %).

^{1}HNMR ($DMSOd_6$): 3.55 (s, 2H) ; 6.59 (s, 1H) ; 7.21 (m, 18H) ; 7.76 (m, 1H) ; 8.39 (s, 1H).

Example 389. Preparation of compound 567 in Table 20

An analogous reaction to that described in example 257, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.75 mmol) yielded title compound (156 mg, 35 %).

MS ES$^+$: 599.4, 601.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H) ; 1.70 (m, 2H) ; 2.12 (m, 2H) ; 2.42 (m, 2H) ; 2.77 (m, 2H) ; 3.42 (m, 1H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.02 (m, 2H) ; 4.18 (m, 1H) ; 4.52 (d, 1H) ; 4.89 (m, 1H) ; 7.12 (d, 1H) ; 7.26 (s, 1H) ; 7.35 (t, 1H) ; 7.38 (s, 1H) ; 7.46 (d, 1H) ; 7.84 (m, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H).

Example 390. Preparation of compound 568 in Table 20

An analogous reaction to that described in example 259, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.75 mmol) yielded title compound (255 mg, 58 %).

MS ES$^+$: 583.5, 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.32 (m, 2H) ; 1.48 (m, 2H) ; 1.62 (m, 2H) ; 1.73 (m, 2H) ; 2.63 (m, 1H) ; 2.72 (m, 1H) ; 3.04 (m, 1H) ; 3.90 (s, 2H) ; 3.97 (m, 4H) ; 4.09 (m, 1H) ; 4.16 (m, 1H) ; 5.05 (m, 1H) ; 7.12 (d, 1H) ; 7.27 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 391. Preparation of compound 569 in Table 20

An analogous reaction to that described in example 260, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (130 mg, 30 %).

MS ES$^+$: 587.5, 589.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 0.97 (s, 6H) ; 2.63 (m, 2H) ; 3.19 (m, 2H) ; 3.90 (m, 3H) ; 3.98 (s, 3H) ; 4.10 (m, 1H) ; 4.18 (m, 1H) ; 4.55 (m, 1H) ; 5.03 (m, 1H) ; 7.13 (d, 1H) ; 7.29 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (d, 1H) ; 7.86 (m, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H).

Example 392. Preparation of compound 570 in Table 20

An analogous reaction to that described in example 258, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.75 mmol) yielded title compound (211 mg, 48 %).

MS ES$^+$: 584.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.37 (m, 6H) ; 2.70 (m, 4H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.05 (m, 2H) ; 4.19 (m, 1H) ; 4.90 (m, 1H) ; 7.12 (d, 1H) ; 7.27 (s, 1H) ; 7.35 (t, 1H) ; 7.37 (s, 1H) ; 7.47 (d, 1H) ; 7.84 (m, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H).

Example 393. Preparation of compound 571 in Table 20

An analogous reaction to that described in example 266, but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-methoxy)propoxy-4-methoxyphenyl)-N,N-dimethyl imidoformamide (252 mg, 0.82 mmol) yielded title compound (200 mg, 50 %).

MS ES$^+$: 530.4, 532.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 3.22 (s, 3H) ; 3.42 (m, 2H) ; 3.91 (s, 2H) ; 3.98 (s, 2H) ; 4.10 (m, 3H) ; 5.21 (d, 1H) ; 7.13 (d, 1H) ; 7.26 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (d, 1H) ; 7.85 (m, 1H) ; 8.13 (m, 1H) ; 8.69 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-methoxy)propoxy-4-methoxy-phenyl)-N,N-dimethylimidoformamide.

N'-(2-cyano-5-(2S)-oxiranylmethoxy-4-methoxyphenyl)-N,N-dimethylimidoformamide (1 g, 3.6 mmol) in methanol (80 ml) was treated with sodium methoxide (10 g, 218 mmol) at reflux in a microwave oven for 0.5 hour. The solvent was evaporated and the mixture purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH 95/5 to give title compound (896 mg, 80 %).

^{1}HNMR ($DMSOd_6$): 2.97 (s, 1H) ; 3.07 (s, 1H) ; 3.29 (s, 1H) ; 3.38 (m, 2H) ; 3.75 (s, 3H) ; 3.98 (m, 3H) ; 5.16 (d, 1H) ; 6.75 (s, 1H) ; 7.10 (s, 1H) ; 7.93 (s, 1H).

Example 394. Preparation of compound 572 in Table 20

An analogous reaction to that described in example 255, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.75 mmol) yielded title compound (268 mg, 61 %).

MS ES$^+$: 583.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.38 (m, 2H) ; 1.50 (m, 4H) ; 2.43 (m, 6H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.05 (m, 2H) ; 4.21 (m, 1H) ; 4.88 (m, 1H) ; 7.14 (d, 1H) ; 7.29 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (d, 1H) ; 7.85 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 395. Preparation of compound 573 in Table 20

An analogous reaction to that described in example 255, but starting with N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (157 mg, 36 %).

MS ES$^+$: 585.5 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.37 (m, 2H) ; 1.50 (m, 4H) ; 2.40 (m, 6H) ; 3.90 (s, 2H) ; 3.96 (s, 3H) ; 4.05 (m, 2H) ; 4.19 (m, 1H) ; 4.88 (m, 1H) ; 6.92 (m, 1H) ; 7.28 (s, 1H) ; 7.34 (m, 2H) ; 7.38 (s, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H).

N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl) acetamide

An analogous reaction to that described in example 255, but starting with N-(3,5-difluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide (11.4 g, 28.5 mmol) yielded title compound (4.75 g, 62 %).

^{1}HNMR (DMSOd_6: 3.64 (s, 2H) ; 6.74 (s, 1H) ; 6.76 (s, 2H) ; 6.89 (m, 1H) ; 7.29 (m, 2H).

N-(3,5-difluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 255, but starting with 3,5-difluoroaniline (1.68 g, 13 mmol) yielded title compound (3.53 g, 69 %).

^{1}HNMR (DMSOd_6: 3.56 (s, 2H) ; 6.59 (s, 1H) ; 6.90 (m, 1H) ; 7.28 (m, 17H) ; 8.40 (s, 1H).

Example 396. Preparation of compound 574 in Table 20

An analogous reaction to that described in example 256 but starting with N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (200 mg, 47 %).

MS ES$^+$: 571.5 $(M+H)^+$

^{1}HNMR (DMSOd_6: 1.65 (m, 4H) ; 2.50 (m, 5H) ; 2.65 (m, 1H) ; 3.91 (s, 1H) ; 3.96 (s, 3H) ; 4.04 (m, 2H) ; 4.20 (m, 1H) ; 4.95 (m, 1H) ; 6.92 (m, 1H) ; 7.26 (s, 1H) ; 7.34 (m, 2H) ; 7.38 (s, 1H) ; 8.11 (s, 1H) ; 8.66 (s, 1H).

Example 397. Preparation of compound 575 in Table 20

An analogous reaction to that described in example 260 but starting with N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (177 mg, 40 %).

MS ES$^+$: 589.4 $(M+H)^+$

^{1}HNMR (DMSOd_6: 0.96 (s, 3H) ; 0.97 (s, 3H) ; 2.64 (m, 2H) ; 3.19 (dd, 2H) ; 3.92 (m, 3H) ; 3.98 (s, 3H) ; 4.09 (m, 1H) ; 4.20 (m, 1H) ; 4.56 (m, 1H) ; 5.05 (m, 1H) ; 6.94 (m, 1H) ; 7.29 (s, 1H) ; 7.35 (m, 2H) ; 7.39 (s, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 398. Preparation of compound 576 in Table 20

An analogous reaction to that described in example 258 but starting with N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (40 mg, 9 %).

MS ES^+: 628.5 $(M+H)^+$

^{1}HNMR (DMSOd_6: 2.05 (s, 3H) ; 2.40 (m, 4H) ; 2.57 (m, 2H) ; 2.69 (m, 4H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.35 (m, 2H) ; 5.31 (m, 1H) ; 6.93 (m, 1H) ; 7.33 (s, 1H) ; 7.35 (m, 2H) ; 7.39 (s, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H).

Example 399. Preparation of compound 577 in Table 20

An analogous reaction to that described in example 258 but starting with N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (192 mg, 44 %).

MS ES^+: 586.5 $(M+H)^+$

^{1}HNMR (DMSOd_6: 2.42 (m, 6H) ; 2.74 (m, 4H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.09 (m, 2H) ; 4.20 (m, 1H) ; 4.92 (m, 1H) ; 6.93 (m, 1H) ; 7.29 (s, 1H) ; 7.35 (m, 2H) ; 7.39 (s, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 400. Preparation of compound 578 in Table 20

An analogous reaction to that described in example 256 but starting with N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.8 mmol) yielded title compound (156 mg, 35 %).

MS ES^+: 553.5 $(M+H)^+$

^{1}HNMR (DMSOd_6: 1.70 (m, 4H) ; 2.5 (m, 5H) ; 2.67 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.06 (m, 2H) ; 4.20 (m, 1H) ; 4.97 (m, 1H) ; 6.92 (m, 1H) ; 7.28 (m, 1H) ; 7.35 (m, 2H) ; 7.39 (s, 1H) ; 7.63 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide

An analogous reaction to that described in example 255 but starting with N-(3-fluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide (14.6 g, 38.4 mmol) yielded title compound (6.21 g, 65 %).

^{1}HNMR (DMSOd_6: 3.65 (s, 2H) ; 6.76 (m, 3H) ; 6.89 (t, 1H) ; 7.35 (m, 2H) ; 7.59 (d, 1H).

N-(3-fluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 255 but starting with 3-fluoroaniline yielded title compound (14.6 g, 79 %).

^{1}HNMR (DMSOd_6: 3.56 (s, 2H) ; 6.61 (s, 1H) ; 6.89 (t, 1H) ; 7.25 (m, 17H) ; 7.56 (d, 1H) ; 8.41 (s, 1H).

Example 401. Preparation of compound 579 in Table 20

An analogous reaction to that described in example 255 but starting with N-(3-fluororphenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.8 mmol) yielded title compound (214 mg, 47 %).

MS ES$^+$: 567.6 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.38 (m, 2H) ; 1.52 (m, 4H) ; 2.42 (m, 6H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.04 (m, 2H) ; 4.20 (m, 1H) ; 4.89 (m, 1H) ; 6.91 (m, 1H) ; 7.29 (s, 1H) ; 7.37 (m, 2H) ; 7.39 (s, 1H) ; 7.63 (m, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H).

Example 402. Preparation of compound 580 in Table 20

An analogous reaction to that described in example 258 but starting with N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.8 mmol) yielded title compound (210 mg, 46 %).

MS ES$^+$: 568.5 $(M+H)^+$

^{1}HNMR (DMSOd_6: 2.38 (m, 6H) ; 2.70 (m, 4H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.02 (m, 2H) ; 4.19 (m, 1H) ; 4.98 (m, 1H) ; 6.89 (m, 1H) ; 7.27 (s, 1H) ; 7.32 (m, 2H) ; 7.37 (s, 1H) ; 7.61 (m, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H).

Example 403. Preparation of compound 581 in Table 20

An analogous reaction to that described in example 258 but starting with N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.8 mmol) yielded title compound (35 mg, 7 %).

MS ES$^+$: 610.5 $(M+H)^+$

^{1}HNMR (DMSOd_6: 2.03 (s, 3H) ; 2.38 (m, 4H) ; 2.57 (m, 2H) ; 2.69 (m, 4H) ; 3.88 (s, 2H) ; 3.95 (s, 3H) ; 4.34 (m, 2H) ; 5.30 (m, 1H) ; 6.89 (m, 1H) ; 7.31 (s, 1H) ; 7.34 (m, 2H) ; 7.37 (s, 1H) ; 7.62 (m, 1H) ; 8.11 (s, 1H) ; 8.66 (s, 1H).

Example 404. Preparation of compound 582 in Table 20

An analogous reaction to that described in example 259 but starting with N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.8 mmol) yielded title compound (196 mg, 43 %).

MS ES^+ : 567.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 1.30 (m, 2H) ; 1.47 (m, 2H) ; 1.61 (m, 2H) ; 1.73 (m, 3H) ; 2.62 (m, 1H) ; 2.71 (m,1H) ; 3.0 (m, 1H) ; 3.89 (m, 1H) ; 3.97 (s, 3H) ; 4.07 (m, 1H) ; 4.13 (m, 1H) ; 5.03 (m, 1H) ; 6.90 (m, 1H) ; 7.25 (s, 1H) ; 7.35 (m, 2H) ; 7.37 (s, 1H) ; 7.62 (m, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H).

Example 405. Preparation of compound 583 in Table 21

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6,7-dimethoxyquinazoline (173 mg, 0.5 mmol) in NMP (2 ml) was reacted with 3,5-difluoroaniline (98 mg, 0.75 mmol) in the presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (285 mg, 0.75 mmol) and DIEA (130 µl, 0.75 mmol) at 50°C for 20 hours. The mixture was cooled, dimethylamine (2M MeOH, 2 ml) was added, and the resulting solution was stirred at room temperature for 15 hours, MeOH was evaporated, and water (20 ml) added to the mixture, the precipitate was recovered, washed with water, and purified by silicagel chromatography, eluant CH_2Cl_2 / MeOH 50/40/10 to give title compound (22 mg, 10 %).

^{1}HNMR ($DMSOd_6$) : 3.90 (s, 2H) ; 3.95 (s, 6H) ; 6.93 (t, 1H) ; 7.26 (s, 1H) ; 7.34 (d, 2H) ; 7.39 (s, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6,7-dimethoxyquinazoline

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6,7-dimethoxyquinazoline (3.92 g, 10.9 mmol) in ethanol 50 ml was treated with sodium hydroxyde (2N, 27 ml, 54.5 mmol) for 45 minutes. The solvent was evaporated, the residue dissolved in CH_2Cl_2 / MeOH triethylamine (3 eq.) was added the solid removed by filtration, the filtrate was evaporated and triturated with ethanol to give title compound as a solid (1.88 g, 50 %).

^{1}HNMR ($DMSOd_6$) : 3.83 (s, 2H) ; 3.96 (s, 6H) ; 7.27 (s, 1H) ; 7.35 (s, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H).

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6,7-dimethoxyquinazoline

N'-(2-cyano-4,5-dimethoxyphenyl)-N,N-dimethylimidoformamide (3.5 g, 15 mmol) in acetic acid (35 ml) was reacted with methyl (2-amino-1,3-thiazole-5-yl)acetate (3.22 g, 18.7 mmol)

at reflux for 4 hours. The solvent was evaporated and the residue purified by silicagel chromatography, Eluant CH_2Cl_2 / MeOH 95/5 to give title compound (3.92 g, 73 %).
^{1}HNMR ($DMSOd_6$) : 3.69 (s, 3H) ; 3.95 (s, 2H) ; 3.96 (s, 6H) ; 7.27 (s, 1H) ; 7.38 (s, 1H) ; 8.12 (s, 1H) ; 8.69 (s, 1H).

Example 406. Preparation of compound 584 in Table 21

An analogous reaction to that described in example 283 but starting with 3-chloroaniline (80 µl, 0.75 mmol) yielded title compound (81 mg, 26 %).
MS ES$^+$: 456.4, 458.4 $(M+H)^+$
^{1}HNMR ($DMSOd_6$) : 3.91 (s, 2H) ; 3.96 (s, 6H) ; 7.14 (d, 1H) ; 7.28 (s, 1H) ; 7.37 (t, 1H) ; 7.48 (d, 1H) ; 7.85 (m, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H).

Example 407. Preparation of compound 585 in Table 21

An analogous reaction to that described in example 283 but starting 3-chloro-4-fluoroaniline (110 mg, 0.75 mmol) yielded title compound (93.7 mg, 40 %).
MS ES$^+$: 474.4, 476.4 $(M+H)^+$
^{1}HNMR : 3.90 (s, 2H) ; 3.97 (s, 3H) ; 7.28 (s, 1H) ; 7.40 (m, 1H) ; 7.40 (s, 1H) ; 7.50 (m, 1H) ; 7.96 (m, 1H) ; 8.14 (s, 1H) ; 8.70 (s, 1H).

Example 408. Preparation of compound 586 in Table 21

An analogous reaction to that described in example 283 but starting 3,4-difluoroaniline (75 mg, 0.75 mmol) yielded title compound (130 mg, 60 %).
MS ES$^+$: 458.5 $(M+H)^+$
^{1}HNMR : 3.89 (s, 2H) ; 3.97 (s, 6H) ; 7.28 (s, 1H) ; 7.33 (m, 1H) ; 7.40 (s, 1H) ; 7.41 (m, 1H) ; 7.82 (m, 1H) ; 8.14 (s, 1H) ; 8.69 (s, 1H).

Example 409. Preparation of compound 587 in Table 22

4-((2-amino-1,3-thiazole-5-yl)(hydroxy)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (143 mg, 0.3 mmol) in DMF (4 ml) was reacted with aniline (36 mg, 0.39 mmol) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (63 mg, 0.33 mmol), 2-hydroxypyridine N-oxyde (33 mg, 0.3 mmol) and DIEA (36 mg, 0.3 mmol) at 90°C for 1 hour. The mixture was cooled, diluted with CH_2Cl_2 (8 ml) and purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH 90/10 to 85/15. The combined fractions

containing product were evaporated, the residue was dissolved in MeOH, water was added and the precipitate recovered, dissolved in MeOH / CH_2Cl_2, dried, concentrated to give title compound (145 mg, 88 %).

MS ES$^+$: 551.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.71 (t, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.31 (t, 2H) ; 5.47 (s, 1H) ; 7.11 (t, 1H) ; 7.31 (s, 1H) ; 7.33 (t, 2H) ; 7.70 (s, 1H) ; 7.73 (d, 2H) ; 7.92 (s, 1H) ; 9.12 (s, 1H).

4-(2-amino-1,3-thiazole-5-yl)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.

N'-(2-cyano-4-methoxy-5-(3-morpholinopropoxy)phenyl)-N,N-dimethylimidoformamide (692 mg, 2 mmol) was reacted with amino-1,3-thiazole (240 mg, 2.4 mmol) in acetic acid (6.9 ml) at reflux for 4 hours. The mixture was concentrated, the residue dissolved in AcOEt, washed with aqueous sodium bicarbonate, the organic phase was dried, concentrated, the residual oil triturated in ether to give a solid (560 mg, 70 %).

MS ES$^+$: 402.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.29 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.31 (t, 2H) ; 7.32 (s, 1H) ; 7.47 (d, 1H) ; 7.75((d, 1H) ; 7.95 (s, 1H) ; 9.11 (s, 1H).

4-((2-amino-1,3-thiazole-5-yl)(hydroxy)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.

4-(2-amino-1,3-thiazole-5-yl)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (1.6 g, 4 mmol) in water (16 ml), MeOH (16 ml), was reacted with glyoxylic acid (740 mg, 8 mmol) at pH 11.5 (NaOH 6N) and 45-50°C for 6 hours. Methanol was evaporated, and the pH of the aqueous phase adjusted to 3 (HCl 6N), and the solution poured on a strong cation exchanger (isolute®) column, washed with water (120 ml), methanol (120 ml) and eluted with CH_2Cl_2/ MeOH, NH_3 (3N) 1/1 200 ml to give title compound (1.58 g, 83 %).

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.15 (t,2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.30 (t, 2H) ; 5.38 (s, 1H) ; 7.32 (s, 1H) ; 7.68 (s, 1H) ; 7.91 (s, 1H) ; 9.12 (s, 1H).

Example 410. Preparation of compound 588 in Table 22

An analogous reaction to that described in example 287 but starting with 3,4(difluoroaniline (34 mg, 0.26 mmol) yielded title compound (30 mg, 26 %).

MS ES$^+$: 587.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.69 (t, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 5.48 (s, 1H) ; 7.32 (s, 1H) ; 7.40 (q, 1H) ; 7.57 (m, 1H) ; 7.70 (s, 1H) ; 7.92 (m, 2H) ; 9.12 (s, 1H).

Example 411. Preparation of compound 589 in Table 22

N'-(2-cyano-4-methoxy-5-(3-N-methylpiperazinylpropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide (144 mg, 0.4 mmol) was reacted with N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)-2-hydroxyacetamide (137 mg, 0.4 mmol) in acetic acid (350 µl) at reflux for 40 minutes. The solvent was removed, and the residue purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH / Et3N, 90.10.1 to give title compound (180 mg, 37 %).

MS ES$^+$: 600.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.30 (t, 2H) ; 5.48 (s, 1H) ; 7.32 (s, 1H) ; 7.40 (q, 1H) ; 7.57 (m, 1H) ; 7.70 (s, 1H) ; 7.92 (m, 2H) ; 9.12 (s, 1H).

Methyl(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)acetate

Methyl(2-amino-1,3-thiazol-5-yl)acetate (4.3 g, 25 mmol) was reacted with di-tert-butyl dicarbonate (10.9 g, 50 mmol) neat, at 100°C for 2 hours. The cold mixture was triturated in ether to give title compound as a solid (4.3 g, 63 %).

^{1}HNMR (DMSOd_6): 1.48 (s, 9H) ; 3.66 (s, 3H) ; 3.86 (s, 2H) ; 7.17 (s, 1H).

Methyl(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)(oxo)acetate.

Methyl(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)acetate (4.08 g, 15 mmol) in dioxane (60 ml) was reacted with selenium dioxide (4 g, 36 mmol) at reflux for 45 minutes. The mixture was cooled, CH_2Cl_2 / MeOH 8/2 (150 ml) was added, the insoluble material was filtered, the organic phase was washed with a saturated solution of sodium bicarbonate, and extracted with CH_2Cl_2, dried, purified by chromatography over alumina, eluant CH_2Cl_2 / MeOH 9/1 to give title compound (1 g, 23 %).

^{1}HNMR (DMSOd_6): 1.57 (s, 9H) ; 3.94 (s, 3H) ; 8.48 (s, 1H).

(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)(oxo)acetic acid.

Methyl(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)(oxo)acetate (1.14 g, 4 mmol) in ethanol (10 ml) was treated with sodium hydroxyde (2N, 4 ml, 8 mmol) for 3M minutes at room temperature. Ethanol was removed, the aqueous solution was acidified (pH 3). The solid was recovered, dried to give title product (900 mg, 82 %).

^{1}HNMR ($DMSOd_6$): 1.53 (s, 9H) ; 8.41 (s, 1H).

N-(3,4-difluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)(oxo)acetamide

2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)(oxo)acetic acid (136 mg, 0.5 mmol) in DMF (2 ml) was reacted with 3,4-difluoroaniline (77 mg, 0.6 mmol) in presence of 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (203 mg, 0.55 mmol) and DIEA (77 mg, 0.6 mmol) for 15 minutes. The mixture was diluted with water, the solid was filtered, washed with water, dried, to give title compound (162 mg, 84 %).

^{1}HNMR ($DMSOd_6$): 1.53 (s, 9H) ; 7.48 (q, 1H) ; 7.68 (m, 1H) ; 7.98 (m, 1H) ; 8.61 (s, 1H).

N-(3,4-difluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide.

N-(3,4-difluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl) (oxo) acetamide (938 mg, 2.4 mmol) in THF (50 ml) and MeOH (10 ml) was treated with sodium borohydride (93 mg, 2.4 mmol) for 30 minutes. The mixture was evaporated, the residue dissolved in ethanol (3 ml) water (25 ml) was added, and the pH adjusted to 6, more water was added, a solid was recovered, dried, recristalized in ether / petroleum ether to give title compound (850 mg, 90 %).

^{1}HNMR ($DMSOd_6$): 1.48 (s, 9H) ; 5.34 (d, 1H) ; 6.78 (d, 1H) ; 7.33 (s, 1H) ; 7.40 (s, 1H) ; 7.56 (m, 1H) ; 7.90 (m, 1H).

N-(3,4-difluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide (847 mg, 2.2 mmol) in CH_2Cl_2 (12 ml) and TFA (4 ml) was stirred at room temperature for 3 hours. The solvent was evaporated, the residue dissolved in MeOH / H_2O, the pH adjusted to 7 and the mixture was extracted with ethyl acetate. The organic layer was dried, evaporated, the residue was triturated in ether, the solid filtered to give title compound (515 mg, 82 %).

^{1}HNMR ($DMSOd_6$): 5.17 (d, 1H) ; 6.51 (d, 1H) ; 6.91 (m, 3H) ; 7.39 (s, 1H) ; 7.52 (m, 1H) ; 7.87 (m, 1H).

Example 412. Preparation of compound 590 in Table 22

N'-(2-cyano-4-methoxy-5-(3-piperidinylpropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide (100 mg, 0.29 mmol) was reacted with N-(3-fluorophenyl)-2-(2-

amino-1,3-thiazole-5-yl)-2-hydroxyacetamide (82 mg, 0.3 mmol) in acetic acid (260 mg) at 105°C for 40 minutes. The mixture was evaporated and purified by silica gel chromatography, eluant CH_2Cl_2 / MeOH (NH_3 3N) 9/1 to give title compound (42 mg, 26 %).

MS ES^+: 567.5 $(M+H)^+$.

^{1}HNMR ($DMSOd_6$): 1.4 (m, 2H) ; 1.51 (m, 4H) ; 1.95 (t, 2H) ; 2.40 (m, 6H) ; 3.95 (s, 3H) ; 4.19 (t, 2H) ; 5.41 (d, 1H) ; 6.78 (d, 1H) ; 6.91 'm, 1H) ; 7.25 (s, 1H) ; 7.35 (q, 1H) ; 7.50 (s, 1H) ; 7.55 (d, 1H) ; 7.71 (m, 1H) ; 8.10 (s, 1H) ; 8.68 (s, 1H).

N'-(2-cyano-4-methoxy-5-(3-piperidinylpropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide.

N'-(2-cyano-4-methoxy-5-(3-chloropropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide (3 g, 10 mmol) in acetonitrile (50 ml) was reacted with piperidine (10 ml, 100 mmol) in presence of KI (300 mg, 1.8 mmol) and K_2CO_3 (2.1 g, 0.015 mmol) at 75°C under argon for 3 hours. The solvent was evaporated, and the residue purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH, NH_3 3N 95/5 to give title compound (3.48 g, 100 %).

MS ES^+: 345.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.4 (m, 2H) ; 1.50 (m, 4H) ; 1.88 (m, 2H) ; 2.35 (m, 6H) ; 2.95 (s, 3H) ; 3.05 (s, 3H) ; 3.72 (s, 3H) ; 4.05 (t, 2H) ; 6.72 (s, 1H) ; 7.07 (s, 1H) ; 7.89 (s, 1H).

N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)-2-hydroxyacetomide.

An analogous reaction to that described in example 289, but starting with N-(3-fluorobenzyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide (2.55 g, 0.69 mmol) yielded title compound (1.37 g, 75 %).

MS ES^+: 268.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 5.16 (d, 1H) ; 6.45 (d, 1H) ; 6.90 (m, 4H) ; 7.34 (q, 1H) ; 7.49 (d, 1H) ; 7.70 (m, 1H).

N-(3-fluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide.

An analogous reaction to that described in example 289, but starting with N-(3-fluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl) (oxo) acetamide (2.92 g, 8 mmol) yielded title compound (2.59 g, 88 %).

^{1}HNMR ($DMSOd_6$): 1.48 (s, 9H) ; 5.34 (d, 1H) ; 6.74 (d, 1H) ; 6.90 (m, 1H) ; 7.33 (m, 2H) ; 7.54 (d, 1H) ; 7.70 (m, 1H).

N-(3-fluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl) (oxo) acetamide.

An analogous reaction to that described in example 289, but starting with 3-fluoroaniline (1.6 g, 14.4 mmol) yielded title compound (4.06 g, 93 %).

^{1}HNMR (DMSOd_6): 1.54 (s, 9H) ; 7.01 (m, 1H) ; 7.42 (m, 1H) ; 7.69 (m, 1H) ; 7.80 (m, 1H) ; 8.6 (s, 1H).

Example 413. Preparation of compound 591 in Table 22

An analogous reaction to that described in example 290, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)-2-hydroxyacetamide (99 mg, 0.35 mmol) yielded title compound (47 mg, 23 %).

MS ES$^+$: 583.4 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 1.38 (m, 2H) ; 1.51 (m, 4H) ; 1.95 (m, 2H) ; 2.38 (m, 6H) ; 3.95 (s, 3H) ; 4.19 (t, 2H) ; 5.40 (d, 1H) ; 6.79 (d, 1H) ; 7.14 (d, 1H) ; 7.24 (s, 1H) ; 7.35 (t, 1H) ; 7.50 (s, 1H) ; 7.67 (d, 1H) ; 7.95 (s, 1H) ; 8.10 (s, 1H) ; 8.68 (s, 1H).

N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)-2-hydroxyacetamide.

An analogous reaction to that described in example 290, but starting with N-(3-chlorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide (2.13 g, 5.5 mmol) yielded title compound (1.02 g, 65 %).

^{1}HNMR (DMSOd_6): 5.15 (d, 1H) ; 6.45 (d, 1H) ; 6.90 (m, 3H) ; 7.12 (dd, 1H) ; 7.33 (t, 1H) ; 7.62 (d, 1H) ; 7.89 (m, 1H).

N-(3-chlorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide.

An analogous reaction to that described in example 290, but starting with N-(3-chlorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl) (oxo) acetamide (2.5 g, 6.5 mmol) yielded title compound (2.23 g, 89 %).

^{1}HNMR (DMSOd_6): 1.48 (s, 9H) ; 5.34 (d, 1H) ; 6.74 (d, 1H) ; 7.14 (m, 1H) ; 7.34 (m, 2H) ; 7.65 (m, 1H) ; 7.92 (m, 1H).

N-(3-chlorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl) (oxo) acetamide.

An analogous reaction to that described in example 290, but starting with 3-chloroaniline (1.84 g, 14 mmol) yielded title compound (3.6 g, 79 %).

^{1}HNMR (DMSOd_6): 1.54 (s, 9H) ; 7.24 (d, 1H) ; 7.43 (t, 1H) ; 7.79 (d, 1H) ; 8.03 (s, 1H) ; 8.61 (s, 1H).

Example 414. Preparation of compound 592 in Table 22

N'-(2(cyano-4-methoxy-5-(N-methyl-3-piperazinylpropoxyphenyl)-N,N-dimethylimidoformamide (140 mg, 0.39 mmol) in acetic acid (0.5 ml) in presence of N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)-2-(hydroxyimino)acetamide (116 mg, 0.39 mmol) was heated at 110°C for 16 hours. The mixture was concentrated and purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH, HN_3 3N 95/5 to 90/10, to give title compound (23 mg, 10 %).

MS ES^+: 613.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.0 (m, 2H) ; 2.22 (s, 3H) ; 2.47 (m, 10H) ; 4.0 (s, 3H) ; 4.22 (t, 2H) ; 7.29 (m, 1H) ; 7.47 (m, 1H) ; 7.57 (m, 1H) ; 7.97 (m, 1H) ; 8.2 (s, 1H) ; 8.38 (s, 1H) ; 8.80 (s, 1H).

N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazol-5-yl)-2-(hydroxyimino)acetamide.

N-(3,4-difluorophenyl)-2-(2-tert-butoxycarbonyl-amino-1,3-thiazol-5-yl)-2-(hydroxyimino)acetamide (600 mg, 1.5 mmol) in CH_2Cl_2 (12 ml) and TFA (4 ml) was stirred at room temperature for 2 hours. The mixture was evaporated, dissolved in methanol, the pH adjusted to 6 with sodium bicarbonate, water was added, the precipitate recovered, dried to give title compound (388 mg, 86 %).

MS ES^+ : 299.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) mixture of isomers 7.05, 7.8 (2s, 1H) ; 7.43 (m, 4H) ; 7.88 (m, 1H).

N-(3,4-difluorophenyl)-2-(2-tert-butoxycarbonyl-amino-1,3-thiazole-5-yl)-2-(hydroxyimino)acetamide.

N-(3,4-difluorophenyl)-2-(2-tert-butoxycarbonyl-amino-1,3-thiazole-5-yl) (oxo) acetamide (100 mg, 0.26 mmol) in pyridine (8 ml) was reacted with hydroxylamine hydrochloride (27 mg, 0.39 mmol) at 70°C for 15 hours. The solvent was evaporated, water was added to the residue, the solid was filtered, washed with water, dried to give title compound (84 mg, 81 %).

^{1}HNMR ($DMSOd_6$) mixture of isomers 7.41, 8.18 (2s, 1H) ; 7.50 (m, 2H) ; 7.90 (m, 1H).

Example 415. Preparation of compound 593 in Table 23

5-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)thiophene-2-carboxylic acid (80 mg, 0.18 mmol) in DMF (2 ml) was reacted with 2-aminopyridine (17 mg, 0.18 mmol) in presence of 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (70 mg, 0.18 mmol) and DIEA (80 µl, 0.46 mmol), at 50°C for 6 hours. A saturated solution

of sodium bicarbonate (2 ml) was added and the mixture stirred for 0.5 hour. A solid is recovered by filtration, washed with water, dried to give title compound (15 mg, 16 %).

MS ES$^+$: 521 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.32 (t, 2H) ; 7.43 (m, 2H) ; 7.53 (t, 1H) ; 7.94 (d, 1H) ; 8.21 (m, 2H) ; 8.35 (t, 1H) ; 8.49 (d, 1H) ; 9.30 (s, 1H).

Example 416. Preparation of compound 594 in Table 23

An analogous reaction to that described in example 293, but starting with 4-methylaniline (19 mg, 0.18 mmol) yielded title compound (69 mg, 72 %).

MS ES$^+$: 535 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.34 (s, 3H) ; 2.40 (t, 2H) ; 3.11 (t, 2H) ; 3.38 (t, 2H) ; 3.60 (d, 2H) ; 3.90 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.35 (t, 2H) ; 7.15 (d, 2H) ; 7.27 (d, 1H) ; 7.52 (s, 1H) ; 7.62 (d, 2H) ; 7.85 (d, 1H) ; 8.15 (s, 1H) ; 8.87 (s, 1H).

Example 417. Preparation of compound 595 in Table 23

An analogous reaction to that described in example 293, but starting 2-methylaniline (19 mg, 0.18 mmol) yielded title compound (28 mg, 29 %).

MS ES$^+$: 535 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2/28 (s, 3H) ; 2.32 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.05 (d, 2H) ; 4.07 (s, 3H) ; 7.30 (m, 4H) ; 7.35 (d, 1H) ; 7.41 (s, 1H) ; 7.96 (d, 1H) ; 8.22 (s, 1H) ; 9.26 (s, 1H).

Example 418. Preparation of compound 596 in Table 23

An analogous reaction to that described in example 293, but starting 3-methoxyaniline (22 mg, 0.18 mmol) yielded title compound (14 mg, 14 %).

MS ES$^+$: 550.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 3.78 (s, 3H) ; 4.04 (d, 2H) ; 4.06 (s, 3H) ; 4.33 (t, 2H) ; 6.7 (d, 1H) ; 7.28 (s, 1H) ; 7.35 (s, 1H) ; 7.36 (d, 1H) ; 7.41 (s, 1H) ; 7.45 (s, 1H) ; 8.01 (d, 1H) ; 8.22 (s, 1H) ; 9.27 (s, 1H).

Example 419. Preparation of compound 597 in Table 23

An analogous reaction to that described in example 293, but starting 2-hydroxymethyl-aniline (22 mg, 0.18 mmol) yielded title compound (7 mg, 7 %).

MS ES$^+$: 550.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (m, 2H) ; 3.18 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.06 (m, 5H) ; 4.32 (t, 2H) ; 4.65 (s, 2H) ; 7.22 (t, 1H) ; 7.32 (t, 1H) ; 7.37 (d, 1H) ; 7.40 (s, 1H) ; 7.46 (d, 1H) ; 7.72 (d, 1H) ; 7.81 (d, 1H) ; 8.22 (s, 1H) ; 9.27 (s, 1H).

Example 420. Preparation of compound 598 in Table 23

An analogous reaction to that described in example 293, but starting 3-nitroaniline (25 mg, 0.18 mmol) yielded title compound (6 mg, 6 %).

MS ES$^+$: 565.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.70 (t, 2H) ; 4.05 (d, 2H) ; 4.07 (s, 3H) ; 4.33 (t, 2H) ; 7.39 (d, 1H) ; 7.42 (s, 1H) ; 7.68 (t, 1H) ; 7.98 (d, 1H) ; 8.08 (d, 1H) ; 8.20 (m, 1H) ; 8.23 (s, 1H) ; 8.77 (s, 1H) ; 9.3 (s, 1H).

Example 421. Preparation of compound 599 in Table 23

An analogous reaction to that described in example 293, but starting 4-trifluoromethylaniline (29 mg, 0.18 mmol) yielded title compound (8 mg, 8 %).

MS ES$^+$: 588.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.33 (m, 2H) ; 3.19 (t, 2H) ; 3.41 (t, 2H) ; 3.61 (d, 2H) ; 3.75 (t, 2H) ; 4.05 (d, 2H) ; 4.08 (s, 1H) ; 4.37 (t, 2H) ; 7.39 (d, 1H) ; 7.43 (s, 1H) ; 7.72 (d, 2H) ; 8.03 (d, 2H) ; 8.10 (d, 1H) ; 8.23 (s, 1H) ; 9.29 (s, 1H).

Example 422. Preparation of compound 600 in Table 23

An analogous reaction to that described in example 293, but starting 3-chloroaniline (23 mg, 0.18 mmol) yielded title compound (21 mg, 21 %).

^{1}HNMR (DMSOd_6, TFA): 2.32 (m, 2H) ; 3.19 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 4.03 (d, 2H) ; 4.07 (s, 3H) ; 4.34 (t, 2H) ; 7.17 (d, 1H) ; 7.37 (t, 1H) ; 7.40 (m, 2H) ; 7.70 (d, 1H) ; 7.95 (m, 1H) ; 8.02 (d, 1H) ; 8.22 (s, 1H) ; 9.29 (s, 1H).

Example 423. Preparation of compound 601 in Table 23

An analogous reaction to that described in example 293, but starting 2-methoxyaniline (22 mg, 0.18 mmol) yielded title compound (32 mg, 32 %).

^{1}HNMR (DMSOd_6, TFA): 2.35 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 3.87 (s, 3H) ; 4.05 (d, 2H) ; 4.06 (s, 3H) ; 4.34 (t, 2H) ; 6.99 (t, 1H) ; 7.11 (d, 1H) ; 7.20 (s, 1H) ; 7.33 (d, 1H) ; 7.40 (s, 1H) ; 7.73 (dd, 1H) ; 7.97 (d, 1H) ; 8.22 (s, 1H) ; 9.27 (s, 1H).

Example 424. Preparation of compound 602 in Table 23

An analogous reaction to that described in example 293, but starting 3-(2-hydroxyethyl) aniline (25 mg, 0.18 mmol) yielded title compound (27 mg, 26 %).

MS ES$^+$: 564.7 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.37 (d, 3H) ; 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.62 (t, 2H) ; 4.06 (d, 2H) ; 4.08 (s, 3H) ; 4.36 (t, 2H) ; 4.76 (q, 1H) ; 7.08 (d, 1H) ; 7.29 (t, 1H) ; 7.35 (d, 1H) ; 7.42 (s, 1H) ; 7.70 (d, 1H) ; 7.76 (s, 1H) ; 8.05 (d, 1H) ; 8.23 (s, 1H) ; 9.28 (s, 1H).

Example 425. Preparation of compound 603 in Table 23

An analogous reaction to that described in example 293, but starting 3-fluoro-4-methoxyaniline (25 mg, 0.18 mmol) yielded title compound (14 mg, 14 %).

MS ES$^+$: 568.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.38 (t, 2H) ; 3.57 (d, 2H) ; 3.72 (t, 2H) ; 3.85 (s, 3H) ; 4.04 (d, 2H) ; 4.07 (s, 3H) ; 4.35 (t, 2H) ; 7.17 (t, 1H) ; 7.36 (d, 1H) ; 7.42 (s, 1H) ; 7.47 (dd, 1H) ; 7.73 (dd, 1H) ; 7.98 (d, 1H) ; 8.24 (s, 1H) ; 9.27 (s, 1H).

Example 426. Preparation of compound 604 in Table 23

An analogous reaction to that described in example 293, but starting 2-methyl-4-fluoroaniline (23 mg, 0.18 mmol) yielded title compound (27 mg, 27 %).

MS ES$^+$: 552.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.28 (s, 3H) ; 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.57 (d, 2H) ; 3.71 (t, 2H) ; 4.05 (d, 2H) ; 4.07 (s, 3H) ; 7.07 (dt, 1H) ; 7.15 (dd, 1H) ; 7.35 (d, 1H) ; 7.36 (m, 1H) ; 7.41 (s, 1H) ; 7.95 (d, 1H) ; 8.23 (s, 1H) ; 9.26 (s, 1H).

Example 427. Preparation of compound 605 in Table 23

An analogous reaction to that described in example 293, but starting 2-fluoro-5-methylaniline (23 mg, 0.18 mmol) yielded title compound (9 mg, 9 %).

MS ES$^+$: 552.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.33 (m, 5H) ; 3.19 (t, 2H) ; 3.38 (t, 2H) ; 3.56 (d, 2H) ; 3.71 (t, 2H) ; 4.04 (d, 2H) ; 4.07 (s, 3H) ; 4.35 (t, 2H) ; 7.09 (m, 1H) ; 7.18 (m, 1H) ; 7.35 (d, 1H) ; 7.40 (s, 1H) ; 7.41 (m, 1H) ; 8.0 (d, 1H) ; 8.23 (s, 1H) ; 9.27 (s, 1H).

Example 428. Preparation of compound 606 in Table 23

An analogous reaction to that described in example 293, but starting 3-cyanoaniline (21 mg, 0.18 mmol) yielded title compound (9 mg, 9 %).

MS ES$^+$: 545.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (t, 2H) ; 3.21 (t, 2H) ; 3.39 (t, 2H) ; 3.60 (d, 2H) ; 3.72 (t, 2H) ; 4.07 (d, 2H) ; 4.10 (s, 3H) ; 4.37 (t, 2H) ; 7.40 (d, 1H) ; 7.44 (s, 1H) ; 7.62 (s, 1H) ; 7.63 (m, 1H) ; 8.06 (m, 1H) ; 8.06 (d, 1H) ; 8.26 (s, 1H) ; 8.30 (s, 1H) ; 9.32 (s, 1H).

Example 429. Preparation of compound 607 in Table 23

An analogous reaction to that described in example 293, but starting isoamylamine (16 mg, 0.18 mmol) yielded title compound (15 mg, 17 %).

MS ES$^+$: 514.7 $(M+H)^+$

^{1}HNMR ($CDCl_3$) : 0.96 (d, 6H) ; 1.77 (m, 5H) ; 2.11 (m, 2H) ; 2.5 (m, 4H) ; 2.56 (t, 2H) ; 3.73 (m, 4H) ; 4.03 (s, 3H) ; 4.22 (t, 2H) ; 6.05 (t, 1H) ; 6.88 (d, 1H) ; 7.24 (s, 1H) ; 7.39 (d, 1H) ; 7.58 (s, 1H) ; 8.70 (s, 1H).

Example 430. Preparation of compound 608 in Table 23

An analogous reaction to that described in example 293, but starting 2-chloroaniline (23 mg, 0.18 mmol) yielded title compound (5 mg, 5 %).

MS ES$^+$: 554.5, 556.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 4.04 (d, 2H) ; 4.07 (s, 3H) ; 4.34 (t, 2H) ; 7.32 (t, 1H) ; 7.36 (d, 1H) ; 7.41 (s, 1H) ; 7.41 (t, 1H) ; 7.57 (d, 1H) ; 7.63 (d, 1H) ; 8.0 (d, 1H) ; 8.23 (s, 1H) ; 9.27 (s, 1H).

Example 431. Preparation of compound 609 in Table 24

An analogous reaction to that described in example 293, but starting with 5-((6-methox-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)thiophene-3-carboxylic acid (80 mg, 0.18 mmol) and aniline (20 µl, 0.22 mmol) yielded title compound (28 mg, 30 %).

MS ES^+: 520 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.56 (d, 2H) ; 3.71 (t, 2H) ; 4.05 (d, 2H) ; 4.06 (s, 3H) ; 4.34 (t, 2H) ; 7.12 (t, 1H) ; 7.37 (t, 2H) ; 7.40 (s, 1H) ; 7.76 (d, 1H) ; 7.79 (d, 2H) ; 8.18 (s, 1H) ; 8.21 (d, 1H) ; 9.17 (s, 1H).

5-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)thiophene-3-carboxylic acid.

Ethyl-5-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino thiophene-3-carboxylate (1.05 g, 2.2 mmol) in methanol (10 ml) was treated with sodium hydroxyde (2N, 10 ml) at 75°C for 1.5 hour. Methanol was evaporated, HCl (2N) was added (pH 3) the solid filtered, redissolved in CH_2Cl_2 / MeOH 1/1, DIEA (1.5 ml, 8.8 mmol) was added the solid removed by filtration, the filtrate was concentrated, and the residue dissolved in ethanol, title material was obtained as a solid (0.7 g, 71 %).

MS ES^+: 445 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.36 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.79 (t, 2H) ; 4.03 (d, 2H) ; 4.08 (s, 3H) ; 4.35 (t, 2H) ; 7.45 (s, 1H) ; 7.81 (s, 1H) ; 8.03 (s, 1H) ; 8.50 (s, 1H) ; 9.15 (s, 1H).

Ethyl-5-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)aminothiophene-3-carboxylate.

4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (1 g, 3 mmol) in isopropanol (25 ml) and isopropanol HCl (0.5 ml) was reacted with ethyl 5-aminothiophene-3-carboxylate (0.6 g, 3.3 mmol) at 110°C for 1 hour. The mixture was cooled, diluted with EtOAc, filtered to give title compound (1.58 g, 99 %).

MS ES^+: 473 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.33 (t, 3H) ; 2.33 (t, 2H) ; 3.17 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.75 (t, 2H) ; 4.03 (d, 2H) ; 4.06 (s, 3H) ; 4.30 (q, 2H) ; 4.33 (t, 2H) ; 7.42 (s, 1H) ; 7.73 (s, 1H) ; 8.09 (s, 1H) ; 8.35 (s, 1H) ; 9.15 (s, 1H).

Example 432. Preparation of compound 610 in Table 24

An analogous reaction to that described in example 309, but starting with 4-fluoroaniline (24 mg, 0.18 mmol) yielded title compound (20 mg, 22 %).

MS ES$^+$: 538.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 3.20 (t, 2H) ; 3.40 (t, 2H) ; 3.60 (d, 2H) ; 3.72 (t, 2H) ; 4.04 (d, 2H) ; 4.07 (s, 3H) ; 4.34 (t, 2H) ; 7.9 (s, 1H) ; 7.20 (m, 2H) ; 7.41 (s, 1H) ; 7.76 (d, 1H) ; 7.82 (m, 1H) ; 8.19 (s, 1H) ; 8.21 (d, 1H) ; 9.17 (s, 1H).

Example 433. Preparation of compound 611 in Table 24

An analogous reaction to that described in example 309, but starting with 3-hydroxyaniline (24 mg, 0.18 mmol) yielded title compound (15 mg, 17 %).

MS ES$^+$: 536.6 $(M+H)^+$

Example 434. Preparation of compound 612 in Table 24

An analogous reaction to that described in example 309, but starting with 3-(methylthio)aniline (30 mg, 0.18 mmol) yielded title compound (23 mg, 24 %).

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (m, 5H) ; 4.33 (t, 2H) ; 7.24 (t, 1H) ; 7.32 (t, 1H) ; 7.41 (s, 1H) ; 7.43 (m, 2H) ; 7.72 (d, 2H) ; 8.16 (m, 2H) ; 9.17 (s, 1H).

Example 435. Preparation of compound 613 in Table 24

An analogous reaction to that described in example 309, but starting with 4-fluoro-3-chloroaniline (32 mg, 0.18 mmol) yielded title compound (21 mg, 21 %).

MS ES$^+$: 577 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.71 (t, 2H) ; 4.06 (m, 5H) ; 4.34 (t, 2H) ; 7.41 (m, 2H) ; 7.75 (m, 2H) ; 8.11 (m, 1H) ; 8.18 (s, 1H) ; 8.21 B(s, 1H) ; 9.18 (s, 1H).

Example 436. Preparation of compound 614 in Table 24

An analogous reaction to that described in example 309, but starting with 2,4-difluorobenzylamine (31 mg, 0.18 mmol) yielded title compound (22 mg, 22 %).

MS ES$^+$: 570.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.34 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.06 (m, 5H) ; 4.34 (t, 2H) ; 4.51 (s, 2H) ; 7.06 (t, 1H) ; 7.15 (t, 1H) ; 7.40 (s, 1H) ; 7.48 (m, 1H) ; 7.69 (d, 1H) ; 8.03 (d, 1H) ; 8.17 (s, 1H) ; 9.14 (s, 1H).

Example 437. Preparation of compound 615 in Table 24

An analogous reaction to that described in example 309, but starting with 3-fluoroaniline (24 mg, 0.18 mmol) yielded title compound (27 mg, 29 %).

MS ES$^+$: 538.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.33 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (d, 2H) ; 4.04 (d, 2H) ; 4.07 (s, 3H) ; 4.35 (t, 2H) ; 6.91 (m, 1H) ; 7.42 (m, 2H) ; 7.59 (d, 1H) ; 7.78 (d, 1H) ; 7.79 (m, 1H) ; 8.19 (s, 1H) ; 8.24 (d, 1H) ; 9.18 (s, 1H).

Example 438. Preparation of compound 616 in Table 25

2-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)imidazole-5-carboxylic acid (200 mg, 0.47 mmol) in DMF (3 ml) was reacted with aniline (43 µl, 0.47 mmol) in presence of 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (178 mg, 0.47 mmol) and DIEA (120 µl, 0.7 mmol) at 40°C for 3 hours. A solution of dimethylamine in methanol (2M, 1 ml) was added and stirring was carried on for 3 hours. The solvent was evaporated, and the mixture was purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH NH_3 (sat.) 95/5 to give title compound (80 mg, 34 %).

MS ES$^+$: 504.1 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.29 (t, 2H) ; 3.18 (t, 2H) ; 3.35 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.96 (s, 3H) ; 4.04 (d, 2H) ; 4.27 (t, 2H) ; 7.15 (t, 1H) ; 7.25 (s, 1H) ; 7.40 (t, 2H) ; 7.74 (d, 2H) ; 7.81 (s, 1H) ; 8.09 (s, 1H) ; 8.75 (s, 1H).

Example 439. Preparation of compound 617 in Table 25

An analogous reaction to that described in example 316, but starting with 4-fluoroaniline (60 µl, 0.58 mmol) yielded title compound (120 mg, 39 %).

MS ES+ : 522.1 (M+H)+

^{1}HNMR (DMSOd_6, TFA) : 2.29 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 1H) ; 3.69 (t, 2H) ; 3.96 (s, 3H) ; 4.04 (d, 2H) ; 4.27 (t, 2H) ; 7.22 (m, 3H) ; 7.74 (m, 2H) ; 7.82 (s, 1H) ; 8.07 (s, 1H) ; 8.76 (s, 1H).

Example 440. Preparation of compound 618 in Table 25

An analogous reaction to that described in example 316, but starting with allylamine 50 µl, 0.7 mmol) yielded title compound (133 mg, 40 %).

MS ES$^+$: 468.1 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.28 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.94 (m, 5H) ; 4.04 (d, 2H) ; 4.26 (t, 2H) ; 5.14 (dd, 1H) ; 5.23 (dd, 1H) ; 5.88 (m, 1H) ; 7.23 (s, 1H) ; 7.77 (s, 1H) ; 7.86 (s, 1H) ; 8.71 (s, 1H).

2 -((6-methoxy-7-(3-morpholinoporpoxy)quinazolin-4-yl)amino)imidazole-5-carboxylic acid.

ethyl-2((4-imino-6-methoxy-7-(3-morpholinopropoxy)quinazolin-3-(4H)-yl)imidazole-5-carboxylate (650 mg, 1.42 mmol) in methanol (14 ml) was treated with sodium hydroxyde (2N, 14 ml) at 80°C for 1.5 hour. Methanol was evaporated, hydrochloric acid (6N) was added (pH 2.5), the precipitate was recovered by filtration, dried to give title compound (650 mg, 100 %).

^{1}HNMR (DMSOd_6, TFA) : 2.35 (t, 2H) ; 3.13 (t, 2H) ; 3.32 (t, 2H) ; 3.5 (d, 2H) ; 3.95 (m, 7H) ; 4.28 (t, 2H) ; 7.42 (s, 1H) ; 7.8 (s, 1H) ; 7.86 (s, 1H) ; 8.72 (s, 1H).

Example 441. Preparation of compound 619 in Table 26

4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (265 mg, 0.79 mmol) in 2-propanol (14 ml) was reacted with 4-amino-N-phenylthiophene-3-carboxamide hydrochloride (210 mg, 0.82 mmol) at 100°C for 2 hours. The solvent was evaporated and the residue purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH, NH_3 sat. 95/5 to give title compound (330 mg, 81 %).

MS ES$^+$: 520.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.30 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (s, 3H) ; 4.04 (d, 2H) ; 4.32 (t, 2H) ; 7.13 (t, 1H) ; 7.35 (t, 2H) ; 7.39 (s, 1H) ; 7.69 (d, 2H) ; 7.79 (s, 1H) ; 8.13 (d, 1H) ; 8.58 (d, 1H) ; 8.95 (s, 1H).

4-(tert-butoxycarbotylamino-N-phenylthiophene-3-carboxamide

4-(tert-butoxycarbonylamino)thiophene-3-carboxylic acid obtained by a literature procedure, Tetrahedron Letters 1997, 2637, (385 mg, 1.58 mmol) in DMF (5 ml) was reacted with aniline (140 µl, 1.58 mmol) in presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (602 mg, 1.58 mmol) at 40°C for 7 hours. The solvent was evaporated,

and the residue purified by silica gel chromatography, Eluant petroleum ether / AcOEt : 80/20 to give title compound (348 mg, 70 %).

^{1}HNMR ($CDCl_3$) : 1.50 (s, 9H) ; 7.19 (t, 1H) ; 7.39 (t, 2H) ; 7.54 (d, 2H) ; 7.69 (s, 2H) ; 7.71 (s, 1H) ; 9.45 (s, 1H).

4-amino-N-phenylthiophene-3-carboxamide

4-(tert-butoxycarbonylamino)-N-phenylthiophene-3-carboxamide (300 mg, 0.94 mmol) in CH_2Cl_2 (3 ml) was treated with TFA (0.36 ml, 4.71 mmol) at room temperature for 2.5 hours. The solvent was evaporated, the residue was dissolved in methanol / HCl, ether was added to the solution, the precipitate was recovered to give title compound (210 mg, 87 %) which was used as is in the next step.

Example 442. Preparation of compound 620 in Table 26

An analogous reaction to that described in example 319, but starting with 4-amino-N-allylthiophene-3-carboxamide (218 mg, 1.06 mmol) yielded title compound (366 mg, 75 %).

MS ES$^+$: 484.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.28 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.95 (d, 2H) ; 4.03 (m, 5H) ; 4.32 (t, 2H) ; 5.14 (dd, 1H) ; 5.24 (dd, 1H) ; 5.91 (m, 1H) ; 7.41 (s, 1H) ; 7.59 (s, 1H) ; 8.28 (d, 1H) ; 8.51 (d, 1H) ; 9.04 (s, 1H).

4-tert-butoxycarbonylamino)-N-allylthiophene-3-carboxamide

An analogous reaction to that described in example 319, but starting with allylamine (150 µl, 2.06 mmol) yielded title compound (385 mg, 66 %).

^{1}HNMR ($CDCl_3$) : 1.51 (s, 9H) ; 4.04 (m, 2H) ; 5.21 (dd, 1H) ; 5.29 (dd, 1H) ; 5.92 (m, 1H) ; 6.1 (m, 1H) ; 7.54 (d, 1H) ; 7.64 (m, 1H) ; 9.64 (s, 1H).

4-amino-N-allylthiophene-3-carboxamide

An analogous reaction to that described in example 319, but starting with 4-tert-butoxycarboxylamino-N-allyl-thiophene-3-carboxamide (320 mg, 1.13 mmol) yielded title compound (218 mg, 94 %) which was used as is in the next step.

Example 443. Preparation of compound 621 in Table 27

4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinzaoline (100 mg, 0.29 mmol) in isopropanol (5 ml) was reacted with methyl-4-amino-thiophene-4-carboxylate hydrochloride (63.6 mg, 0.33 mmol) at reflux for 1 hour. Ethyl acetate was added to the reaction mixture, the solid was recovered by filtration, dried, to give title compound (140 mg, 89 %).

MS ES$^+$: 459.1 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.39 (t, 2H) ; 3.19 (t, 2H) ; 3.40 (t, 2H) ; 3.58 (d, 2H) ; 3.77 (m, 5H) ; 4.06 (m, 5H) ; 4.37 (t, 2H) ; 7.42 (s, 1H) ; 7.95 (s, 1H) ; 8.01 (d, 1H) ; 8.49 (d, 1H) ; 8.93 (s, 1H).

Example 444. Preparation of compound 622 in Table 28

4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (110 mg, 0.3 mmol) in 2-pentanol (5 ml) and isopropanol / HCl (55 µl) was reacted with 2-amino-5-isopropylthiophene-3-carboxamide (60 mg, 0.33 mmol) at 100°C for 1 hour, ether and ethylacetate was added to the mixture, the precipitate was filtered to give title compound (155 mg, 93 %).

MS ES$^+$: 486.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) ; 1.38 (d, 6H) ; 2.38 (t, 2H) ; 3.20 (m, 3H) ; 3.38 (t, 2H) ; 3.57 (d, 2H) ; 3.82 (t, 2H) ; 4.05 (d, 2H) ; 4.08 (s, 3H) ; 4.39 (t, 2H) ; 7.40 (s, 1H) ; 7.47 (s, 1H) ; 7.52 (s, 1H) ; 9.23 (s, 1H).

Example 445. Preparation of compound 623 in Table 28

An analogous reaction to that described in example 322 but starting with allyl-5-aminothiophene-2-carboxylate (67 mg, 0.33 mmol) at 100°C for 2 hours yielded title compound (151 mg, 85 %).

MS ES$^+$: 485.6 $(M+H)^+$

^{1}HNMR (DMSOd_6,TFA) : 2.38 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.57 (d, 2H) ; 3.80 (t, 2H) ; 4.06 (d, 2H) ; 4.12 (s, 3H) ; 4.38 (t, 2H) ; 4.84 (d, 2H) ; 5.33 (d, 1H) ; 5.45 (d, 1H) ; 6.10 (m, 1H) ; 7.48 (s, 1H) ; 7.65 (d, 1H) ; 7.84 (d, 1H) ; 8.64 (s, 1H) ; 9.30 (s, 1H).

Example 446. Preparation of compound 624 in Table 28

An analogous reaction to that described in example 322 but starting with 2-aminothiophene-3-carboxamide (46 mg, 0.33 mmol) yielded title commound (154 mg, 99 %).

MS ES$^+$: 444.6 $(M+H)^+$

^{1}HNMR (DMSOd_6,TFA) : 2.34 (t, 2H) ; 3.15 (t, 2H) ; 3.36 (t, 2H) ; 3.54 (d, 2H) ; 3.76 (t, 2H) ; 4.02 (d, 2H) ; 4.05 (s, 3H) ; 4.36 (t, 2H) ; 7.32 (d, 1H) ; 7.41 (s, 1H) ; 7.48 (s, 1H) ; 7.66 (d, 1H) ; 9.23 (s, 1H).

Example 447. Preparation of compound 625 in Table 28

An analogous reaction to that described in example 322 but starting with 2-amino-5-ethylthiophene-3-carboxamide (55 mg, 0.33 mmol) yielded title compound (147 mg, 90 %).

MS ES^+ : 472.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.34 (t, 3H) ; 2.38 (t, 2H) ; 2.86 (q, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.57 (d, 2H) ; 3.80 (t, 2H) ; 4.05 (d, 2H) ; 4.07 (s, 3H) ; 4.38 (t, 2H) ; 7.40 (s, 1H) ; 7.43 (s, 1H) ; 7.52 (s, 1H) ; 9.21 (s, 1H).

Example 448. Preparation of compound 626 in Table 29

Methyl-2-cyano-4-methoxy-5-(3-morpholinopropoxy)phenylimidoformate (100 mg ; 0.3 mmol) in DMF (1.5 ml) was reacted with 2-amino-4-phenyl-1,3-thiazole (58 mg ; 0.33 mmol) in presence of sodium hydride (13.2 mg ; 0.33 mmol) at 75°C for 1.5 h. Acetic acid (1.5 eq.) was added and the solvent was evaporated to give 6-methoxy-7-(3-morpholinopropoxy)-3-(4-phenyl-1,3-thiazol-2-yl)quinazolin-4(3H)-imine as an intermediate which was redissolved in DMF (1.5 ml) and ammonium acetate (95 mg ; 0.9 mmol) added. The mixture was stirred at 75°C for 1 h, the solvent was evaporated and the residue purified by silica gel chromatography, CH_2Cl_2/MeOH 95/5 → 90/10 to give title compound (44 mg, 31 %).

^{1}HNMR ($DMSOd_6$, TFA) : 2.30 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.05 (m, 5H) ; 4.33 (t, 2H) ; 7.42 (m, 2H) ; 7.51 (t, 2H) ; 7.90 (s, 1H) ; 8.00 (d, 2H) ; 8.35 (s, 1H) ; 9.27 (s, 1H).

Example 449. Preparation of compound 627 in Table 29

An analogous reaction to that described in example 326 but starting with 2-amino-4-methyl-5-acetyl-1,3-thiazole (103 mg, 0.66 mmol), heating at 75°C for 1 h in the first step, and stirring the intermediate in the above conditions at room temperature for 1 h, gave title compound (71 mg, 52 %).

MS ES^+ : 458 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.32 (t, 2H) ; 2.55 (s, 3H) ; 2.67 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.0 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.37 (s, 1H) ; 7.99 (s, 1H) ; 9.26 (s, 1H).

Example 450. Preparation of compound 628 in Table 29

An analogous reaction to that described in example 326 but starting with ethyl-2-amino-4-trifluoromethyl-1,3-thiazole-5-carboxylate (79 mg, 0.33 mmol) yielded title compound (81 mg, 50 %).

MS ES$^+$: 542 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA) : 1.34 (t, 3H) ; 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.03 (s, 3H) ; 4.04 (d, 2H) ; 4.36 (m, 4H) ; 7.47 (s, 1H) ; 8.41 (s, 1H) ; 9.34 (s, 1H).

Example 451. Preparation of compound 629 in Table 29

An analogous reaction to that described in example 326 but starting with ethyl-2-amino-4-phenyl-1,3-thiazole-5-carboxylate (82 mg, 0.33 mmol) yielded title compound (133 mg, 81 %).

MS ES$^+$: 550 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA) : 1.25 (t, 2H) ; 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 1H) ; 4.04 (d, 2H) ; 4.26 (q, 2H) ; 4.35 (t, 2H) ; 7.45 (s, 1H) ; 7.50 (m, 3H) ; 7.79 (m, 2H) ; 8.33 (s, 1H) ; 9.37 (s, 1H).

Example 452. Preparation of compound 630 in Table 29

An analogous reaction to that described in example 326 but starting with 4,5,6,7-tetrahydro-1,3-benzothiazole-2-amine (51 mg, 0.33 mmol) yielded title compound (97 mg, 71 %).

MS ES$^+$: 456 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA) : 1.83 (m, 4H) ; 2.29 (t, 2H) ; 2.61 (m, 2H) ; 2.67 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.28 (s, 1H) ; 7.84 (s, 1H) ; 9.0 (s, 1H).

Example 453. Preparation of compound 631 in Table 29

An analogous reaction to that described in example 326 but starting with N-(4-(2-amino-1,3-thiazol-4-yl)phenyl)acetamide (77 mg, 0.33 mmol) yielded title compound (58 mg, 36 %).

MS ES$^+$: 535 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.09 (s, 3H) ; 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.05 (s, 3H) ; 4.06 (d, 2H) ; 4.35 (t, 2H) ; 7.40 (s, 1H) ; 7.72 (d, 2H) ; 7.77 (s, 1H) ; 7.92 (d, 2H) ; 8.33 (s, 1H) ; 9.25 (s, 1H).

Example 454. Preparation of compound 632 in Table 29

An analogous reaction to that described in example 326 but starting with 5-phenyl-4-(trifluoromethyl)-1,3-thiazole-2-amine (81 mg, 0.33 mmol) yielded title compound (144 mg, 88 %).

MS ES$^+$: 546 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (d, 2H) ; 4.05 (s, 3H) ; 4.36 (t, 2H) ; 7.49 (s, 1H) ; 7.54 (s, 5H) ; 8.46 (s, 1H) ; 9.30 (s, 1H).

Example 455. Preparation of compound 633 in Table 29

An analogous reaction to that described in example 326 but starting with 4-(trifluoromethyl)-1,3-thiazole-2-amine (55 mg, 0.33 mmol) yielded title compound (62 mg, 44 %).

MS ES$^+$: 470 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (s, 3H) ; 4.05 (d, 2H) ; 4.36 (t, 2H) ; 7.49 (s, 1H) ; 8.23 (s, 1H) ; 8.44 (s, 1H) ; 9.34 (s, 1H).

Example 456. Preparation of compound 634 in Table 29

An analogous reaction to that described in example 326 but starting with 4-tert-butyl-1,3-thiazole-2-amine (52 mg, 0.33 mmol) yielded title compound (90 mg, 65 %).

MS ES$^+$: 458 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.46 (s, 9H) ; 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (d, 2H) ; 7.38 (s, 1H) ; 7.95 (s, 1H) ; 9.18 (s, 1H).

Example 457. Preparation of compound 635 in Table 29

An analogous reaction to that described in example 326 but starting with 4,5-dimethyl-1,3-thiazole-2-amine (42 mg, 0.33 mmol) yielded title compound (61 mg, 47 %).

MS ES$^+$: 430 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.25 (s, 3H) ; 2.30 (m, 5H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.96 (s, 3H) ; 4.04 (d, 2H) ; 4.28 (t, 1H) ; 7.28 (s, 1H) ; 7.82 (s, 1H) ; 8.98 (s, 1H).

Example 458. Preparation of compound 636 in Table 29

An analogous reaction to that described in example 326 but starting with 4-methyl-1,3-thiazole-2-amine (38 mg, 0.33 mmol) yielded title compound (40 mg, 32 %).

MS ES$^+$: 415 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (t, 2H) ; 2.34 (s, 3H) ; 3.15 (t, 2H) ; 3.37 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.03 (s, 1H) ; 7.29 (s, 1H) ; 7.87 (s, 1H) ; 9.05 (s, 1H).

Example 459. Preparation of compound 637 in Table 29

1-(2-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)-4-methyl-1,3-thiazole-5-yl)ethanone (50 mg, 0.11 mmol) in ethanol (4 ml) and pyridine (1 ml) was reacted with hydroxylamine hydrochloride (19.5 mg, 0.27 mmol) at reflux for 3 h. The solvent was evaporated, water was added to the residue and a solid was recovered, washed with water to give title compound (14 mg, 27 %)

MS ES$^+$: 473 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.25 (s, 3H) ; 2.30 (t, 2H) ; 2.53 (s, 3H) ; 3.17 (t, 2H) ; 3.38 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.05 (d, 2H) ; 4.32 (t, 2H) ; 7.32 (s, 1H) ; 7.88 (s, 1H) ; 9.12 (s, 1H).

Example 460. Preparation of compound 638 in Table 29

2-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)-1,3-thiazole-5-carboxylic acid (89 mg, 0.2 mmol) in DMF (1.5 ml) was treated with diphenylphosporyl azide (66 mg, 0.24 mmol) and triethylamine (26 mg, 0.26 mmol). The solution was stirred at room temperature for 1 h and at 45°C for 1 h. Tert-butanol (1 ml) was added, and the mixture heated at 90°C for 2 h. The mixture was diluted with ethylacetate, aqueous sodium bicarbonate, the organic phase was recovered, dried over $MgSO_4$, filtered, concentrated and purified by silica gel chromatography, eluent CH_2Cl_2/MeOH 95/5 to 85/15 to give title compound as a yellow solid (25 mg, 24 %).

MS ES$^+$: 517 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.50 (s, 9H) ; 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.13 (s, 1H) ; 7.26 (s, 1H) ; 7.94 (s, 1H) ; 9.11 (s, 1H).

Example 461. Preparation of compound 639 in Table 29

An analogous reaction to that described in example 337 but starting with O-methylhydroxylamine hydrochloride (18 mg, 0.22 mmol) and heating at reflux for 72 h yielded title compound (39 mg, 63 %).

MS ES$^+$: 487 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.26 (s, 3H) ; 2.31 (t, 2H) ; 3.53 (s, 3H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.76 (s, 2H) ; 3.94 (s, 3H) ; 3.99 (s, 3H) ; 4.02 (d, 2H) ; 4.33 (t, 2H) ; 7.35 (s, 1H) ; 7.89 (s, 1H) ; 9.11 (s, 1H).

Example 462. Preparation of compound 640 in Table 29

An analogous reaction to that described in example 339 but starting with O-phenylhydroxylamine hydrochloride (32 mg, 0.22 mmol) yielded title compound (8 mg, 12 %).

MS ES$^+$: 549 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.28 (t, 2H) ; 3.12 (t, 2H) ; 3.32 (t, 2H) ; 3.52 (d, 2H) ; 3.65 (t, 2H) ; 3.96 (s, 3H) ; 4.0 (d, 2H) ; 4.27 (t, 2H) ; 7.06 (t, 1H) ; 7.20 (d, 2H) ; 7.28 (s, 1H) ; 7.34 (t, 2H) ; 7.91 (s, 1H) ; 9.17 (s, 1H).

Example 463. Preparation of compound 641 in Table 29

An analogous reaction to that described in example 326 but starting with 2-amino-5-(4-methoxyphenyl)-1,3-thiazole, HBr (86 mg, 0.33 mmol) yielded title compound (105 mg, 77 %).

MS ES$^+$: 508.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.33 (t, 2H) ; 3.20 (t, 2H) ; 3.40 (t, 2H) ; 3.60 (d, 2H) ; 3.73 (t, 2H) ; 3.86 (s, 3H) ; 4.08 (s, 3H) ; 4.09 (d, 2H) ; 4.36 (t, 2H) ; 7.10 (d, 2H) ; 7.44 (s, 1H) ; 7.76 (s, 1H) ; 7.96 (d, 2H) ; 8.33 (s, 1H) ; 9.26 (s, 1H).

Example 464. Preparation of compound 642 in Table 29

An analogous reaction to that described in example 326 but starting with 2-amino-5-phenyl)-1,3-thiazole (58 mg, 0.33 mmol) yielded title compound (120 mg, 84 %)..

MS ES$^+$: 478.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.01 (s, 3H) ; 4.05 (d, 2H) ; 4.32 (t, 2H) ; 7.34 (s, 1H) ; 7.41 (t, 1H) ; 7.51 (t, 2H) ; 7.72 (d, 2H) ; 7.97 (s, 1H) ; 8.24 (s, 1H) ; 9.16 (s, 1H).

Example 465. Preparation of compound 643 in Table 29

Methyl-2-cyano-4-methoxy-5-(3-morpholinopropoxy)phenyl-imidoformate (300 mg, 0.9 mmol) in DMF (4.5 ml) was reacted with 2-amino-5-ethyl-1,3-thiazole (127 mg, 0.99 mmol) in presence of sodium hydride (39.6 mg, 0.99 mmol) at 75°C for 2 h. Acetic acid (77 µl, 1.35 mmol) was added to the mixture at room temperature, followed by MeOH/Me_2NH (2M) (90 µl, 0.18 mmol) and the mixture was stirred at 75°C for 1 h. The solvent was evaporated and the mixture was purified by silica gel chromatography, eluent CH_2Cl_2/MeOH 95/5 → 90/10 to give title compound (193 mg, 50 %).

MS ES$^+$: 430.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.29 (t, 3H) ; 2.32 (t, 2H) ; 2.81 (q, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.98 (s, 3H) ; 4.05 (d, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.50 (s, 1H) ; 7.87 (s, 1H) ; 9.04 (s, 1H).

Example 466, Preparation of compound 644 in Table 29

An analogous reaction to that described in example 343 but starting with 2-amino-5-isopropyl)-1,3-thiazole (141 mg, 0.99 mmol) yielded title compound (107 mg, 26 %).

MS ES$^+$: 444.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.33 (d, 6H) ; 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.29 (s, 1H) ; 7.49 (s, 1H) ; 7.87 (s, 1H) ; 9.05 (s, 1H).

Example 467. Preparation of compound 645 in Table 29

An analogous reaction to that described in example 343 but starting with 2-amino-5-benzyl)-1,3-thiazole (188 mg, 0.99 mmol) yielded title compound (370 mg, 84 %).

MS ES^+ : 492.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.18 (s, 2H) ; 4.29 (t, 2H) ; 7.27 (s, 1H) ; 7.28 (m, 1H) ; 7.35 (m, 4H) ; 7.61 (s, 1H) ; 7.88 (s, 1H) ; 9.02 (s, 1H).

Example 468. Preparation of compound 646 in Table 29

An analogous reaction to that described in example 343 but starting with 2-amino-5-methyl)-1,3-thiazole (113 mg, 0.99 mmol) yielded title compound (300 mg, 80 %).

MS ES^+ : 416.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.31 (t, 2H) ; 2.42 (s, 3H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.30 (s, 1H) ; 7.48 (s, 1H) ; 7.86 (s, 1H) ; 9.03 (s, 1H).

Example 469. Preparation of compound 647 in Table 29

An analogous reaction to that described in example 343 but starting with 2-amino-5-butyl)-1,3-thiazole (155 mg, 0.99 mmol) yielded title compound (385 mg, 93 %).

MS ES^+ : 458.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 0.93 (t, 3H) ; 1.36 (m, 2H) ; 1.64 (m, 2H) ; 2.29 (t, 2H) ; 2.79 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.51 (s, 1H) ; 7.86 (s, 1H) ; 9.03 (s, 1H).

Example 470. Preparation of compound 648 in Table 29

An analogous reaction to that described in example 343 but starting with 2-amino-5-formyl-1,3-thiazole (499.4 mg, 3.9 mmol) yielded title compound (244 mg, 39 %).

MS ES^+ : 430.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 4.03 (s, 3H) ; 4.06 (d, 2H) ; 4.35 (t, 2H) ; 7.45 (s, 1H) ; 8.12 (s, 1H) ; 8.71 (s, 1H) ; 9.32 (s, 1H).

Example 471. Preparation of compound 649 in Table 29

An analogous reaction to that described in example 337 but starting with 2-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino-1,3-thiazol-5-carbaldehyde (100 mg, 0.23 mmol) and heating at 80°C for 4 h, yielded title compound (21 mg, 20 %).

MS ES^+ : 445.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (s, 3H) ; 4.05 (d, 2H) ; 4.32 (t, 2H) ; 7.36 (s, 1H) ; 7.92 (s, 1H) ; 7.98 (s, 1H) ; 8.33 (s, 1H) ; 9.20 (s, 1H).

Example 472. Preparation of compound 650 in Table 30

An analogous reaction to that described in example 326, but starting with 2-amino-5-tert-butyl-1,3,4-thiadiazol (52 mg, 0.33 mmol) yielded title compound (80 mg, 58 %).

MS ES^+ : 458 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.45 (s, 9H) ; 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.38 (s, 1H) ; 7.95 (s, 1H) ; 9.18 (s, 1H).

Example 473. Preparation of compound 651 in Table 30

An analogous reaction to that described in example 326, but starting with 2-amino-5-cyclopropyl-1,3,4-thiadiazol (47 mg, 0.33 mmol) yielded title compound (105 mg, 83 %).

MS ES^+ : 443 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.08 (m, 2H) ; 1.23 (m, 3H) ; 2.32 (t, 2H); 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.32 (t, 2H) ; 7.38 (s, 1H) ; 7.93 (s, 1H) ; 9.14 (s, 1H).

Example 474. Preparation of compound 652 in Table 30

An analogous reaction to that described in example 326, but starting with 2-amino-5-ethylthio-1,3,4-thiadiazol (53 mg, 0.33 mmol) yielded title compound (103 mg, 75 %).

MS ES^+ : 463 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.41 (t, 3H) ; 2.31 (t, 2H); 3.15 (t, 2H) ; 3.31 (q, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.41 (s, 1H) ; 8.08 (s, 1H) ; 9.19 (s, 1H).

Example 475. Preparation of compound 653 in Table 30

An analogous reaction to that described in example 326, but starting with 2-amino-5-phenyl-1,3,4-thiadiazol (91 mg, 0.33 mmol) yielded title compound (110 mg, 76 %).

MS ES$^+$: 479 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H); 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.69 (t, 2H) ; 4.03 (s, 3H) ; 4.05 (d, 2H) ; 4.34 (t, 2H) ; 7.42 (s, 1H) ; 7.61 (m, 3H) ; 7.99 (m, 2H) ; 8.06 (s, 1H) ; 9.25 (s, 1H).

Example 476. Preparation of compound 654 in Table 30

An analogous reaction to that described in example 326, but starting with N-phenyl-4H-1,2,4-triazole-3,5-diamine (58 mg, 0.33 mmol) yielded title compound (70 mg, 49 %).

MS ES$^+$: 477 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H); 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 4.02 (s, 3H) ; 4.05 (d, 2H) ; 4.34 (t, 2H) ; 6.92 (t, 1H) ; 7.30 (t, 1H) ; 7.42 (s, 1H) ; 7.58 (d, 2H) ; 8.19 (s, 1H) ; 8.95 (s, 1H).

Biological Data

The compounds of the invention inhibit the serine/threonine kinase activity of the aurora2 kinase and thus inhibit the cell cycle and cell proliferation. These properties may be assessed, for example, using one or more of the procedures set out below:

(a) In Vitro aurora2 kinase inhibition test

This assay determines the ability of a test compound to inhibit serine/threonine kinase activity. DNA encoding aurora2 may be obtained by total gene synthesis or by cloning. This DNA may then be expressed in a suitable expression system to obtain polypeptide with serine/threonine kinase activity. In the case of aurora2, the coding sequence was isolated from cDNA by polymerase chain reaction (PCR) and cloned into the BamH1 and Not1 restriction endonuclease sites of the baculovirus expression vector pFastBac HTc (GibcoBRL/Life

technologies). The 5' PCR primer contained a recognition sequence for the restriction endonuclease BamH1 5' to the aurora2 coding sequence. This allowed the insertion of the aurora2 gene in frame with the 6 histidine residues, spacer region and rTEV protease cleavage site encoded by the pFastBac HTc vector. The 3' PCR primer replaced the aurora2 stop codon with additional coding sequence followed by a stop codon and a recognition sequence for the restriction endonuclease Not1 . This additional coding sequence (5' TAC CCA TAC GAT GTT CCA GAT TAC GCT TCT TAA 3') encoded for the polypeptide sequence YPYDVPDYAS. This sequence, derived from the influenza hemagglutin protein, is frequently used as a tag epitope sequence that can be identified using specific monoclonal antibodies. The recombinant pFastBac vector therefore encoded for an N-terminally 6 his tagged, C terminally influenza hemagglutin epitope tagged aurora2 protein. Details of the methods for the assembly of recombinant DNA molecules can be found in standard texts, for example Sambrook et al. 1989, Molecular Cloning - A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory press and Ausubel et al. 1999, Current Protocols in Molecular Biology, John Wiley and Sons Inc.

Production of recombinant virus can be performed following manufacturer's protocol from GibcoBRL. Briefly, the pFastBac-1 vector carrying the aurora2 gene was transformed into E. coli DH10Bac cells containing the baculovirus genome (bacmid DNA) and via a transposition event in the cells, a region of the pFastBac vector containing gentamycin resistance gene and the aurora2 gene including the baculovirus polyhedrin promoter was transposed directly into the bacmid DNA. By selection on gentamycin, kanamycin, tetracycline and X-gal, resultant white colonies should contain recombinant bacmid DNA encoding aurora2. Bacmid DNA was extracted from a small scale culture of several BH10Bac white colonies and transfected into Spodoptera frugiperda Sf21 cells grown in TC100 medium (GibcoBRL) containing 10% serum using CellFECTIN reagent (GibcoBRL) following manufacturer's instructions. Virus particles were harvested by collecting cell culture medium 72 hrs post transfection. 0.5 mls of medium was used to infect 100 ml suspension culture of Sf21s containing 1 x 10^7 cells/ml. Cell culture medium was harvested 48 hrs post infection and virus titre determined using a standard plaque assay procedure. Virus stocks were used to infect Sf9 and "High 5" cells at a multiplicity of infection (MOI) of 3 to ascertain expression of recombinant aurora2 protein.

For the large scale expression of aurora2 kinase activity, Sf21 insect cells were grown at 28°C in TC100 medium supplemented with 10% foetal calf serum (Viralex) and 0.2% F68

Pluronic (Sigma) on a Wheaton roller rig at 3 r.p.m. When the cell density reached $1.2x10^6$ cells ml^{-1} they were infected with plaque-pure aurora2 recombinant virus at a multiplicity of infection of 1 and harvested 48 hours later. All subsequent purification steps were performed at 4°C. Frozen insect cell pellets containing a total of 2.0×10^8 cells were thawed and diluted with lysis buffer (25 mM HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulphonic acid]) pH7.4 at 4°C , 100 mM KCl, 25 mM NaF, 1 mM Na_3VO_4, 1 mM PMSF (phenylmethylsulphonyl fluoride), 2 mM 2-mercaptoethanol, 2 mM imidazole, 1 µg/ml aprotinin, 1 µg/ml pepstatin, 1 µg/ml leupeptin), using 1.0 ml per 3×10^7 cells. Lysis was achieved using a dounce homogeniser, following which the lysate was centrifuged at 41,000g for 35 minutes. Aspirated supernatant was pumped onto a 5 mm diameter chromatography column containing 500 µl Ni NTA (nitrilo-tri-acetic acid) agarose (Qiagen, product no. 30250) which had been equilibrated in lysis buffer. A baseline level of UV absorbance for the eluent was reached after washing the column with 12 ml of lysis buffer followed by 7 ml of wash buffer (25 mM HEPES pH7.4 at 4°C , 100 mM KCl, 20 mM imidazole, 2 mM 2-mercaptoethanol). Bound aurora2 protein was eluted from the column using elution buffer (25 mM HEPES pH7.4 at 4°C , 100 mM KCl, 400 mM imidazole, 2 mM 2-mercaptoethanol). An elution fraction (2.5 ml) corresponding to the peak in UV absorbance was collected. The elution fraction, containing active aurora2 kinase, was dialysed exhaustively against dialysis buffer (25 mM HEPES pH7.4 at 4°C , 45% glycerol (v/v), 100 mM KCl, 0.25% Nonidet P40 (v/v), 1 mM dithiothreitol).

Each new batch of aurora2 enzyme was titrated in the assay by dilution with enzyme diluent (25mM Tris-HCl pH7.5, 12.5mM KCl, 0.6mM DTT). For a typical batch, stock enzyme is diluted 1 in 666 with enzyme diluent & 20µl of dilute enzyme is used for each assay well. Test compounds (at 10mM in dimethylsulphoxide (DMSO)) were diluted with water & 10µl of diluted compound was transferred to wells in the assay plates. "Total" & "blank" control wells contained 2.5% DMSO instead of compound. Twenty microlitres of freshly diluted enzyme was added to all wells, apart from "blank" wells. Twenty microlitres of enzyme diluent was added to "blank" wells. Twenty microlitres of reaction mix (25mM Tris-HCl, 78.4mM KCl, 2.5mM NaF, 0.6mM dithiothreitol, 6.25mM $MnCl_2$, 6.25mM ATP, 7.5µM peptide substrate [biotin-LRRWSLGLRRWSLGLRRWSLGLRRWSLG]) containing 0.2µCi [γ^{33}P]ATP (Amersham Pharmacia, specific activity $\geq$2500Ci/mmol) was then added to all test wells to start the reaction. The plates were incubated at room temperature for 60

minutes. To stop the reaction 100µl 20% v/v orthophosphoric acid was added to all wells. The peptide substrate was captured on positively-charged nitrocellulose P30 filtermat (Whatman) using a 96-well plate harvester (TomTek) & then assayed for incorporation of ^{33}P with a Beta plate counter. "Blank" (no enzyme) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity. In this test, compound 52 in Table 2 gave 50% inhibition of enzyme activity at a concentration of 0.167µM, and Compound 253 in Table 21 gave 50% inhibition of enzyme activity at 0.089µM.

(a) <u>In Vitro cell proliferation assay</u>

This assay determines the ability of a test compound to inhibit the growth of adherent mammalian cell lines, for example the human tumour cell line MCF7. MCF-7 (ATCC HTB-22) or other adherent cells were typically seeded at 1 x 10^3 cells per well (excluding the peripheral wells) in DMEM (Sigma Aldrich) without phenol red, plus 10% foetal calf serum, 1% L-glutamine and 1% penicillin/streptomycin in 96 well tissue culture treated clear plates (Costar). The following day (day 1), the media was removed from a no treatment control plate and the plate stored at -80°C. The remaining plates were dosed with compound (diluted from 10mM stock in DMSO using DMEM (without phenol red, 10% FCS, 1% L-glutamine, 1% penicillin/streptomycin). Untreated control wells were included on each plate. After 3 days in the presence / absence of compound (day 4) the media was removed and the plates stored at -80^{0}C. Twenty four hours later the plates were thawed at room temperature and cell density determined using the CyQUANT cell proliferation assay kit (c-7026/c-7027 Molecular Probes Inc.) according to manufacturers directions. Briefly, 200µl of a cell lysis / dye mixture (10µl of 20X cell lysis buffer B, 190µl of sterile water, 0.25µl of CYQUANT GR dye) was added to each well and the plates incubated at room temperature for 5 minutes in the dark. The fluorescence of the wells was then measured using a fluorescence microplate reader (gain 70, 2 reads per well, 1 cycle with excitation 485nm and emission 530nm using a CytoFluor plate reader (PerSeptive Biosystems Inc.)). The values from day 1 and day 4 (compound treated) together with the values from the untreated cells were used to determine the dilution range of a test compound that gave 50% inhibition of cell proliferation. Compound 52 in Table 2 was effective in this test at 0.616µM and Compound 253 in Table 20 was effective at 5.9µM.

These values could also be used to calculate the dilution range of a test compound at which the cell density dropped below the day 1 control value. This indicates the cytotoxicity of the compound.

(a) <u>In Vitro cell cycle analysis assay</u>

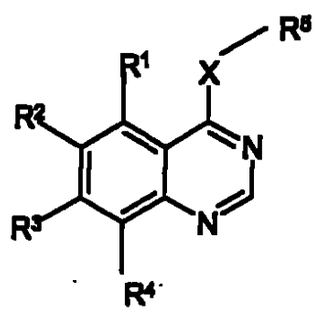
This assay determines the ability of a test compound to arrest cells in specific phases of the cell cycle. Many different mammalian cell lines could be used in this assay and MCF7 cells are included here as an example. MCF-7 cells were seeded at 3 x 10^5 cells per T25 flask (Costar) in 5 ml DMEM (no phenol red 10% FCS, 1% L-glutamine 1% penicillin / streptomycin). Flasks were then incubated overnight in a humidified 37°C incubator with 5% CO_2. The following day 1ml of DMEM (no phenol red 10% FCS, 1% L-glutamine 1% penicillin / streptomycin) carrying the appropriate concentration of test compound solubilised in DMSO was added to the flask . A no compound control treatments was also included (0.5% DMSO). The cells were then incubated for a defined time (usually 24 hours) with compound. After this time the media was aspirated from the cells and they were washed with 5ml of prewarmed (37°C) sterile PBSA, then detached from the flask by brief incubation with trypsin and followed by resuspension in 10ml of 1% Bovine Serum Albumin (BSA, Sigma-Aldrich Co.) in sterile PBSA. The samples were then centrifuged at 2200rpm for 10 min. The supernatant was aspirated and the cell pellet was resuspended in 200µl of 0.1% (w/v) Tris sodium citrate, 0.0564% (w/v) NaCl, 0.03% (v/v) Nonidet NP40, [pH 7.6]. Propridium Iodide (Sigma Aldrich Co.) was added to 40µg/ml and RNAase A (Sigma Aldrich Co.) to 100µg/ml. The cells were then incubated at 37°C for 30 minutes. The samples were centrifuged at 2200rpm for 10 min, the supernatant removed and the remaining pellet (nuclei) resuspended in 200µl of sterile PBSA. Each sample was then syringed 10 times using 21 gauge needle. The samples were then transferred to LPS tubes and DNA content per cell analysed by Fluorescence activated cell sorting (FACS) using a FACScan flow cytometer (Becton Dickinson). Typically 25000 events were counted and recorded using CellQuest v1.1 software (Verity Software). Cell cycle distribution of the population was calculated using Modfit software (Verity Software) and expressed as percentage of cells in G0/G1, S and G2/M phases of the cell cycle.

Treating MCF7 cells with 1µM Compound 52 in Table 2 for 24 hours produced the following changes in cell cycle distribution:

Treatment	% Cells in G2/M
DMSO (control)	9.27%
10μM Compound 52	>50%

CLAIMS

1. The use of a compound of formula (I)



(I)

or a salt, ester or amide thereof;

where X is O, or S, S(O) or $S(O)_2$, or NR^6 where R^6 is hydrogen or C_{1-6}alkyl,;

R^5 is an optionally substituted 5-membered heteroaromatic ring,

R^1, R^2, R^3, R^4 are independently selected from, halo, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, -NR^7R^8 (wherein R^7 and R^8, which may be the same or different, each represents hydrogen or C_{1-3}alkyl), or -X^1R^9 (wherein X^1 represents a direct bond, -O-, -CH_2-, -OCO-, carbonyl, -S-, -SO-, -SO_2-, -$NR^{10}CO$-, -$CONR^{11}$-, -SO_2NR^{12}-, -$NR^{13}SO_2$- or -NR^{14}- (wherein R^{10}, R^{11}, R^{12}, R^{13} and R^{14} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), and R^9 is selected from one of the following groups:

1) hydrogen or C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro or amino,

2) C_{1-5}alkylX^2COR^{15} (wherein X^2 represents -O- or -NR^{16}- (in which R^{15} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{16} represents C_{1-3}alkyl, -$NR^{17}R^{18}$ or -OR^{19} (wherein R^{17}, R^{18} and R^{19} which may be the same or different each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkylX^3R^{20} (wherein X^3 represents -O-, -S-, -SO-, -SO_2-, -OCO-, -$NR^{21}CO$-, -$CONR^{22}$-, -SO_2NR^{23}-, -$NR^{24}SO_2$- or -NR^{25}- (wherein R^{21}, R^{22}, R^{23}, R^{24} and R^{25} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{20} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2

heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

4) C_{1-5}alkylX^4C_{1-5}alkylX^5R^{26} (wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO-, $-SO_2-$, $-NR^{27}CO-$, $-CONR^{28}-$, $-SO_2NR^{29}-$, $-NR^{30}SO_2-$ or $-NR^{31}-$ (wherein R^{27}, R^{28}, R^{29}, R^{30} and R^{31} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{26} represents hydrogen or C_{1-3}alkyl);

5) R^{32} (wherein R^{32} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkylsulphonylC_{1-4}alkyl);

6) C_{1-5}alkylR^{32} (wherein R^{32} is as defined hereinbefore);

7) C_{2-5}alkenylR^{32} (wherein R^{32} is as defined hereinbefore);

8) C_{2-5}alkynylR^{32} (wherein R^{32} is as defined hereinbefore);

9) R^{33} (wherein R^{33} represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents on an available carbon atom selected from hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, $-CONR^{34}R^{35}$ and $-NR^{36}COR^{37}$ (wherein R^{34}, R^{35}, R^{36} and R^{37}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

10) C_{1-5}alkylR^{33} (wherein R^{33} is as defined hereinbefore);

11) C_{2-5}alkenylR^{33} (wherein R^{33} is as defined hereinbefore);

12) C_{2-5}alkynylR^{33} (wherein R^{33} is as defined hereinbefore);

13) C_{1-5}alkylX^6R^{33} (wherein X^6 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{38}CO-$, $-CONR^{39}-$, $-SO_2NR^{40}-$, $-NR^{41}SO_2-$ or $-NR^{42}-$ (wherein R^{38}, R^{39}, R^{40}, R^{41} and R^{42} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore);

14) C_{2-5}alkenylX^7R^{33} (wherein X^7 represents -O-, -S-, -SO-, $-SO_2-$, $-NR^{43}CO-$, $-CONR^{44}-$, $-SO_2NR^{45}-$, $-NR^{46}SO_2-$ or $-NR^{47}-$ (wherein R^{43}, R^{44}, R^{45}, R^{46} and R^{47} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore);

15) C_{2-5}alkynylX^{8}R^{33} (wherein X^{8} represents -O-, -S-, -SO-, -SO_2-, -NR^{48}CO-, -CONR^{49}-, -SO_2NR^{50}-, -NR^{51}SO_2- or -NR^{52}- (wherein R^{48}, R^{49}, R^{50}, R^{51} and R^{52} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore);

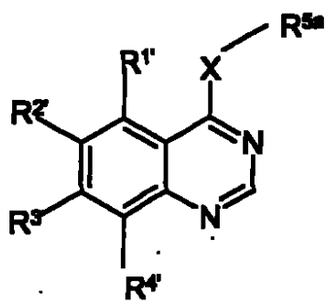
16) C_{1-3}alkylX^{9}C_{1-3}alkylR^{33} (wherein X^{9} represents -O-, -S-, -SO-, -SO_2-, -NR^{53}CO-, -CONR^{54}-, -SO_2NR^{55}-, -NR^{56}SO_2- or -NR^{57}- (wherein R^{53}, R^{54}, R^{55}, R^{56} and R^{57} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore); and

17) C_{1-3}alkylX^{9}C_{1-3}alkylR^{32} (wherein X^{9} and R^{28} are as defined hereinbefore);

in the preparation of a medicament for use in the inhibition of aurora 2 kinase.

2. A method for inhibiting aurora 2 kinase in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I), as defined in claim 1 or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

3. A compound of formula (IA)



(IA)

or a salt, ester or amide thereof;

where X is as defined in relation to formula (I);

R$^{1'}$, R$^{2'}$, R$^{3'}$, R$^{4'}$ are equivalent to R^{1}, R^{2}, R^{3}, R^{4} as defined in relation to formula (I) and R^{5a} is an optionally substituted 5-membered heteroaromatic ring, subject to the following provisos:

(i) that where R^{5a} is a pyrazole group, it carries a substitutent of formula (k), (ll) of (VI) above,

(ii) that where X is NH and R^{5a} is a substituted pyrazolone or tetrazolyl group, at least one of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ is other than hydrogen; or

(iii) that where X is O and R^{5a} is 1-methyl-4-nitro-1H-imidazol-5-yl, at least one of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ is other than hydrogen;

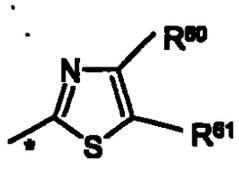
or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

4. A method for inhibiting aurora 2 kinase in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I), as defined in claim 3 or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

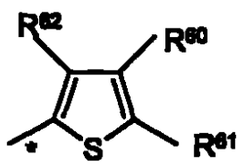
5. A compound according to claim 1 or 3 for use in a method of treatment of the human or animal body by therapy.

6. A pharmaceutical composition comprising a compound according to claim 1 or 3, in combination with a pharmaceutically acceptable carrier.

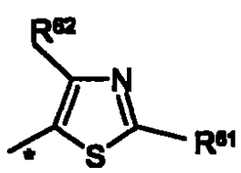
7. The composition as recited in Claim 3 wherein R^{5a} is selected from the group consisting of:



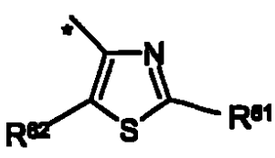
(a)



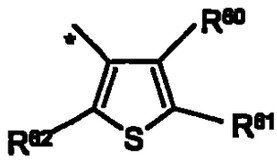
(b)



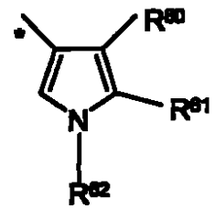
(c)

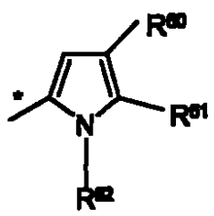


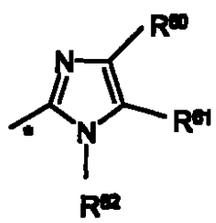
(d)

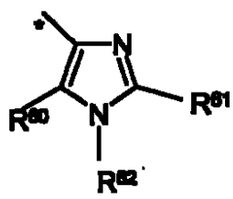


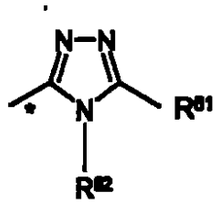
(e)


(f)


(g)

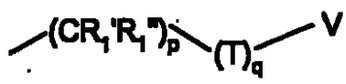

(h)


(i)


(j)

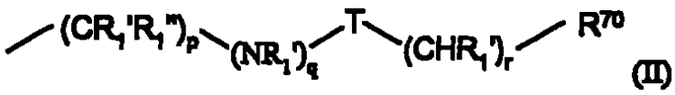
wherein where R^{60}, R^{61} and R^{62} are independently selected from hydrogen or a substituent group and * indicates the point of attachment to the group X in formula (IA).

8. The composition as recited in Claim 7 wherein R^{60}, R^{61} or R^{62} is a group of sub-formula (k):


(k)

wherein p and q are independently 0 or 1 and R_1' and R_1'' are independently hydrogen, hydroxy, optionally substituted alkyl, optionally substituted cycloalkyl, halogen, cyano, optionally substitued alkyl, or optionally substituted alkyenyl, wherein R_1' can form with R_1'' a 3 to 6 membered ring; wherein T is C=O, SO_n, C(=NOR)CO, C(O)C(O), C=NCN, or CV=NO or wherein n = 0, 1 or 2 and V is independently R^{63} or $N(R^{63})R^{64}$ wherein R^{63} and R^{64} are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted heterocyclyl, or R^{63} and R^{64} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring.

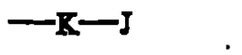
9. The composition as recited in Claim 7 wherein R^{60}, R^{61} or R^{62} is a group of sub-formula:



(II)

wherein p and q are independently 0 or 1, and r is 0, 1, 2, 3 or 4 and wherein R and R' are independently hydrogen, hydroxy, optionally substituted alkyl, optionally substituted cycloalkyl, halogen, cyano, optionally substitued alkyl, optionally substituted alkyenyl, wherein R can form with R' a 3 to 6 membered ring; wherein T is C=O, SO_n, C(=NOR)CO, C(O)C(O), C=NCN, or CV=NO or wherein n = 0, 1 or 2 and V is independently R^{63} or $N(R^{63})R^{64}$ wherein R^{63} and R^{64} are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted heterocyclyl, or R^{63} and R^{64} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring; wherein R^{70} is hydrogen, hydroxy (other than where q is 0), C_{1-6}alkyl, C_{1-6}alkoxy, amino, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, hydroxyC_{2-6}alkoxy, C_{1-6}alkoxyC_{2-6}alkoxy, aminoC_{2-6}alkoxy, *N*-C_{1-6}alkylaminoC_{2-6}alkoxy, *N,N*-(C_{1-6}alkyl)$_2$aminoC_{2-6}alkoxy or C_{3-7}cycloalkyl,

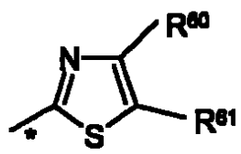
or R^{70} is of the Formula (III):



(III)

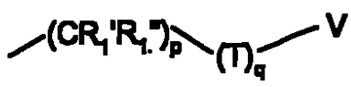
wherein J is aryl, heteroaryl or heterocyclyl and K is a bond, oxy, imino, *N*-(C_{1-6}alkyl)imino, oxyC_{1-6}alkylene, iminoC_{1-6}alkylene, *N*-(C_{1-6}alkyl)iminoC_{1-6}alkylene, -NHC(O) -, $-SO_2NH-$, $-NHSO_2-$ or -NHC(O)-C_{1-6}alkylene.

10. The composition as recited in Claim 7 wherein R^{3a} is represented by:



(a)

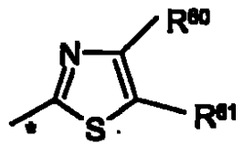
and wherein R^{60} is halogen, CN, or $CONR^{63}R^{64}$, and wherein R61 is sub-formula (k):



(k)

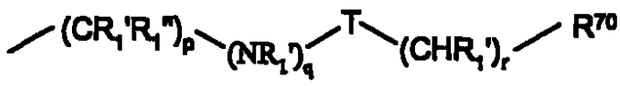
wherein p and q are independently 0 or 1 and R_1' and R_1'' are indedpendently hydrogen, hydroxy, optionally substituted alkyl, optionally substituted cycloalkyl, halogen, cyano, optionally substitued alkyl, optionally substituted alkyenyl, R_1' can form with R_1'' a 3 to 6 membered ring; wherein T is C=O, SO_n, C(=NOR)CO, C(O)C(O)), C=NCN, or V=NO or wherein n = 0, 1 or 2 and V is independently R^{63} or $N(R^{63})R^{64}$ wherein R^{63} and R^{64} are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted heterocyclyl, or R^{63} and R^{64} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring.

11. The composition as recited in Claim 7 wherein R^{5a} is represented by:



(a)

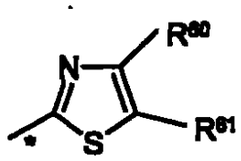
and wherein R^{60} is halogen, CN, or $CONR^{63}R^{64}$, and wherein R61 is sub-formula (k):



(II)

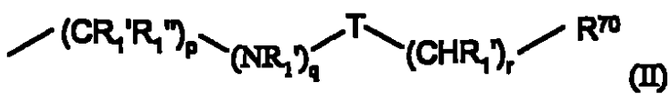
wherein p and q are independently 0 or 1, r is 0, 1, 2, 3 or 4 and R and R' are independently hydrogen, hydroxy, optionally substituted alkyl, optionally substituted cycloalkyl, halogen, cyano, optionally substitued alkyl, optionally substituted alkyenyl, R can form with the other R group a 3 to 6 membered ring; wherein T is C=O, SO_n, C(=NOR)CO, C(O)C(O)), C=NCN, or V=NO or wherein n = 0, 1 or 2 and V is independently R^{63} or $N(R^{63})R^{64}$ wherein R^{63} and R^{64} are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted heterocyclyl, or R^{63} and R^{64} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring; wherein R^{70} is hydrogen, hydroxy (other than where q is 0), C_{1-6}alkyl, C_{1-6}alkoxy, amino, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, hydroxyC_{2-6}alkoxy, C_{1-6}alkoxyC_{2-6}alkoxy, aminoC_{2-6}alkoxy, *N*-C_{1-6}alkylaminoC_{2-6}alkoxy, *N,N*-(C_{1-6}alkyl)$_2$aminoC_{2-6}alkoxy or C_{3-7}cycloalkyl.

12. The composition as recited in Claim 7 wherein R^{5a} is represented by:



(a)

and wherein R^{60} is halogen, CN, or $CONR^{63}R^{64}$, and wherein R61 is sub-formula (k):



(II)

wherein p and q are independently 0 or 1, r is 0, 1, 2, 3 or 4 and R and R' are independently hydrogen, hydroxy, optionally substituted alkyl, optionally substituted cycloalkyl, halogen,

cyano, optionally substitued alkyl, optionally substituted alkyenyl, R can form with the other R group a 3 to 6 membered ring; wherein T is C=O, SO_n, C(=NOR)CO, C(O)C(O)), C=NCN, or V=NO or wherein n = 0, 1 or 2 and V is independently R^{63} or $N(R^{63})R^{64}$ wherein R^{63} and R^{64} are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted heterocyclyl, or R^{63} and R^{64} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring; wherein R^{70} is of the Formula (III):

—K—J (III)

wherein J is aryl, heteroaryl or heterocyclyl and K is a bond, oxy, imino, *N*-(C_{1-6}alkyl)imino, oxyC_{1-6}alkylene, iminoC_{1-6}alkylene, *N*-(C_{1-6}alkyl)iminoC_{1-6}alkylene, -NHC(O) -, $-SO_2NH-$, $-NHSO_2-$ or -NHC(O)-C_{1-6}alkylene-,

and any aryl, heteroaryl or heterocyclyl group in a R^{70} group may be optionally substituted by one or more groups selected from hydroxy, halo, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy, carbamoyl, formyl, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -O-(C_{1-3}alkyl)-O-, C_{1-6}alkylS(O)$_n$- (wherein n is 0-2), *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{2-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkanoylamino, *N*-C_{1-6}alkylsulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino and C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino,

or any aryl, heteroaryl or heterocyclyl group in a R^{70} group may be optionally substituted with one or more groups of the Formula (IV):

—B^1—$(CH_2)_p$—A^1 (IV)

wherein A^1 is halo, hydroxy, C_{1-6}alkoxy, cyano, amino, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, carboxy, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-C_{1-6}alkylcarbamoyl or *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, p is 1 - 6, and B^1 is a bond, oxy, imino, *N*-(C_{1-6}alkyl)imino or -NHC(O)-, with the proviso that p is 2 or more unless B^1 is a bond or -NHC(O)-;

or any aryl, heteroaryl or heterocyclyl group in a R^{70} group may be optionally substituted with one or more groups of the Formula (V):

—E[1]—D[1] (V)

wherein D^1 is aryl, heteroaryl or heterocyclyl and E^1 is a bond, C_{1-6}alkylene, oxyC_{1-6}alkylene, oxy, imino, *N*-(C_{1-6}alkyl)imino, iminoC_{1-6}alkylene, *N*-(C_{1-6}alkyl)-iminoC_{1-6}alkylene, C_{1-6}alkylene-oxyC_{1-6}alkylene, C_{1-6}alkylene-iminoC_{1-6}alkylene, C_{1-6}alkylene-*N*-(C_{1-6}alkyl)-iminoC_{1-6}alkylene, -NHC(O)-, -NHSO$_2$-, -SO$_2$NH- or -NHC(O)-C_{1-6}alkylene-, and any aryl, heteroaryl or heterocyclyl group in a substituent on D^1 may be optionally substituted with one or more groups selected from hydroxy, halo, C_{1-6}alkyl, C_{1-6}alkoxy, carboxy, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-C_{1-6}alkylcarbamoyl, *N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{2-6}alkanoyl, amino, *N*-C_{1-6}alkylamino and *N*,*N*-(C_{1-6}alkyl)$_2$amino,

and any C_{3-7}cycloalkyl or heterocyclyl group in a R^{70} group may be optionally substituted with one or two oxo or thioxo substituents,

and any of the R^{70} groups defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, C_{1-6}alkoxy, *N*-C_{1-6}alkylamino, *N*,*N*-(C_{1-6}alkyl)$_2$amino and heterocyclyl.

13. A method for inhibiting aurora 2 kinase in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I), as defined in any one of Claims 7-12 or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

14. A compound as in any one of Claims 7-12, for use in a method of treatment of the human or animal body by therapy.

15. A pharmaceutical composition comprising a compound according to Claims 7-12 in combination with a pharmaceutically acceptable carrier.

16. A method for inhibiting aurora 2 kinase in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of

a compound of any one of Claims 7-12 or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01450

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 403/12, C07D 409/12, C07D 413/12, A61K 31/505, A61P 35/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9935132 A1 (GLAXO GROUP LIMITED), 15 July 1999 (15.07.99) ---	1-16
X	WO 9703069 A1 (GLAXO GROUP LIMITED), 30 January 1997 (30.01.97) ---	1-16
X	WO 9515758 A1 (PHONEPOULEC RORER PHARMACEUTICALS INC.), 15 June 1995 (15.06.95) ---	1-16
A	WO 9909016 A1 (AMERICAN CYANAMID COMPANY), 25 February 1999 (25.02.99) ---	1-16

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2001	08-11-2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/BS Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01450

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 0121597 A1 (ASTRAZENECA AB), 29 March 2001 (29.03.01)	1-16

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INTERNATIONAL SEARCH REPORT

Intern _ al application No.
PCT/SE01/01450

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 2, 4, 13 and 16
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Claims 2,4,13 and 16 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/01

International application No.
PCT/SE 01/01450

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9935132 A1	15/07/99	AU 733047 B	03/05/01
		AU 1978699 A	26/07/99
		AU 6302498 A	09/09/98
		EP 0969813 A	12/01/00
		GB 9800575 D	00/00/00
		IL 131477 D	00/00/00
WO 9703069 A1	30/01/97	AU 6613996 A	10/02/97
		EP 0843671 A	27/05/98
		GB 9514265 D	00/00/00
		HR 960316 A	28/02/98
		JP 11508906 T	03/08/99
WO 9515758 A1	15/06/95	AU 1305095 A	27/06/95
		EP 0871448 A	21/10/98
		SG 54172 A	16/11/98
		US RE36256 E	20/07/99
		US 5480883 A	02/01/96
		US 5646153 A	08/07/97
		US 5710158 A	20/01/98
		US 5714493 A	03/02/98
		US 5721237 A	24/02/98
		US 5795889 A	18/08/98
		US 6057320 A	02/05/00
WO 9909016 A1	25/02/99	AU 8602398 A	08/03/99
		BR 9811805 A	15/08/00
		CN 1271349 T	25/10/00
		EP 1000039 A	17/05/00
		HU 0002893 A	28/05/01
		NO 20000487 A	31/03/00
WO 0121597 A1	29/03/01	AU 7301900 A	24/04/01
		GB 9922171 D	00/00/00

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WO 02/00649
PCT/SE01/01450

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DATA ENTERED
FINAL CHECK

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

To:
GLOBAL INTELLECTUAL PROPERTY
ASTRAZENCA AB
Global Intellectual Property
S-151 85 Södertälje
SUÈDE

CODE | DATE | NTD

ANKOM 11 JAN 2002 GIPS

DATA ENTERED EF/08

FINAL CHECK MC

NOTIFICATION INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 03 January 2002 (03.01.02)	IMPORTANT NOTICE
Applicant's or agent's file reference 100108-1 WO	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/SE01/01450	21 June 2001 (21.06.01)	28 June 2000 (28.06.00)

Applicant
ASTRAZENECA AB et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:
KP,KR,US.

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
AE,AG,AL,AM,AP,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EA,EC, EE,EP,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MA, MD,MG,MK,MN,MW,MX,MZ,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 03 January 2002 (03.01.02) under No. WO 02/00649.

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and the PCT Applicant's Guide, Volume II.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.91.11

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Continuation of Form PCT/IB/308

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year)	IMPORTANT NOTICE
03 January 2002 (03 01 02)	
Applicant's or agent's file reference	**International application No**
100108 1 WO	PCT/SE01/01450

The applicant is hereby notified that, at the time of establishment of this Notice the time limit under Rule 46 1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

CODE | DATE | NTD
REC D JAN 1 6 2001 GIPUS
DATA ENTERED
FINAL CHECK

B3 89.360

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 100108-1 WO

Box No. I TITLE OF INVENTION
CHEMICAL COMPOUNDS

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

AstraZeneca AB
S-151 85 Södertälje
Sweden

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality:
SE

State *(that is, country)* of residence:
SE

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MORTLOCK, Andrew
AstraZeneca R&D Alderley
Alderley Park
Macclesfield, Cheshire SK10 4TG
United Kingdom

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:
GB

State *(that is, country)* of residence:
GB.

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

Global Intellectual Property
AstraZeneca AB
S-151 85 Södertälje
Sweden

Telephone No.
+46 8 553 260 00

Facsimile No.
+46 8 553 288 20

Teleprinter No.

Agent's registration No. with the Office

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

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Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

(If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

JUNG, Frederic
AstraZeneca Pharma
Parc Industriel Pompelle
Chemin de Vrilly, BP 1050
FR-51689 Reims Cedex 2
France

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: FR

State *(that is, country)* of residence: FR

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

---

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

---

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

---

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

---

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

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Box No.V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ AP **ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ EA **Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ EP **European Patent:** AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ OA **OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ AE United Arab Emirates	☒ GE Georgia	☒ MW Malawi
☒ AG Antigua and Barbuda	☒ GH Ghana	☒ MX Mexico
☒ AL Albania	☒ GM Gambia	☒ MZ Mozambique
☒ AM Armenia	☒ HR Croatia	☒ NO Norway
☒ AT Austria	☒ HU Hungary	☒ NZ New Zealand
☒ AU Australia	☒ ID Indonesia	☒ PL Poland
☒ AZ Azerbaijan	☒ IL Israel	☒ PT Portugal
☒ BA Bosnia and Herzegovina	☒ IN India	☒ RO Romania
☒ BB Barbados	☒ IS Iceland	☒ RU Russian Federation
☒ BG Bulgaria	☒ JP Japan	☒ SD Sudan
☒ BR Brazil	☒ KE Kenya	☒ SE Sweden
☒ BY Belarus	☒ KG Kyrgyzstan	☒ SG Singapore
☒ BZ Belize	☒ KP Democratic People's Republic of Korea	☒ SI Slovenia
☒ CA Canada	☒ KR Republic of Korea	☒ SK Slovakia
☒ CH & LI Switzerland and Liechtenstein	☒ KZ Kazakhstan	☒ SL Sierra Leone
☒ CN China	☒ LC Saint Lucia	☒ TJ Tajikistan
☒ CO Colombia	☒ LK Sri Lanka	☒ TM Turkmenistan
☒ CR Costa Rica	☒ LR Liberia	☒ TR Turkey
☒ CU Cuba	☒ LS Lesotho	☒ TT Trinidad and Tobago
☒ CZ Czech Republic	☒ LT Lithuania	☒ TZ United Republic of Tanzania
☒ DE Germany	☒ LU Luxembourg	☒ UA Ukraine
☒ DK Denmark	☒ LV Latvia	☒ UG Uganda
☒ DM Dominica	☒ MA Morocco	☒ US United States of America
☒ DZ Algeria	☒ MD Republic of Moldova	☒ UZ Uzbekistan
☒ EE Estonia	☒ MG Madagascar	☒ VN Viet Nam
☒ ES Spain	☒ MK The former Yugoslav Republic of Macedonia	☒ YU Yugoslavia
☒ FI Finland	☒ MN Mongolia	☒ ZA South Africa
☒ GB United Kingdom		☒ ZW Zimbabwe
☒ GD Grenada		

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ ...EC. Ecuador..... ☐ ..... ☐ .....

☐ ..... ☐ ..... ☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

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Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 28.06.2000 (28 June 2000)	00401842.0		EP	
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

** Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* ....

.....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):*

ISA / SE .....

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

☐ Box No. VIII (i) Declaration as to the identity of the inventor :

☐ Box No. VIII (ii) Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent :

☐ Box No. VIII (iii) Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application :

☐ Box No. VIII (iv) Declaration of inventorship (only for the purposes of the designation of the United States of America) :

☐ Box No. VIII (v) Declaration as to non-prejudicial disclosures or exceptions to lack of novelty :

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) the following number of sheets in paper form:

request (including declaration sheets)	:	5
description (excluding sequence listing part)	:	232
claims	:	11
abstract	:	1
drawings	:	
Sub-total number of sheets	:	249
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)*	:	
Total number of sheets	:	249

(b) sequence listing part of description filed in computer readable form

(i) ☐ only (under Section 801(a)(i))

(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*: .....

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:

		Number of items
1. ☒ fee calculation sheet	:	1
2. ☒ original separate power of attorney	:	2
3. ☐ original general power of attorney	:	
4. ☒ copy of general power of attorney; reference number, if any: GF1519/2001	:	1
5. ☐ statement explaining lack of signature	:	
6. ☒ priority document(s) identified in Box No. VI as item(s): (1)	:	1
7. ☐ translation of international application into *(language)*:	:	
8. ☐ separate indications concerning deposited microorganism or other biological material	:	
9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))		
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	:	
10. ☐ other *(specify)*:	:	

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Södertälje, 21 June 2001

Christer Wahlström
Global Intellectual Property, AstraZeneca AB

For receiving Office use only

1. Date of actual receipt of the purported international application:

2. Drawings:
☐ received:
☐ not received:

3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:

4. Date of timely receipt of the required corrections under PCT Article 11(2):

5. International Searching Authority (if two or more are competent): ISA /

6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

138 HPO ANKOM 2002-10-09

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Global Intellectual Property
AstraZeneca AB
151 85 Södertälje

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

10 OCT 2002 (PCT Rule 71.1)

Date of mailing *(day/month/year)*	08-10-2002
Applicant's or agent's file reference: 100108-1 WO	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE01/01450	21-06-2001	28-06-2000

Applicant
AstraZeneca Aktiebolag
et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in som Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/
Patent- och registreringsverket
Box 5055
S-102 42 STOCKHOLM
Facsimile No. 08-697 72 88
Telex
17978
PATOREG-S

Authorized officer
Staffan Rennermalm
Telephone No. 08-782 25 00

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
100108-1 WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SE01/01450	21.06.2001	28.06.2000
International Patent Classification (IPC) or national classification and IPC7		
C07D 403/12, C07D 409/12, C07D 413/15, A61K 31/505, A61P 35/00		
Applicant		
AstraZeneca AB *et al*		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 233 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.12.2001	04.10.2002
Name and mailing address of the IPEA/SE	Authorized officer
Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Telex 17978 PATOREG-S Facsimile No. 08-667 72 88	Eva Johansson/BS Telephone No. 08-782 25 00

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE01/01450

I. Basis of the report

1. With regard to the elements of the international application:*

☐ the international application as originally filed

☒ the description:
pages see Supplemental Box, as originally filed
pages _____, filed with the demand
pages see Supplemental Box, filed with the letter of 2002-08-21

☒ the claims:
pages 233-243, as originally filed
pages _____, as amended (together with any statement) under article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheet/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under Item I and annexed to this report.*

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE01/01450

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 2, 4, 13 and 16

because:

☒ the said international application, or the said claims Nos. 2, 4, 13 and 16
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE01/01450

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 3, 5-12, 14-15	YES
	Claims		NO
Inventive step (IS)	Claims	1, 3, 5-13, 14-15	YES
	Claims		NO
Industrial applicability (IA)	Claims	1, 3 5-12, 14-15	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Cited documents:

D1) WO 9935132 A1
D2) WO 9703069 A1
D3) WO 9515758 A!
D4) WO 9909016 A1

D1, D2 and D3 the most relevant documents disclose quinazoline derivatives where X in position 4 is O, S, SO, S(O)2, NH or NR which can be substituted with a 5-membered heterocyclic ring. The substitution on the aromatic part of the ring system can vary in the same way as for the claimed compound. The known compounds can be used for the treatment of diseases mediated by protein tyrosine kinase activity e. g. cancer.

The claimed invention discloses the use quinazoline derivatives in the preparation of a medicament for use in the inhibition of aurora 2 kinase e.g. cancer. The invention also discloses new derivatives of quinazolines.

The known compounds are structurally close to those claimed compounds and are used for treating cancer.

There is no information in the cited documents that the known compounds can inhibit the effect of aurora 2 kinase. Thus the activity in the cited documents and in this application are different.

Thus, claims 1, 3,5-12, 14 and 15 are considered to fulfil the requirement of novelty, inventive step and industrial applicability.

D4) discloses the general state of art and is not considered to be of particular relevance.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/SE01/01450

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: I Basis of report

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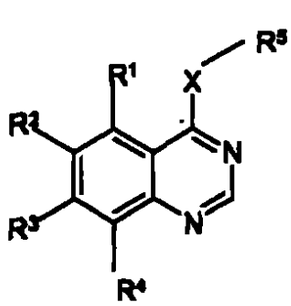
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(54) Title: SUBSTITUTED QUINAZOLINE DERIVATIVES AND THEIR USE AS INHIBITORS



(I)

(57) Abstract: The use of a compound of formula (I) or a salt, ester or amide thereof; where X is O, or S, S(O) or $S(O)_2$, or NR^6 where R^6 is hydrogen or C_{1-4}alkyl; R^5 is an optionally substituted 5-membered heteroaromatic ring, R^1, R^2, R^3, R^4 are independently selected from various specified moieties, in the preparation of a medicament for use in the inhibition of aurora 2 kinase. Certain compounds are novel and these, together with pharmaceutical compositions containing them are also described and claimed.

WO 02/00649 A1

SUBSTITUTED QUINAZOLINE DERIVATES AND THEIR USE AS INHIBITORS

The present invention relates to certain quinazoline derivatives for use in the treatment of certain diseases in particular to proliferative disease such as cancer and in the preparation of medicaments for use in the treatment of proliferative disease, to novel quinazoline compounds and to processes for their preparation, as well as pharmaceutical compositions containing them as active ingredient.

Cancer (and other hyperproliferative disease) is characterised by uncontrolled cellular proliferation. This loss of the normal regulation of cell proliferation often appears to occur as the result of genetic damage to cellular pathways that control progress through the cell cycle.

In eukaryotes, the cell cycle is largely controlled by an ordered cascade of protein phosphorylation. Several families of protein kinases that play critical roles in this cascade have now been identified. The activity of many of these kinases is increased in human tumours when compared to normal tissue. This can occur by either increased levels of expression of the protein (as a result of gene amplification for example), or by changes in expression of co activators or inhibitory proteins.

The first identified, and most widely studied of these cell cycle regulators have been the cyclin dependent kinases (or CDKs). Activity of specific CDKs at specific times is essential for both initiation and coordinated progress through the cell cycle For example, the CDK4 protein appears to control entry into the cell cycle (the G0-G1-S transition) by phosphorylating the retinoblastoma gene product pRb. This stimulates the release of the transcription factor E2F from pRb, which then acts to increase the transcription of genes necessary for entry into S phase . The catalytic activity of CDK4 is stimulated by binding to a partner protein, Cyclin D. One of the first demonstrations of a direct link between cancer and the cell cycle was made with the observation that the Cyclin D1 gene was amplified and cyclin D protein levels increased (and hence the activity of CDK4 increased) in many human tumours (Reviewed in Sherr, 1996, Science 274: 1672-1677; Pines, 1995, Seminars in Cancer Biology 6: 63-72). Other studies (Loda et al., 1997, Nature Medicine 3(2): 231-234; Gemma et al., 1996, International Journal of Cancer 68(5): 605-11; Elledge et al. 1996, Trends in Cell Biology 6; 388-392) have shown that negative regulators of CDK function are frequently down regulated or deleted in human tumours again leading to inappropriate activation of these kinases.

More recently, protein kinases that are structurally distinct from the CDK family have been identified which play critical roles in regulating the cell cycle and which also appear to be important in oncogenesis. These include the newly identified human homologues of the *Drosophila* aurora and *S.cerevisiae* Ipl1 proteins. *Drosophila* aurora and *S.cerevisiae* Ipl1, which are highly homologous at the amino acid sequence level, encode serine/threonine protein kinases. Both aurora and Ipl1 are known to be involved in controlling the transition from the G2 phase of the cell cycle through mitosis, centrosome function, formation of a mitotic spindle and proper chromosome separation / segregation into daughter cells. The two human homologues of these genes, termed aurora1 and aurora2, encode cell cycle regulated protein kinases. These show a peak of expression and kinase activity at the G2/M boundary (aurora2) and in mitosis itself (aurora1). Several observations implicate the involvement of human aurora proteins, and particularly aurora2 in cancer. The aurora2 gene maps to chromosome 20q13, a region that is frequently amplified in human tumours including both breast and colon tumours. Aurora2 may be the major target gene of this amplicon, since aurora2 DNA is amplified and aurora2 mRNA overexpressed in greater than 50% of primary human colorectal cancers. In these tumours aurora2 protein levels appear greatly elevated compared to adjacent normal tissue. In addition, transfection of rodent fibroblasts with human aurora2 leads to transformation, conferring the ability to grow in soft agar and form tumours in nude mice (Bischoff et al., 1998, The EMBO Journal. 17(11): 3052-3065). Other work (Zhou et al., 1998, Nature Genetics. 20(2): 189-93) has shown that artificial overexpression of aurora2 leads to an increase in centrosome number and an increase in aneuploidy.

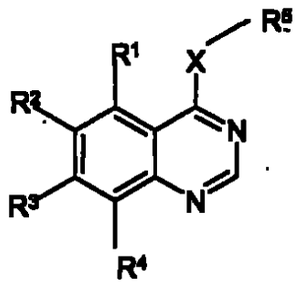
Importantly, it has also been demonstrated that abrogation of aurora2 expression and function by antisense oligonucleotide treatment of human tumour cell lines (WO 97/22702 and WO 99/37788) cads to cell cycle arrest in the G2 phase of the cell cycle and exerts an antiproliferative effect in these tumour cell lines. This indicates that inhibition of the function of aurora2 will have an antiproliferative effect that may be useful in the treatment of human tumours and other hyperproliferative diseases.

A number of quinazoline derivatives have been proposed hitherto for use in the inhibition of various kinases. Examples of such proposals are included in WO 92/20642 and EP-B-584222 which relates to bicyclic compounds which inhibit epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) receptor tyrosine kinase, WO 95/15758 which describes the use of bis ring systems for the selective inhibition of CSF-1R tyrosine

kinase activity, and WO 99/09016, WO 97/03069 and US 570158 which describe the use of certain quinazoline compounds as tyrosine kinase inhibitors in other contexts.

The applicants have found a series of compounds which inhibit the effect of the aurora2 kinase and which are thus of use in the treatment of proliferative disease such as cancer, in particular in such diseases such as colorectal or breast cancer where aurora 2 kinase is known to be active.

The present invention provides the use of a compound of formula (I)



(I)

or a salt, ester or amide thereof;

where X is O, or S, S(O) or $S(O)_2$, or NR^6 where R^6 is hydrogen or C_{1-6}alkyl,;

R^5 is an optionally substituted 5-membered heteroaromatic ring,

R^1, R^2, R^3, R^4 are independently selected from, halo, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, -NR^7R^8 (wherein R^7 and R^8, which may be the same or different, each represents hydrogen or C_{1-3}alkyl), or -X^1R^9 (wherein X^1 represents a direct bond, -O-, -CH_2-, -OCO-, carbonyl, -S-, -SO-, -SO_2-, -NR^{10}CO-, -$CONR^{11}$-, -SO_2NR^{12}-, -$NR^{13}SO_2$- or -NR^{14}- (wherein R^{10}, R^{11}, R^{12}, R^{13} and R^{14} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), and R^9 is selected from one of the following groups:

1) hydrogen or C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro or amino,

2) C_{1-5}alkylX^2COR^{15} (wherein X^2 represents -O- or -NR^{16}- (in which R^{15} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{16} represents C_{1-3}alkyl, -$NR^{17}R^{18}$ or -OR^{19} (wherein R^{17}, R^{18} and R^{19} which may be the same or different each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkylX^3R^{20} (wherein X^3 represents -O-, -S-, -SO-, -SO_2-, -OCO-, -NR^{21}CO-, -$CONR^{22}$-, -SO_2NR^{23}-, -$NR^{24}SO_2$- or -NR^{25}- (wherein R^{21}, R^{22}, R^{23}, R^{24} and R^{25} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{20} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2 heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

4) C_{1-5}alkylX^4C_{1-5}alkylX^5R^{26} (wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO-, -SO_2-, -NR^{27}CO-, -$CONR^{28}$-, -SO_2NR^{29}-, -$NR^{30}SO_2$- or -NR^{31}- (wherein R^{27}, R^{28}, R^{29}, R^{30} and R^{31} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{26} represents hydrogen or C_{1-3}alkyl);

5) R^{32} (wherein R^{32} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkylsulphonylC_{1-4}alkyl);

6) C_{1-5}alkylR^{32} (wherein R^{32} is as defined hereinbefore);

7) C_{2-5}alkenylR^{32} (wherein R^{32} is as defined hereinbefore);

8) C_{2-5}alkynylR^{32} (wherein R^{32} is as defined hereinbefore);

9) R^{33} (wherein R^{33} represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents on an available carbon atom selected from hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, -$CONR^{34}R^{35}$ and -$NR^{36}COR^{37}$ (wherein R^{34}, R^{35}, R^{36} and R^{37}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

10) C_{1-5}alkylR^{33} (wherein R^{33} is as defined hereinbefore);

11) C_{2-5}alkenylR^{33} (wherein R^{33} is as defined hereinbefore);

12) C_{2-5}alkynylR^{33} (wherein R^{33} is as defined hereinbefore);

13) C_{1-5}alkylX^6R^{33} (wherein X^6 represents -O-, -S-, -SO-, -SO_2-, -NR^{38}CO-, -$CONR^{39}$-, -SO_2NR^{40}-, -$NR^{41}SO_2$- or -NR^{42}- (wherein R^{38}, R^{39}, R^{40}, R^{41} and R^{42} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore);

14) C_{2-5}alkenylX^7R^{33} (wherein X^7 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{43}CO$-, $-CONR^{44}$-, $-SO_2NR^{45}$-, $-NR^{46}SO_2$- or $-NR^{47}$- (wherein R^{43}, R^{44}, R^{45}, R^{46} and R^{47} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore);

15) C_{2-5}alkynylX^8R^{33} (wherein X^8 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{48}CO$-, $-CONR^{49}$-, $-SO_2NR^{50}$-, $-NR^{51}SO_2$- or $-NR^{52}$- (wherein R^{48}, R^{49}, R^{50}, R^{51} and R^{52} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore);

16) C_{1-3}alkylX^9C_{1-3}alkylR^{33} (wherein X^9 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{53}CO$-, $-CONR^{54}$-, $-SO_2NR^{55}$-, $-NR^{56}SO_2$- or $-NR^{57}$- (wherein R^{53}, R^{54}, R^{55}, R^{56} and R^{57} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore); and

17) C_{1-3}alkylX^9C_{1-3}alkylR^{32} (wherein X^9 and R^{28} are as defined hereinbefore):

in the preparation of a medicament for use in the inhibtion of aurora 2 kinase. In particular, such medicaments are useful in the treatment of proliferative disease such as cancer, and in particular cancers where aurora 2 is upregulated such as colon or breast cancers.

In this specification the term 'alkyl' when used either alone or as a suffix includes straight chained, branched structures. Unless otherwise stated, these groups may contain up to 10, preferably up to 6 and more preferably up to 4 carbon atoms. Similarly the terms "alkenyl" and "alkynyl" refer to unsaturated straight or branched structures containing for example from 2 to 10, preferably from 2 to 6 carbon atoms. Cyclic moieties such as cycloalkyl, cycloalkenyl and cycloalkynyl are similar in nature but have at least 3 carbon atoms. Terms such as "alkoxy" comprise alkyl groups as is understood in the art.

The term "halo" includes fluoro, chloro, bromo and iodo. References to aryl groups include aromatic carbocylic groups such as phenyl and naphthyl. The term "heterocyclyl" includes aromatic or non-aromatic rings, for example containing from 4 to 20, suitably from 5 to 8 ring atoms, at least one of which is a heteroatom such as oxygen, sulphur or nitrogen. Examples of such groups include furyl, thienyl, pyrrolyl, pyrrolidinyl, imidazolyl, triazolyl, thiazolyl, tetrazolyl, oxazolyl, isoxazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazinyl, quinolinyl, isoquinolinyl, quinoxalinyl, benzothiazolyl, benzoxazolyl, benzothienyl or benzofuryl.

"Heteroaryl" refers to those groups described above which have an aromatic character. The term "aralkyl" refers to aryl substituted alkyl groups such as benzyl.

Other expressions used in the specification include "hydrocarbyl" which refers to any structure comprising carbon and hydrogen atoms. For example, these may be alkyl, alkenyl, alkynyl, aryl, heterocyclyl, alkoxy, aralkyl, cycloalkyl, cycloalkenyl or cycloalkynyl.

The term "functional group" refers to reactive substituents such as nitro, cyano, halo, oxo, $=CR^{78}R^{79}$, $C(O)_xR^{77}$, OR^{77}, $S(O)_yR^{77}$, $NR^{78}R^{79}$, $C(O)NR^{78}R^{79}$, $OC(O)NR^{78}R^{79}$, $=NOR^{77}$, $-NR^{77}C(O)_xR^{78}$, $-NR^{77}CONR^{78}R^{79}$, $-N=CR^{78}R^{79}$, $S(O)_yNR^{78}R^{79}$ or $-NR^{77}S(O)_yR^{78}$ where R^{77}, R^{78} and R^{79} are independently selected from hydrogen or optionally substituted hydrocarbyl, or R^{78} and R^{79} together form an optionally substituted ring which optionally contains further heteroatoms such as $S(O)_y$ oxygen and nitrogen, x is an integer of 1 or 2, y is 0 or an integer of 1-3.

Suitable optional substituents for hydrocarbyl groups R^{77}, R^{78} and R^{79} include halo, perhaloalkyl such as trifluoromethyl, mercapto, hydroxy, carboxy, alkoxy, aryl, heteroaryl, heteroaryloxy, alkenyloxy, alkynyloxy, alkoxyalkoxy, aryloxy (where the aryl group may be substituted by halo, nitro, or hydroxy), cyano, nitro, amino, mono- or di-alkyl amino, oximino or $S(O)_y$ where y is as defined above.

Preferably R^4 is hydrogen.

Suitably R^1 is hydrogen or a group set out for R^2 or R^3 below. Frequently, R^1 is hydrogen.

In a preferred embodiment, at least one group R^1, R^2 or R^3, preferably R^3, comprises a chain of at least 3 and preferably at least 4 optionally substituted carbon atoms or heteroatoms such as oxygen, nitrogen or sulphur. Most preferably the chain is substituted by a polar group which assists in solubility.

Suitably R^3 is a group X^1R9. Preferably in this case, X^1 is oxygen and R^9 is selected from a group of formula (1) or (10) above. Particular groups R^9 are those in group (1) above, especially alkyl such as methyl or halo substituted alkyl, or those in group (10) above. In one preferred embodiment, at least one of R^2 or R^3 is a group $-OC_{1-3}alkylR^{33}$ and R^{33} is a heterocyclic ring such as an N-linked morpholine ring such as 3-morpholinopropoxy.

Suitably R^2 is selected from, halo, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, $-NR^9R^{10}$ (wherein R^9 and R^{10}, which may be the same or different, each represents hydrogen or C_{1-3}alkyl), or a group $-X^1R^{11}$. Preferred examples of $-X^1R^{11}$ for R^2 include those listed above in relation to R^3.

Other examples for R^2 and R^3 include methoxy or 3,3,3-trifluoroethoxy.

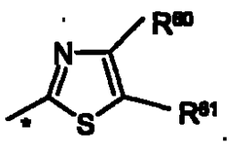
Preferably X is NH or O and is most preferably NH.

Examples of 5-membered aromatic rings R^5 include rings containing one or more heteroatoms selected from sulphur, oxygen and nitrogen. Such rings include pyrrole, pyrazole, pyrazolone, imidazole, oxazole, furan, tetrazole, triazole, thiazole, thiophene, or thiadiazole, any of which may be optionally substituted. In particular, R^5 includes at least one nitrogen or sulphur heteroatoms. Preferred rings for R^5 include pyrrole, pyrazole, imidazole, triazole, thiazole, thiophene, or thiadiazole.

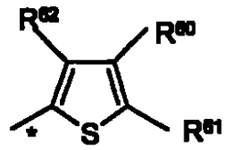
In a particular embodiment, R^5 is a sulphur containing ring. Suitably R^5 is optionally substituted thiazole, optionally substituted thiophene or optionally substituted thiadiazole and preferably, optionally substituted thiazole or optionally substituted thiophene.

More preferably, R^5 is a substituted thiazole or substituted thiophene group.

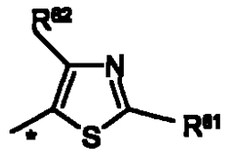
In particular, R^5 is a group of formula (a), (b), (c) or (d) and preferably (a) or (b):



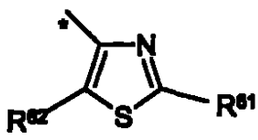
(a)



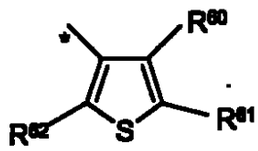
(b)



(c)



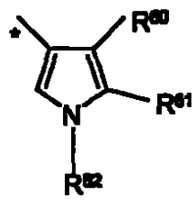
(d)

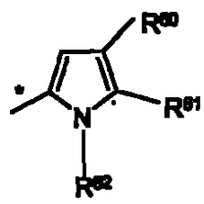


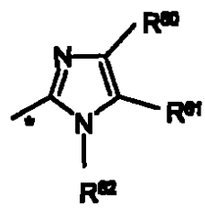
(e)

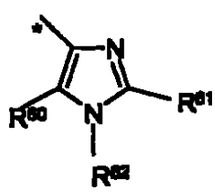
where R^{60}, R^{61} and R^{62} are independently selected from hydrogen or a substituent group and * indicates the point of attachment to the group X in formula (I). In particular, one of R^{60}, R^{61} or R^{62} is a substituent group and the others are either hydrogen or a small substituent such as C_{1-3} alkyl, for instance methyl. Suitably R^{62} is hydrogen. Preferably R^{61} is other than hydrogen,

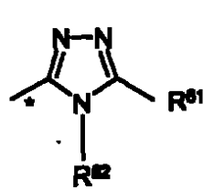
Alternatively, R^5 is an optionally substituted nitrogen containing ring such as a group of formula (f), (g), (h), (i) or (j):


(f)


(g)

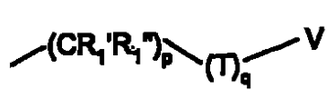

(h)


(i)


(j)

Suitable substituents for groups R^5 include optionally substituted hydrocarbyl, optionally substituted heterocylyl or a functional group as defined above.

In particular, R^{60}, R^{61} or R^{62} is a group of sub-formula (k)



(k)

where p and q are independently 0 or 1 and wherein R_1' and R_1'' are independently hydrogen, hydroxy, optionally substituted alkyl, optionally substituted cycloalkyl, halogen, cyano, optionally substituted alkyl, optionally substituted alkyenyl. The optionally substituted alkyl or alkynyl may be substituted with halo, nitro, cyano, hydroxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulfamoyl, C_{1-4} alkyl, C_{2-4}alkenyl, C_{2-4} alkynyl, C_{3-6} cycloalkyl, C_{3-6} cycloalkenyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkanoyloxy, N-(C_{1-4} alkyl), N(C_{1-4} alkyl)$_2$, C_{1-4} alkanoylamino, (C_{1-4} alkanoyl)$_2$amino, N-(C_{1-4}alkyl)carbamoyl, N,N-(C_{1-4})$_2$carbamoyl, C_{1-4})S, C_{1-4}S(O), (C_{1-4}alkyl)S(O)$_2$, (C_{1-4}) alkoxycarbonyl, N-(C_{1-4} alkyl)sulfamoyl, N,N-C_{1-4} alkyl)sulfamoyl, C_{1-4} alkylsolfonylamino, or heterocyclyl. R is preferably C_{1-4} alkyl, C_{2-4}alkenyl, or C_{2-4} alkynyl, and R_1' can form with R_1'' a 3 to 6 membered ring.

T is C=O, SO_n, C(=NOR)CO, C(O)C(O), C=NCN, CV=NO or wherein n = 0, 1 or 2 and V is independently R^{63} or N(R^{63})R^{64} wherein R^{63} and R^{64} are independently selected

from hydrogen, optionally substituted hydrocarbyl or optionally substituted heterocyclyl, or R^{63} and R^{64} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring.

Examples of groups for R^{63} and R^{64} include the group $-(CH_2)_qR^{70}$ where q and R^{70} are as defined below in relation to formula (II).

Suitably one of R^{63} or R^{64} is hydrogen, or methyl, ethyl or propyl optionally substituted with hydroxy and preferably one of R^{63} or R^{64} is hydrogen. In this case, the other is suitably a larger substituent for example of at least 4 carbon or heteroatoms, and is optionally substituted hydrocarbyl or optionally substituted heterocyclyl. Particular optionally substituted hydrocarbyl groups for R^{63} or R^{64} include alkyl, cycloalkyl, alkenyl, or aryl any of which is optionally substituted with a functional group as defined above, or in the case of aryl groups, with an alkyl group and in the case of alkyl group, with an aryl or heterocyclic group either of which may themselves be optionally substituted with alkyl or a functional group. Examples of optionally substituted aryl groups R^{63} or R^{64} include phenyl optionally substituted with one or more groups selected from C_{1-6} alkyl group such as methyl or ethyl (either of which may be optionally substituted with a functional group such as hydroxy), or a functional group as defined above (such as halo like fluoro, chloro or bromo, hydroxy, alkoxy such as methoxy, trifluoromethyl, nitro, cyano, trifluromethoxy, $CONH_2$, $C(O)CH_3$, amino, or dimethylamino).

When R^{63} or R^{64} is an optionally substituted alkyl group, it is suitably a C_{1-6}alkyl group, optionally substituted with one or more functional groups (such as cyano, hydroxy, alkoxy, in particular methoxy, COOalkyl such as $COOCH_3$), or aryl optionally substituted with a functional group as defined above (in particular in relation to R^{63} or R^{64} themselves, or an optionally substituted heterocyclic group such as N-methyl pyrrole.

When R^{63} and R^{64} is optionally substituted cycloalkyl, it is suitable cyclohexyl optionally substituted with a functional group such as hydroxy.

When R^{63} and R^{64} is optionally substituted alkenyl, it is suitably prop-2-enyl.

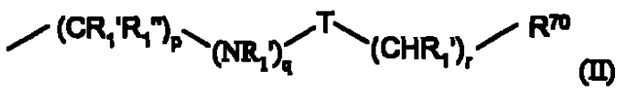
When R^{63} or R^{64} is optionally substituted heterocyclyl, or R^{63} and R^{64} together form a heterocyclic group, then this may be aromatic or non-aromatic and includes in particular, piperidine, piperazine, morpholino, pyrrolidine or pyridine any of which may be optionally substituted with a functional group such as hydroxy, alkoxy such as methoxy, or alkyl such as methyl which may itself be substituted with for instance a hydroxy group.

Alternatively at least one of R^{60}, R^{61} or R^{62} is a functional group, and in particular, one of R^{60}, R^{61} or R^{62} is a functional group a group of formula $(CR_2)_pC(O)_xR^{77}$ where R, p, x and R^{77} are as defined above, and in particular x is 2 and R^{77} is hydrogen or alkyl such as methyl.

Alternatively, R^5 is substituted by one or more groups selected from nitro, halo, C_{1-6}alkyl, optionally substituted C_{1-6} alkoxy, C_{1-4}alkoxymethyl, di(C_{1-4}alkoxy)methyl, C_{1-6}alkanoyl, trifluoromethyl, cyano, amino, C_{2-4}alkenyl, C_{2-6}alkynyl, a phenyl group, a benzyl group or a 5-6-membered heterocyclic group with 1-3 heteroatoms, selected independently from O, S and N, which heterocyclic group may be aromatic or non-aromatic and may be saturated (linked via a ring carbon or nitrogen atom) or unsaturated (linked vis a ring carbon atom), and which phenyl, benzyl or heterocyclic group may bear on one or more ring carbon atoms up to 5 substituents selected from hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino, nitro, C_{2-4}alkanoyl, C_{1-4}alkanoylamino, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulphanyl, C_{1-4}alkylsulphinyl, C_{1-4}alkylsulphonyl, carbamoyl, N-C_{1-4}alkylcarbamoyl, N,N-di(C_{1-4}alkyl)carbamoyl, aminosulphonyl, N-C_{1-4}alkylaminosulphonyl, N,N-di(C_{1-4}alkyl)aminosulphonyl, C_{1-4}alkylsulphonylamino, and a saturated heterocyclic group selected from morpholino, thiomorpholino, pyrrolidinyl, piperazinyl, piperidinyl imidazolidinyl and pyrazolidinyl, which saturated heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-3}alkyl, C_{1-3}alkoxy, C_{1-3}alkanoyloxy, trifluoromethyl, cyano, amino, nitro and C_{1-4}alkoxycarbonyl.

Suitably R^5 is substituted with at least one group which has at least 4 atoms which may be carbon or heteroatoms forming a chain. A particular example of such a substituent is optionally substituted alkoxy or alkoxy methyl. Suitable substituents for the alkoxy group include those listed above in relation to R^{77}, R^{78} and R^{79}.

A further particular substituent group for R^5 is a group of sub-formula (II)



(II)

where p and q are independently 0 or 1, and r is 0, 1, 2, 3 or 4 and, R1', R1'' and T are as previously defined above;

R^{70} is hydrogen, hydroxy (other than where q is 0), C_{1-6}alkyl, C_{1-6}alkoxy, amino, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, hydroxyC_{2-6}alkoxy, C_{1-6}alkoxyC_{2-6}alkoxy,

aminoC$_{2-6}$alkoxy, *N*-C$_{1-6}$alkylaminoC$_{2-6}$alkoxy, *N*,*N*-(C$_{1-6}$alkyl)$_2$aminoC$_{2-6}$alkoxy or C$_{3-7}$cycloalkyl,

or R^{70} is of the Formula (III):



(III)

wherein J is aryl, heteroaryl or heterocyclyl and K is a bond, oxy, imino, *N*-(C$_{1-6}$alkyl)imino, oxyC$_{1-6}$alkylene, iminoC$_{1-6}$alkylene, *N*-(C$_{1-6}$alkyl)iminoC$_{1-6}$alkylene, -NHC(O) -, -SO_2NH-, -NHSO_2- or -NHC(O)-C$_{1-6}$alkylene-,

and any aryl, heteroaryl or heterocyclyl group in a R^{70} group may be optionally substituted by one or more groups selected from hydroxy, halo, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy, carbamoyl, formyl, sulphamoyl, C$_{1-6}$alkyl, C$_{2-6}$alkenyl, C$_{2-6}$alkynyl, C$_{1-6}$alkoxy, -O-(C$_{1-3}$alkyl)-O-, C$_{1-6}$alkylS(O)$_n$- (wherein n is 0-2), *N*-C$_{1-6}$alkylamino, *N*,*N*-(C$_{1-6}$alkyl)$_2$amino, C$_{1-6}$alkoxycarbonyl, *N*-C$_{1-6}$alkylcarbamoyl, *N*,*N*-(C$_{1-6}$alkyl)$_2$carbamoyl, C$_{2-6}$alkanoyl, C$_{1-6}$alkanoyloxy, C$_{1-6}$alkanoylamino, *N*-C$_{1-6}$alkylsulphamoyl, *N*,*N*-(C$_{1-6}$alkyl)$_2$sulphamoyl, C$_{1-6}$alkylsulphonylamino and C$_{1-6}$alkylsulphonyl-*N*-(C$_{1-6}$alkyl)amino,

or any aryl, heteroaryl or heterocyclyl group in a R^{70} group may be optionally substituted with one or more groups of the Formula (IV):



(IV)

wherein A^1 is halo, hydroxy, C$_{1-6}$alkoxy, cyano, amino, *N*-C$_{1-6}$alkylamino, *N*,*N*-(C$_{1-6}$alkyl)$_2$amino, carboxy, C$_{1-6}$alkoxycarbonyl, carbamoyl, *N*-C$_{1-6}$alkylcarbamoyl or *N*,*N*-(C$_{1-6}$alkyl)$_2$carbamoyl, p is 1 - 6, and B^1 is a bond, oxy, imino, *N*-(C$_{1-6}$alkyl)imino or -NHC(O)-, with the proviso that p is 2 or more unless B^1 is a bond or -NHC(O)-;

or any aryl, heteroaryl or heterocyclyl group in a R^{70} group may be optionally substituted with one or more groups of the Formula (V):



(V)

wherein D^1 is aryl, heteroaryl or heterocyclyl and E^1 is a bond, C_{1-6}alkylene, oxyC_{1-6}alkylene, oxy, imino, *N*-(C_{1-6}alkyl)imino, iminoC_{1-6}alkylene, *N*-(C_{1-6}alkyl)-iminoC_{1-6}alkylene, C_{1-6}alkylene-oxyC_{1-6}alkylene, C_{1-6}alkylene-iminoC_{1-6}alkylene, C_{1-6}alkylene-*N*-(C_{1-6}alkyl)-iminoC_{1-6}alkylene, -NHC(O)-, -$NHSO_2$-, -SO_2NH- or -NHC(O)-C_{1-6}alkylene-, and any aryl, heteroaryl or heterocyclyl group in a substituent on D^1 may be optionally substituted with one or more groups selected from hydroxy, halo, C_{1-6}alkyl, C_{1-6}alkoxy, carboxy, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-C_{1-6}alkylcarbamoyl, *N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{2-6}alkanoyl, amino, *N*-C_{1-6}alkylamino and *N,N*-(C_{1-6}alkyl)$_2$amino,

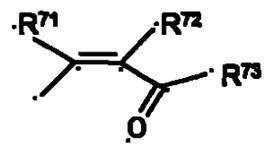
and any C_{3-7}cycloalkyl or heterocyclyl group in a R^{70} group may be optionally substituted with one or two oxo or thioxo substituents,

and any of the R^{70} groups defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, C_{1-6}alkoxy, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino and heterocyclyl.

A preferred example of a substituent of formula (II) is a group where q is 0.

A particular example of a group R^{70} in formula (II) is phenyl.

Another preferred substituent group for R^5 is a group of formula (VI)



(VI)

where R^{71} and R^{72} are independently selected from hydrogen or C_{1-4}alkyl, or R^{71} and R^{72} together form a bond, and R^{73} is a group OR^{74}, $NR^{75}R^{76}$ where R^{74}, R^{75} and R^{76} are independently selected from optionally substituted hydrocarbyl or optionally substituted heterocyclic groups, and R^{75} and R^{76} may additionally form together with the nitrogen atom to which they are attached, an aromatic or non-aromatic heterocyclic ring which may contain further heteroatoms.

Suitable optional substituents for hydrocarbyl or heterocyclic groups R^{74}, R^{75} and R^{76} include functional groups as defined above. Heterocyclic groups R^{74}, R^{75} and R^{76} may further be substituted by hydrocarbyl groups.

In particular, R^{71} and R^{72} in sub-formula (VI) are hydrogen.

Particular examples of R^{73} are groups OR^{74} where R^{74} is C_{1-4}alkyl.

Further examples of R^{73} are groups of formula $NR^{75}R^{76}$ where one of R^{75} or R^{76} is hydrogen and the other is optionally substituted C_{1-6}alkyl, optionally substituted aryl or optionally substituted heterocyclyl.

In particular, one of R^{75} or R^{76} is hydrogen and the other is C_{1-6}alkyl optionally substituted with trifluoromethyl, C_{1-3} alkoxy such as methoxy, cyano, thioC_{1-4}alkyl such as methylthio, or heterocyclyl optionally substituted with hydrocarbyl, such as indane, furan optionally substituted with C_{1-4} alkyl such as methyl.

In another embodiment, one of R^{75} or R^{76} is hydrogen and the other is an optionally substituted heterocyclic group such as pyridine, or a phenyl group optionally substituted with for example one or more groups selected from halo, nitro, alkyl such as methyl, or alkoxy such as methoxy.

Suitable pharmaceutically acceptable salts of compounds of Formula (I) or Formula (IA) include acid addition salts such as methanesulfonate, fumarate, hydrochloride, hydrobromide, citrate, maleate and salts formed with phosphoric and sulphuric acid. There may be more than one cation or anion depending on the number of charged functions and the valency of the cations or anions. Where the compound of Formula (I) or Formula (IA) includes an acid functionality, salts may be base salts such as an alkali metal salt for example sodium, an alkaline earth metal salt for example calcium or magnesium, an organic amine salt for example triethylamine, morpholine, *N*-methylpiperidine, *N*-ethylpiperidine, procaine, dibenzylamine, *N,N*-dibenzylethylamine or amino acids for example lysine. A preferred pharmaceutically acceptable salt is a sodium salt.

An *in vivo* hydrolysable ester of a compound of the Formula (I) or Formula (IA) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol.

Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkyl esters such as methyl or ethyl esters, C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxy-carbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

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An *in vivo* hydrolysable ester of a compound of the Formula (I) or Formula (IA) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy: A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl.

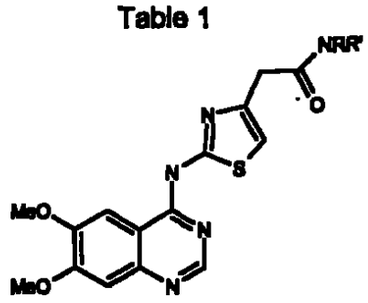
Suitable amides are derived from compounds of Formula (I) or Formula (IA) which have a carboxy group which is derivatised into an amide such as a N-C_{1-6}alkyl and N,N-di-(C_{1-6}alkyl)amide such as N-methyl, N-ethyl, N-propyl, N,N-dimethyl, N-ethyl-N-methyl or N,N-diethylamide.

Preferred compounds of Formula (I) or Formula (IA) are those that are stable in mouse, rat, or human serum, preferably those that are stable in human serum.

Esters which are not *in vivo* hydrolysable may be useful as intermediates in the production of the compounds of Formula (I) or Formula (IA).

Particular examples of compounds of Formula (I) or Formula (IA) are set out in Tables 1 to 30 below.

Table 1



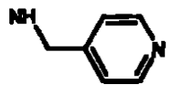
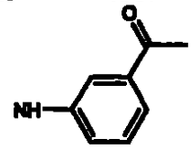
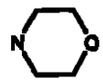
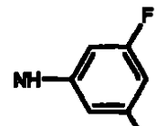
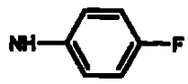
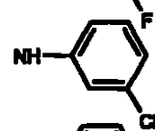
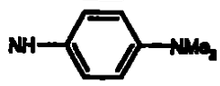
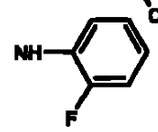
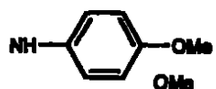
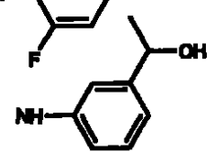
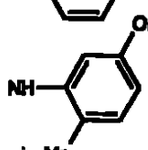
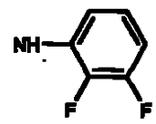
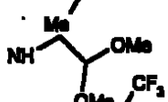
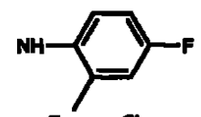
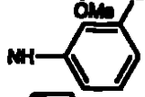
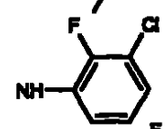
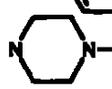
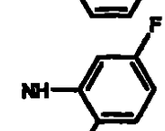
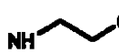
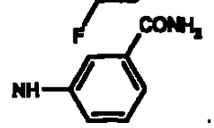
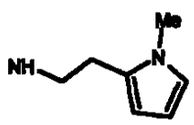
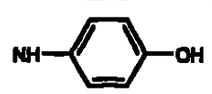
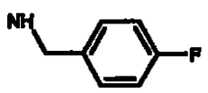
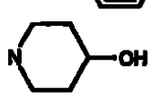
Compound No	NRR'	Compound No	NRR'
1		15	
2		16	
3		17	
4		18	
5		19	
6		20	
7		21	
8		22	
9		23	
10		24	
11		25	
12			
13			
14			

Table 1 (contd)

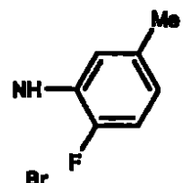
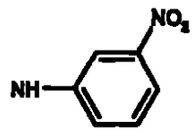
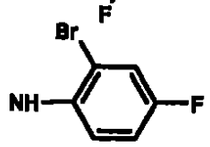
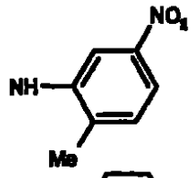
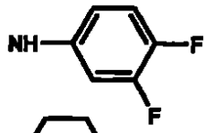
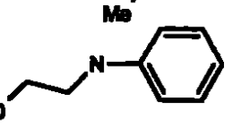
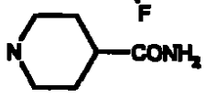
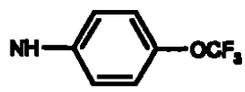
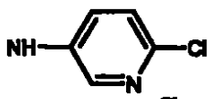
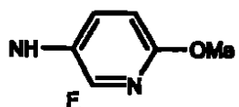
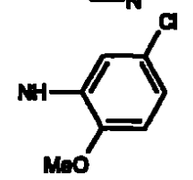
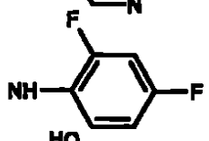
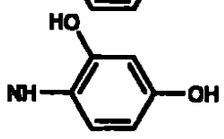
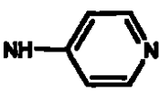
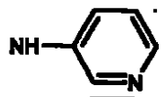
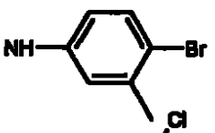
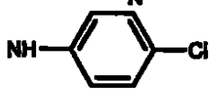
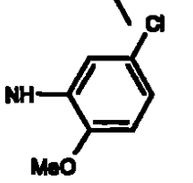
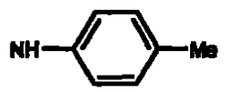
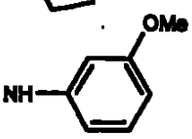
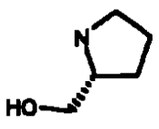
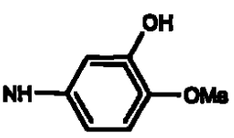
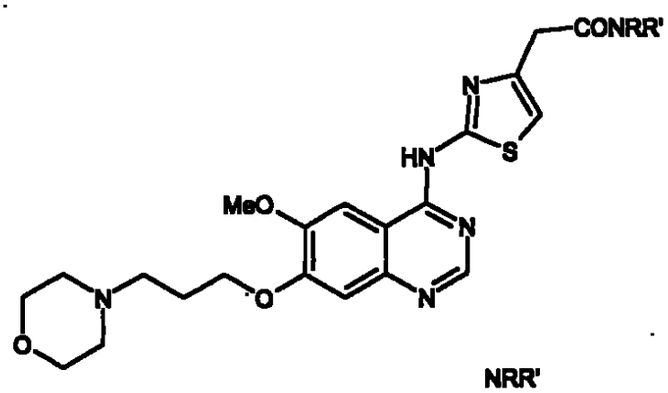
Compound No	NRR'	Compound No.	NRR'
26		39	
27		40	
28		41	
29		42	
30		43	
31		44	
32		45	
33		46	
34		47	
35		48	
36		49	
37		50	
38			

Table 2



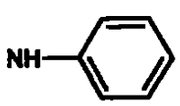
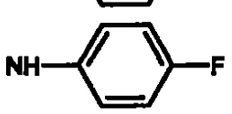
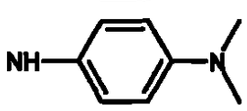
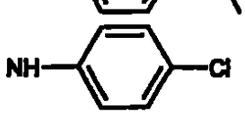
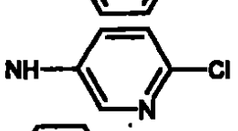
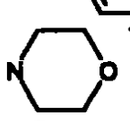
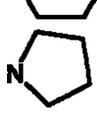
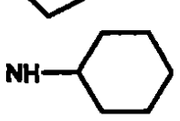
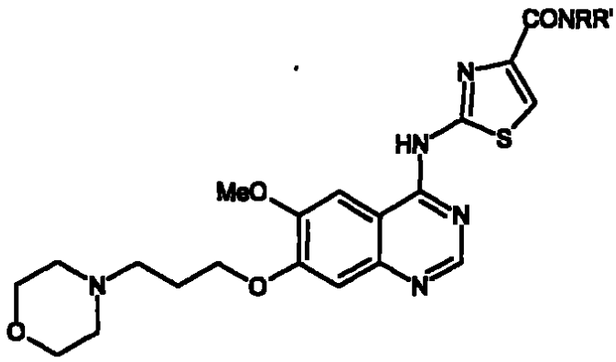
Compound No	NRR'
51	
52	
53	
54	
55	
56	
57	
58	

Table 3



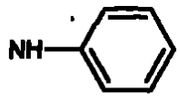
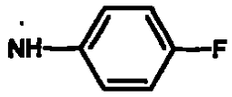
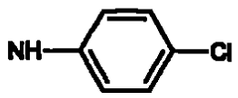
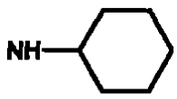
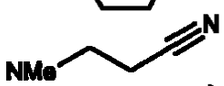
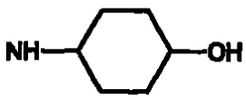
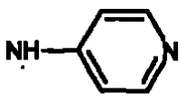
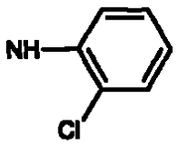
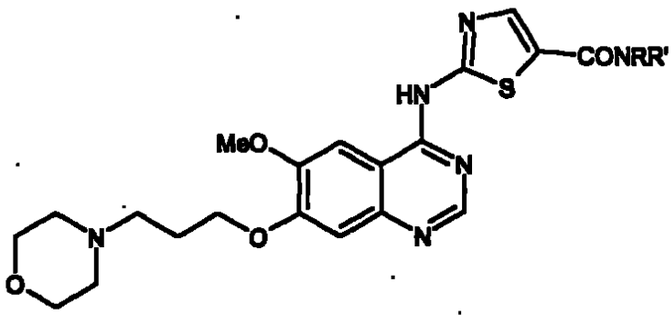
Compound No	NRR'
59	
60	
61	
62	
63	
64	
65	
66	

Table 4



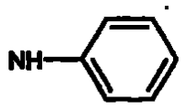
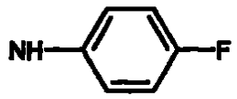
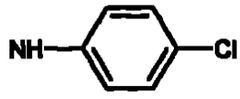
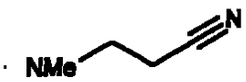
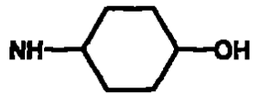
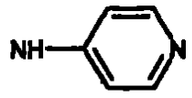
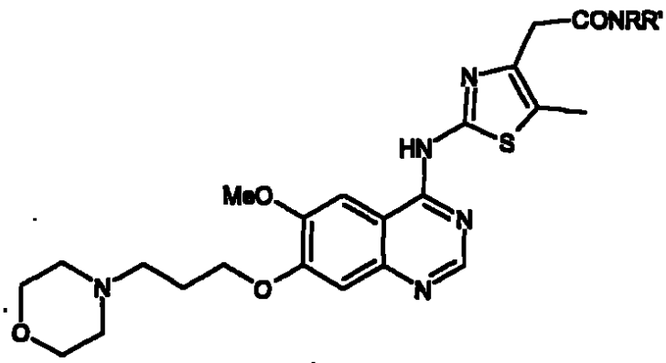
Compound No	NRR'
67	
68	
69	
70	
71	
72	
73	

Table 5



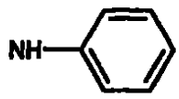
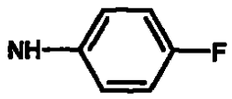
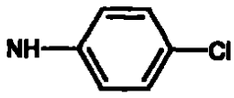
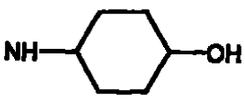
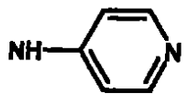
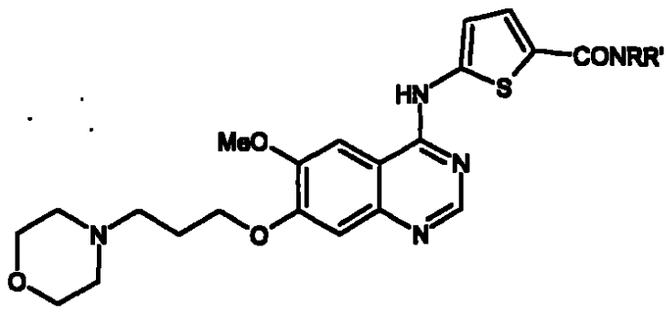
Compound No	NRR'
74	
75	
76	
77	
78	

Table 6



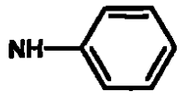
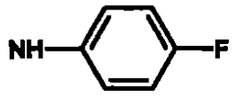
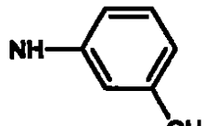
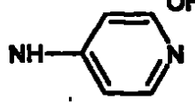
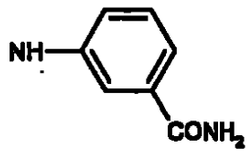
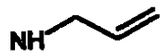
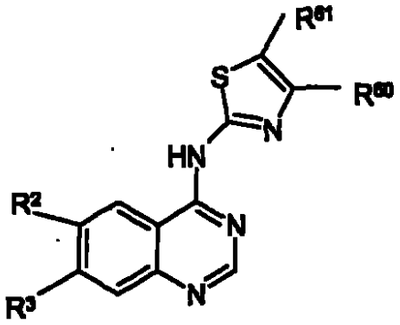
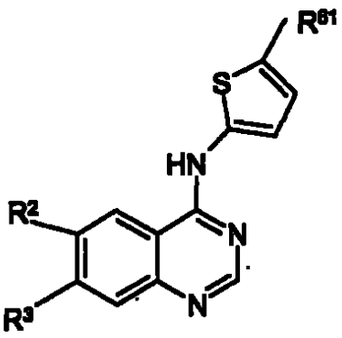
Compound No.	NRR'
79	
80	
81	
82	
83	
84	
85	
86	

Table 7



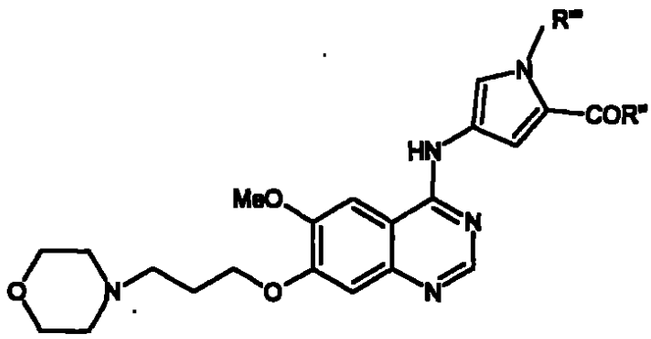
No.	R^2	R^3	R^{60}	R^{61}
200	OCH_3	OCH_3	$CH_2COOCH_2CH_3$	H
201	OCH_3	OCH_3	CH_2COOH	H
202	OCH_3	OCH_3	CH_3	$COOCH_2CH_3$
203	OCH_3	$O(CH_2)_3$-N-morpholino	CH_3	$COOCH_2CH_3$
204	OCH_3	$O(CH_2)_3$-N-morpholino	CH_3	COOH
205	OCH_3	$O(CH_2)_3$-N-morpholino	$CH_2COOCH_2CH_3$	H
206	OCH_3	$O(CH_2)_3$-N-morpholino	$COOCH_2CH_3$	H
207	OCH_3	$O(CH_2)_3$-N-morpholino	COOH	H
208	OCH_3	$O(CH_2)_3$-N-morpholino	H	$COOCH_2CH_3$
209	OCH_3	$O(CH_2)_3$-N-morpholino	H	COOH
210	OCH_3	$O(CH_2)_3$-N-morpholino	$CH_2COOCH_2CH_3$	CH_3
211	OCH_3	$O(CH_2)_3$-N-morpholino	CH_2COOH	CH_3

Table 8



No.	R^2	R^3	R^{61}
212	OCH_3	$O(CH_2)_3$-N-morpholino	COOH
213	OCH_3	OCH_3	$COOCH_2CH_3$
214	OCH_3	OCH_3	COOH

Table 9



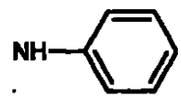
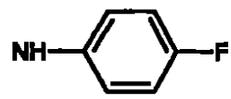
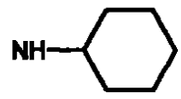
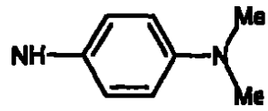
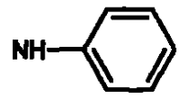
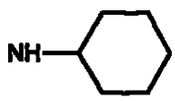
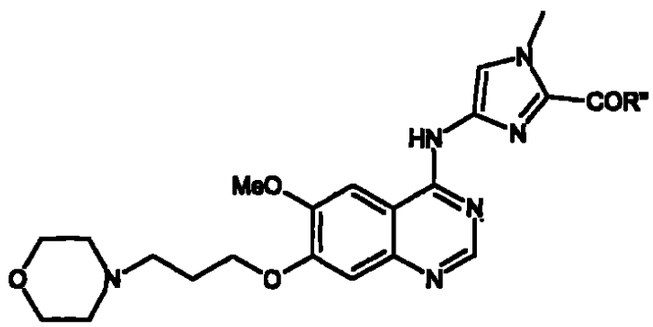
Compound No	R'''	R''
250	CH_3	OCH_3
251	CH_3	OH
252	CH_3	
253	CH_3	
254	CH_3	
255	CH_3	
256	H	OCH_2CH_3
257	H	OH
258	H	
259	H	

Table 10



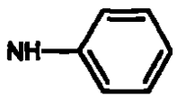
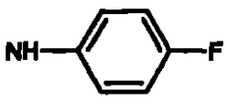
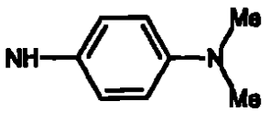
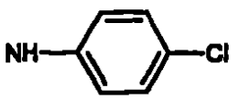
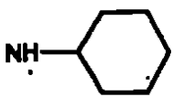
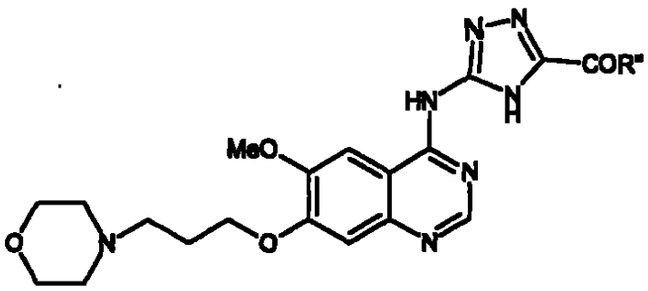
Compound No	R"
260	$COOCH_3$
261	COOH
262	
263	
264	
265	
266	
267	

Table 11



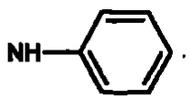
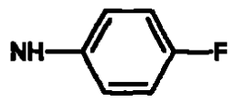
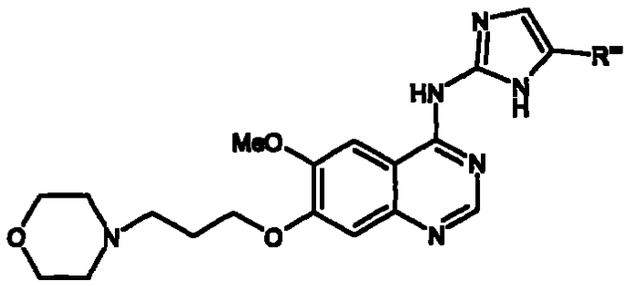
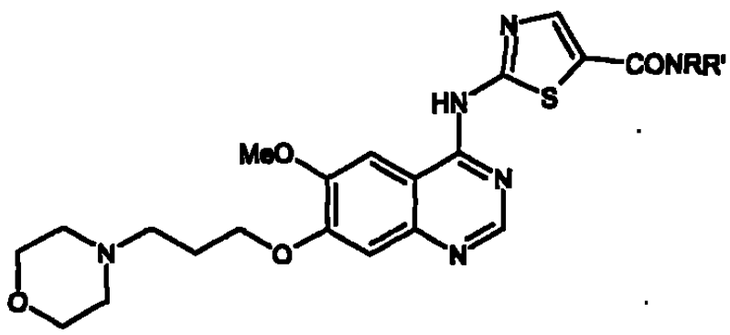
Compound No	R"
268	$COOCH_2CH_3$
269	COOH
270	
271	
272	

Table 12



Compound No.	R'''
300	H
301	$COOCH_2CH_3$

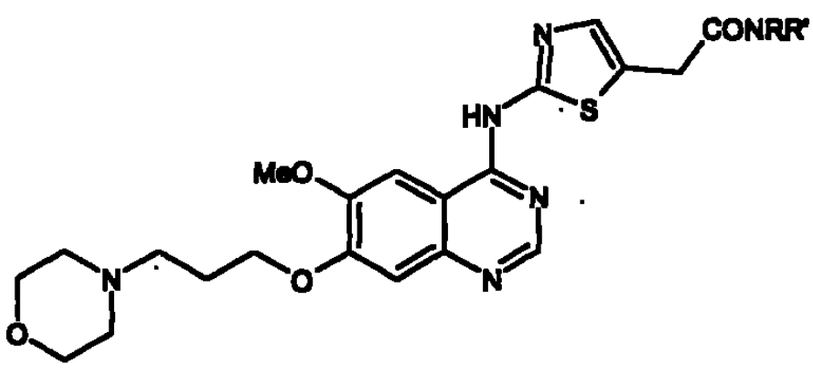
TABLE 13



N°	NRR'	N°	NRR'
302	4-methoxyaniline	320	2-methyl-4-fluoroaniline
303	4-methylaniline	321	2-fluoro-5-methylaniline
304	2-aminopyridine	322	4-fluorobenzylamine
305	2-aminobenzyl alcohol	323	3,4-difluorobenzylamine
306	4-methoxybenzylamine	324	3-methylaniline
307	3-nitroaniline	325	2-(methylthio)aniline
308	Aminoacetonitrile	326	5-aminoindole
309	2-methyl-5-nitroaniline	327	3-aminobenzonitrile
310	Cyclopropylamine	328	2,4-difluorobenzylamine
311	4-nitrobenzylamine	329	3-(2-aminoethyl)pyridine
312	2-anilinoethanol	330	N-methylisobutylamine
313	Furfurylamine	331	2-aminobenzylamine
314	3-chloroaniline	332	3-methylbutylamine

315	2-methoxyaniline	333	1-aminomethyl-1-cyclohexanol
316	thiophene-2-methylamine	334	2-aminomethylpyrazine
317	Neopentylamine	335	3-methoxyaniline
318	2,6-difluorobenzylamine	336	4-chlorobenzylamine
319	2-methylallylamine		

TABLE 14



N°	NRR'	N°	NRR'
337	Aniline	357	2-methoxyaniline
338	3-chloro-4-fluoroaniline	358	2-fluoroaniline
339	4-chloroaniline	359	thiophene-2-methylamine
340	3,4-difluoroaniline	360	2-amino-1-phenylethanol
341	3-methoxyaniline	361	3-(1-hydroxyethyl)aniline
342	2-chloroaniline	362	neopentylamine

343 4-methoxyaniline

344 4-methylaniline

345 2-methylaniline

346 2-aminopyridine

347 2-aminobenzylalcohol

348 2-amino-3-methyl-1-butanol

349 2-anilino ethanol

350 3-chloro-4-methylaniline

351 3-nitroaniline

352 aminoacetonitrile

353 2-methyl-5-nitroaniline

354 2-amino-5-chloropyridine

355 4-trifluoromethylaniline

356 3-chloroaniline

363 3-fluoro-4-methoxyaniline

364 2-methyl-4-fluoroaniline

365 2,5-difluoroaniline

366 2-fluoro-4-chloroaniline

367 2-fluoro-4-methylaniline

368 3-methylaniline

369 2-(methylthio)aniline

370 5-aminoindole

371 2,4-difluoroaniline

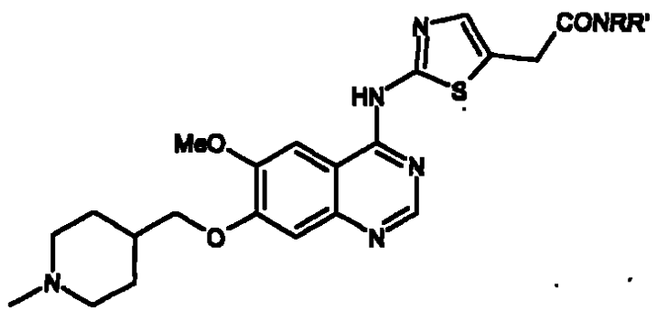
372 2-fluoro-4-methylaniline

373 3-cyanoaniline

374 2-methyl-5-fluoroaniline

375 2-methyl-5-chloroaniline

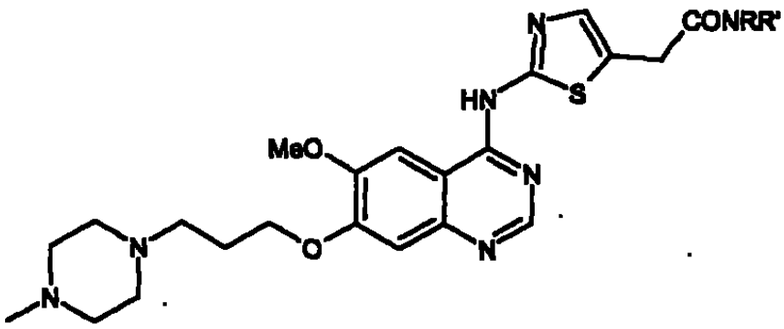
TABLE 15



Nº	NRR'	Nº	NRR'
376	aniline	390	3-fluoro-4-methoxyaniline
377	3-chloro-4-fluoroaniline	391	2-methyl-4-fluoroaniline
378	2-aminopyridine	392	2-amino-4-methylpyridine
379	3,4-difluoroaniline	393	2,5-difluoroaniline
380	2-chloroaniline	394	2-fluoro-4-chloroaniline
381	4-methylaniline	395	2-fluoro-5-methylaniline
382	2-methylaniline	396	3-methylaniline
383	4-chloroaniline	397	2,4-difluoroaniline
384	4-fluoroaniline	398	2-fluoro-4-methylaniline
385	2-amino-6-methylpyridine	399	3-cyanoaniline
386	3-methoxyaniline	400	2-methyl-5-fluoroaniline
387	2-amino-5-chloropyridine	401	3,5-difluoroaniline
388	3-chloroaniline	402	3-fluoroaniline

389 2-fluoroaniline

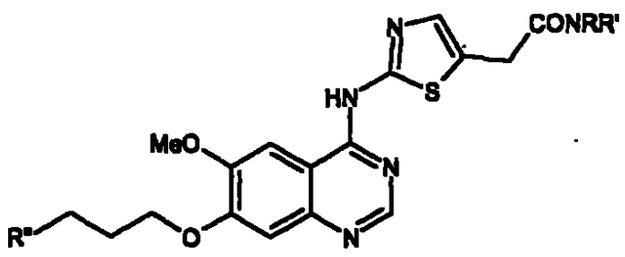
TABLE 16



Nº	NRR'	Nº	NRR'
403	Aniline		
404	3,4-difluoroaniline		
405	2-aminopyridine	418	2-fluoro-4-methylaniline
406	3-chloro-4-fluoroaniline	419	3-fluoro-4-methoxyaniline
407	2-chloroaniline		
408	4-methylaniline	420	2-methyl-4-fluroaniline
409	2-methylaniline	421	2-amino-4-methylpyridine
410	4-chloroaniline	422	2,5-difluoraniline
411	4-fluoroaniline	423	2-fluoro-4-chloroaniline
412	2-amino-6-methylpyridine	424	2-fluoro-5-methylaniline
413	3-methoxyaniline	425	3-methylaniline
414	2-amino-5-chloropyridine	426	2,4-difluoroaniline
415	3-chloroaniline	427	2-methyl-5-fluoroamline

416	2-fluoroaniline	428	3,5-difluoroaniline
417	3-cyanoaniline	429	3-fluoroaniline

TABLE 17



N°	R"	NRR'
430	pyrrolidine	3-chloroaniline
431	pyrrolidine	3,4-difluoroaniline
432	dimethylamine	3,5-difluoroaniline
433	2-amino-2-methyl-1-propanol	3-chloro-4-fluoroaniline
434	2-amino-2-methyl-1-propanol	3-fluoroaniline
435	4-hydroxypiperidine	3,4-difluoroaniline
436	N,N-dimethylethylenediamine	3,4-difluoroaniline
437	piperidine	3,4-difluoroaniline
438	2-methylaminoethanol	3,4-difluoroaniline
439	1,2-diamino-2-methylpropane	3,4-difluoroaniline
440	cyclohexylamine	3,4-difluoroaniline
441	N,N,N'-trimethylethylenediamine	3,4-difluoroaniline
442	D-prolinol	3,4-difluoroaniline

443	L-prolinol	3,4-difluoroaniline
444	3-pyrrolidinol	3,4-difluoroaniline
445	1-(2-aminoethyl)pyrrolidine	3,4-difluoroaniline
446	1-acetylpiperazine	3,4-difluoroaniline
447	1-(2-morpholinoethyl)piperazine	3,4-difluoroaniline
448	2-(2-hydroxyethyl)piperidine	3,4-difluoroaniline
449	1-(2-hydroxyethyl)piperazine	3,4-difluoroaniline
450	cyclopentylamine	3,4-difluoroaniline
451	4-(2-hydroxyethyl)piperidine	3,4-difluoroaniline
452	L-alanine tert-butyester	3,4-difluoroaniline
453	3-hydroxypiperidine	3,4-difluoroaniline
454	4-hydroxymethylpiperidine	3,4-difluoroaniline
455	1-amino-2-propanol	3,4-difluoroaniline
456	L-alanine-tert-butylester	3-chloroaniline
457	2-methylaminoethanol	3-chloroaniline
458	1,2-diamino-2-methylpropane	3-chloroaniline
459	cyclohexylamine	3-chloroaniline
460	N,N-dimethylethylenediamine	3-chloroaniline
461	N,N,N'-trimethylethylenediamine	3-chloroaniline
462	D-prolinol	3-chloroaniline

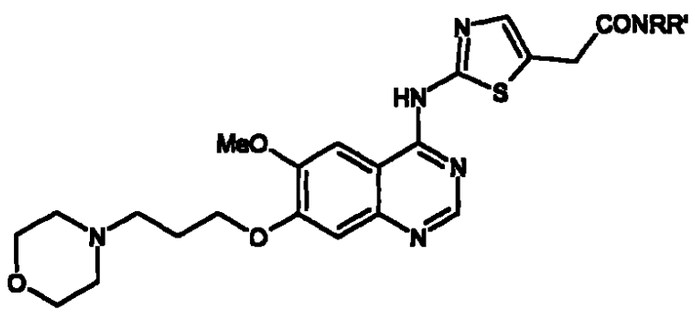
463	L-prolinol	3-chloroaniline
464	4-hydroxypiperidine	3-chloroaniline
465	3-pyrrolidinol	3-chloroaniline
466	1-(2-aminoethyl)pyrrolidine	3-chloroaniline
467	4-hydroxymethylpiperidine	3-chloroaniline
468	1-(2-hydroxyethyl)piperazine	3-chloroaniline
469	cyclopentylamine	3-chloroaniline
470	4-(2-hydroxyethyl)piperidine	3-chloroaniline
471	3-hydroxypiperidine	3-chloroaniline
472	(S)-1-amino-2-porpanol	3-chloroaniline
473	(R)-1-amino-2-propanol	3-chloroaniline
474	piperazine	3-chloroaniline
475	2-(2-hydroxyethyl)piperidine	3-chloroaniline
476	2-amino-2-methyl-1-propanol	3-chloroaniline
477	1-(2-dimethylaminoethyl)piperazine	3-chloroaniline
478	dimethylamine	3-chloroaniline
479	aminomethylcyclopropane	3-chloroaniline
480	piperidine	3-chloroaniline
481	1-(2-dimethylaminoethyl)piperazine	3,5-difluoroaniline
482	(S)-(+)-2-Pyrrolidine methanol	3,5-difluoroaniline

483	4-hydroxypiperidine	3,5-difluoroaniline
484	3-pyrrolidinol	3,5-difluoroaniline
485	1-(2-aminoethyl)pyrrolidine	3,5-difluoroaniline
486	4-hydroxymethylpiperidine	3,5-difluoroaniline
487	2-(2-hydroxyethyl)piperidine	3,5-difluoroaniline
488	1-(2-hydroxyethyl)piperazine	3,5-difluoroaniline
489	4-(2-hydroxyethyl)piperidine	3,5-difluoroaniline
490	3-hydroxypiperidine	3,5-difluoroaniline
491	N,N,N'-trimethylethylenediamine	3,5-difluoroaniline
492	piperidine	3,5-difluoroaniline
493	pyrrolidine	3,5-difluoroaniline
494	2-amino-2-methyl-1-propanol	3,5-difluoroaniline
495	2-methylaminoethanol	3,5-difluoroaniline
496	N,N-dimethylethylenediamine	3,5-difluoroaniline
497	(S)-(+)-1-amino-2-propanol	3,5-difluoroaniline
498	(R)-(-)-1-amino-2-propanol	3,5-difluoroaniline
499	piperazine	3,5-difluoroaniline
500	N-allylpiperazine	3,5-difluoroaniline
501	(R)-(-)-2-pyrrolidinemethanol	3,5-difluoroaniline
502	cyclopentylamine	3,5-difluoroaniline

503	2-methylaminoethanol	3-chloro-4-fluoroaniline
504	N,N,N'-trimethylethylenediamine	3-chloro-4-fluoroaniline
505	N-allylpiperazine	3-chloro-4-fluoroaniline
506	4-hydroxypiperidine	3-chloro-4-fluoroaniline
507	3-pyrrolidinol	3-chloro-4-fluoroaniline
508	1-(2-aminoethyl)pyrrolidine	3-chloro-4-fluoroaniline
509	N-acetylpiperazine	3-chloro-4-fluoroaniline
510	2-(2-hydroxyethyl)piperidine	3-chloro-4-fluoroaniline
511	1-(2-hydroxyethyl)piperazine	3-chloro-4-fluoroaniline
512	cyclopentylamine	3-chloro-4-fluoroaniline
513	4-(2-hydroxyethyl)piperidine	3-chloro-4-fluoroaniline
514	3-hydroxypiperidine	3-chloro-4-fluoroaniline
515	4-hydroxymethylpiperidine	3-chloro-4-fluoroaniline
516	1-amino-2-propanol	3-chloro-4-fluoroaniline
517	piperazine	3-chloro-4-fluoroaniline
518	1-(2-morpholinoethyl)piperazine	3-chloro-4-fluoroaniline
519	pyrrolidine	3-chloro-4-fluoroaniline
520	2-methylaminoethanol	3-fluoroaniline
521	1,2-diamino-2-methylpropane	3-fluoroaniline
522	N,N-dimethylethylenediamine	3-fluoroaniline

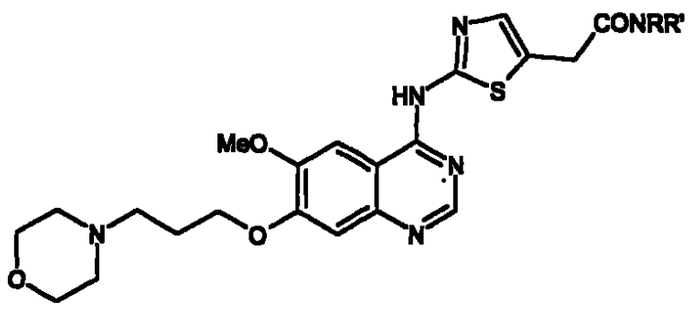
523	N,N,N'-trimethylethylenediamine	3-fluoroaniline
524	N-allylpiperazine	3-fluoroaniline
525	4-hydroxypiperidine	3-fluoroaniline
526	3-pyrrolidinol	3-fluoroaniline
527	1-(aminoethyl)pyrrolidine	3-fluoroaniline
528	N-acetylpiperazine	3-fluoroaniline
529	1-(2-hydroxyethyl)piperazine	3-fluoroaniline
530	cyclopentylamine	3-fluoroaniline
531	4-(2-hydroxyethyl)piperidine	3-fluoroaniline
532	3-hydroxypiperidine	3-fluoroaniline
533	4-hydroxymethylpiperidine	3-fluoroaniline
534	1-amino-2-propanol	3-fluoroaniline
535	(R)-(-)-2-pyrrolidinemethanol	3-fluoroaniline
536	(S)-(+)-2-pyrrolidinemethanol	3-fluoroaniline
537	piperazine	3-fluoroaniline
538	1-(2-morpholinoethyl)piperazine	3-fluoroaniline

TABLE 18



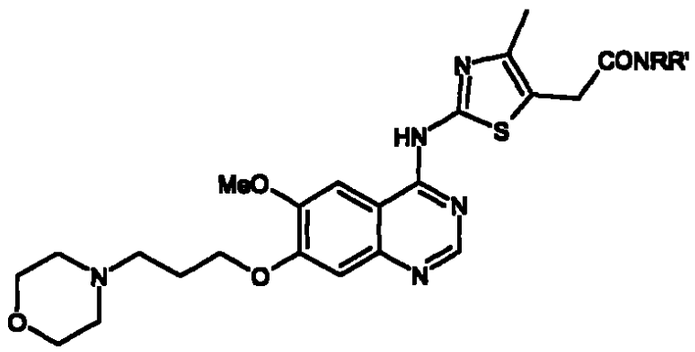
Nº	NRR'
539	N-ethylaniline
540	3-chloro-4-fluoro-N-methylaniline
541	ethyl-2-(3-chloro-4-fluoroanilino)acetate
542	2-anilinoacetronitrile
543	3-anilinoproponitrile
544	N-(2-tert-butoxyethyl)-3-chloro-4-fluoroaniline
545	N-allylaniline
546	N-ethyl-3,4-(methylmedioxy)aniline
547	ethyl-4-(N-butylamino)benzate
548	N-ethyl-M-toluidine
549	N-(2-hydroxy"thyl)-3-chloro-4-fluoroaniline

TABLE 18



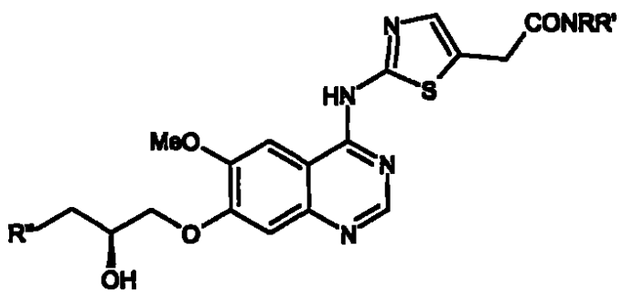
Nº	NRR'
550	N-ethylaniline
551	3-chloro-4-fluoro-N-methylaniline
552	ethyl-2-(3-chloro-4-fluoroanilino)acetate
553	2-anilinoacetronitrile
554	3-anilinoproponitrile
555	N-(2-tert-butoxyethyl)-3-chloro-4-fluoroaniline
556	N-allylaniline
557	N-ethyl-3,4-(methylmedioxy)aniline
558	ethyl-4-(N-butylamino)benzate
559	N-ethyl-M-toluidine
560	N-(2-hydroxy"thyl)-3-chloro-4-fluoroaniline

TABLE 19



N°	NRR'
561	aniline
562	3-chloro-4-fluoroaniline
563	2-aminopyridine
564	3,4-difluoroaniline

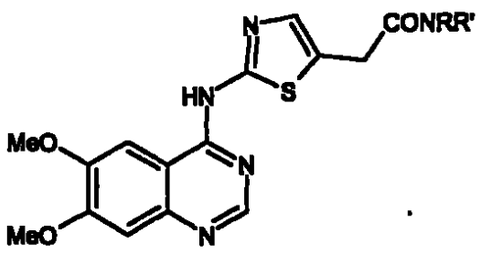
TABLE 20



Nº	R""	NRR'
565	piperidine	3-chloro-4-fluoroaniline
566	pyrrolidine	3-chloro-4-fluoroaniline
567	4-hydroxypiperidine	3-chloro-4-fluoroaniline
568	piperazine	3-chloro-4-fluoroaniline
569	cyclopentylamine	3-chloro-4-fluoroaniline
570	2-amino-2-methyl-1-propanol	3-chloro-4-fluoroaniline
571	piperidine	3,4-difluoroaniline
572	pyrrolidine	3,4-difluoroaniline
573	4-hydroxypiperidine	3,4-difluoroaniline
574	cyclopentylamine	3,4-difluoroaniline

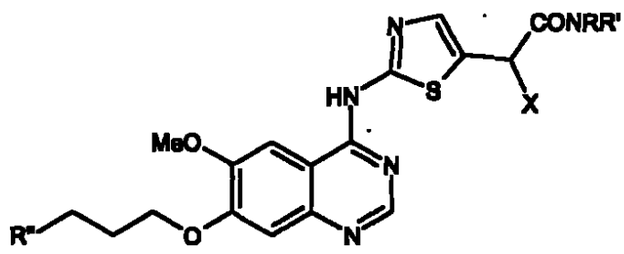
575	pyrrolidine	3-chloroaniline
576	4-hydroxypiperidine	3-chloroaniline
577	cyclopentylamine	3-chloroaniline
578	2-amino-2-methyl-1-propanol	3-chloroaniline
579	piperazine	3-chloroaniline
580	OMe	3-chloroaniline
581	piperidine	3-chloroaniline
582	piperidine	3,5-difluoroaniline
583	pyrrolidine	3,5-difluoroaniline
584	2-amino-2-methyl-1-propanol	3,5-difluoroaniline
585	piperazine (acetate)	3,5-difluoroaniline
586	piperazine	3,5-difluoroaniline
587	pyrrolidine	3-fluoroaniline
588	piperidine	3-fluoroaniline
589	piperazine	3-fluoroaniline
590	piperazine (acetate)	3-fluoroaniline
591	cyclopentylamine	3-fluoroaniline

TABLE21



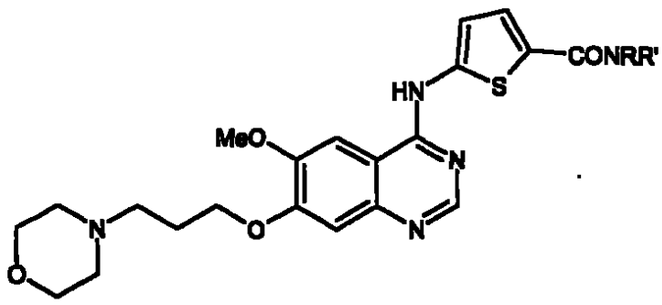
Nº	NRR'
592	3,5-difluoroaniline
593	3-chloroaniline
594	3-chloro-4-fluoroaniline
595	3,4-difluoroaniline

TABLE 22



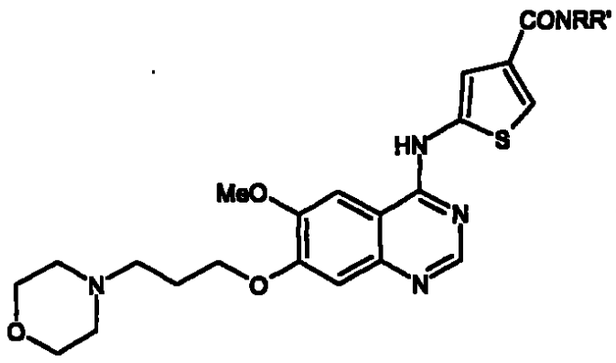
Nº	R""	Y	NRR'
596	morpholine	OH	aniline
597	morpholine	OH	3,4-difluoroaniline
598	N-Me-piperazine	OH	3,4-difluoroaniline
599	piperidine	OH	3-fluoroaniline
600	piperidine	OH	3-chloroaniline
601	N-Me-piperazine	=N-OH	3,4-difluoroaniline

TABLE 23



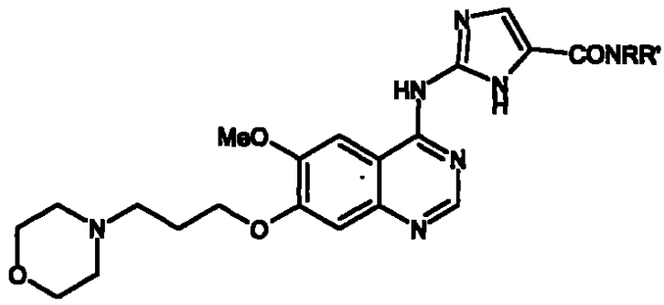
Nº	NRR'	Nº	NRR'
602	2-aminopyridine	610	2-methoxyaniline
603	4-methylaniline	611	3-(2-hydroxyethyl)aniline
604	2-methylaniline	612	3-fluoro-4-methoxyaniline
605	3-methoxyaniline	613	2-methyl-4-fluoroaniline
606	2-hydroxymethylaniline	614	2-fluoro-5-methylaniline
607	3-nitroaniline	615	3-cyanoaniline
608	4-trifluoromethylaniline	616	isoamylamine
609	3-chloroaniline	617	2-chloroaniline

TABLE 24



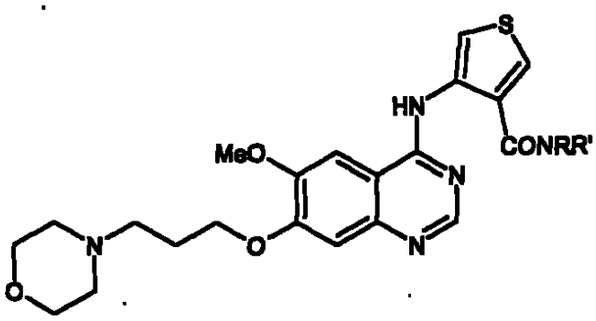
Nº	NRR'
618	aniline
619	4-fluoroaniline
620	3-hydroxyaniline
621	3-(methylthio)aniline
622	4-fluoro-3-chloroaniline
623	2,4-difluorobenzylamine
624	3-fluoroaniline

TABLE 25



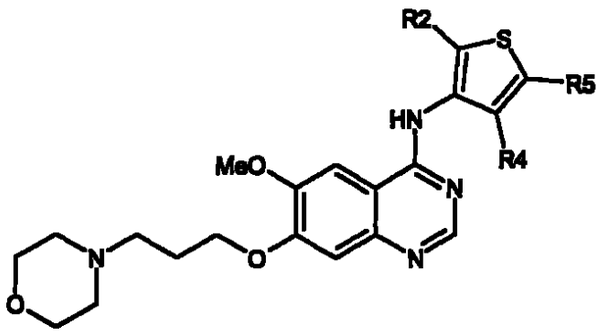
Nº	NRR'
625	aniline
626	4-fluoroaniline
627	allylamine

TABLE 26



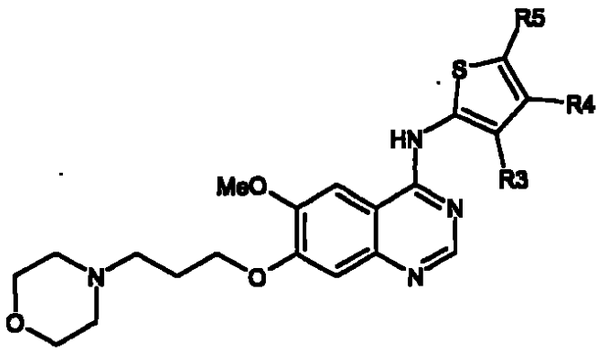
Nº	NRR'
628	aniline
629	allylamine

TABLE 27



Nº	R_2	R_4	R_5
630	COOMe	H	H

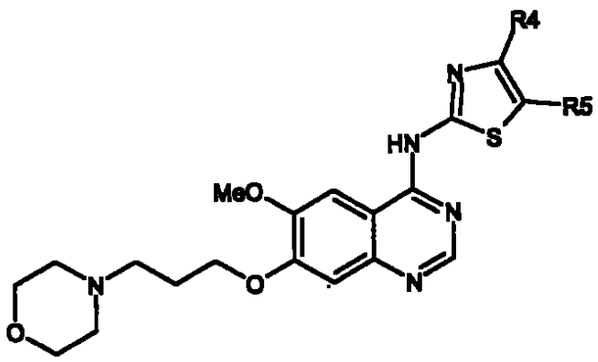
TABLE 28



Nº	R_2	R_4	R_5
631	CONH2	H	isopropyl
632	H	H	COO allyl

633	CONH2	H	H
634	CONH2	H	ethyl

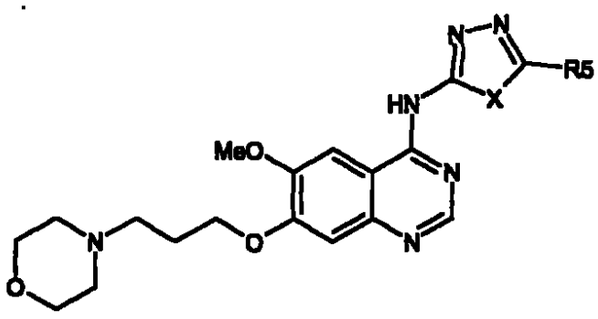
TABLE 29



	R4	R5
635	Ph	H
636	Me	COCH3
637	CF3	COOEt
638	Ph	COOEt
639	-(CH2)4-	
640	4-acetylaminophenyl	H
641	CF3	Ph
642	CF3	H
643	tert-butyl	H
644	Me	Me
645	Me	H
646	Me	-C(=N-OH)-Me
647	H	-NHCOO-tert-butyl
648	Me	-C(=NOMe)-Me
649	Me	-C(=NOPh)-Me
650	H	4-methoxyphenyl
651	H	Ph
652	H	Et
653	H	isopropyl

654	H	-CH2Ph
655	H	Me
657	H	n-butyl
658	H	CHO
659	H	-CH=N-OH

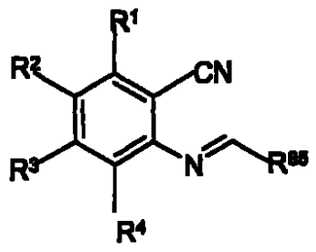
TABLE 30



	X	R5
660	S	tert-butyl
661	S	cyclopropyl
662	S	-S-CH2-CH3
662	S	-Ph
664	NH	-NH-Ph

Other compounds of Formula (I) or Formula (IA), in particular those in which R^5 carries a carboxy or carboxyl ester substituent are described below in the Examples.

Compounds of Formula (I) or Formula (IA) may be prepared by various methods which would be apparent from the literature. For example compounds of formula (I) where X is NH may be prepared by reacting a compound of formula (VII)



(VII)

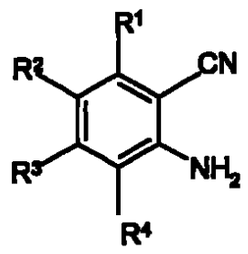
where R^1, R^2, R^3, and R^4 are as defined in relation to formula (I) and R^{85} is a group $NR^{86}R^{87}$ where R^{86} and R^{87} are independently selected from alkyl such as methyl , with a compound of formula (VIII)

$$H_2N\text{-}R^{5'} \qquad \text{(VIII)}$$

where $R^{5'}$ is a group R^5 as defined in relation to formula (I) or a precursor group thereof; and thereafter if desired or necessary, converting a precursor group $R^{5'}$ to a group R^5 and/or modifying substituents on the group R^5. The reaction is suitably effected in an organic solvent such as an acetic acid at elevated temperatures, conveniently at the reflux temperature of the solvent.

Examples of reactions in which a precursor group $R^{5'}$ is converted to a group R^5 and/or substituents on the group R^5 are modified are standard chemical reactions, such as conversion of esters to acids, and thereafter, if required to the preferred amides. Examples of such reactions are provided hereinafter.

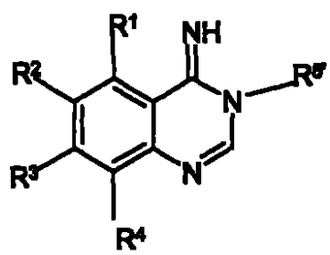
Compounds of formula (VII) are suitably prepared by reacting a compound of formula (IX)



(IX)

with an appropriate acetal such as N,N-dimethylformamide dimethyl acetal. The reaction is suitably effected in an organic solvent such as benzene, at elevated temperature, conveniently at the reflux temperature of the solvent.

Alternatively, compounds of formula (I) where X is NH may be prepared by rearranging a compound of formula (X)

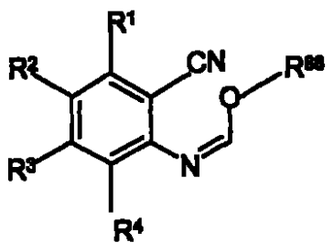


(X)

where R^1, R^2, R^3 and R^4 are as defined in relation to formula (I) and $R^{5'}$ is as defined in relation to formula (VIII) above, and thereafter if desired or necessary, converting a precursor group $R^{5'}$ to a group R^5 and/or modifying substituents on the group R^5, for example as described generally above.

The rearrangement reaction is suitably effected in an organic solvent such as an alkyl alcohol, in particular methanol, ethanol or cyclohexanol, acetic acid, or dimethylformamide, using a strong base such as sodium hydroxide, sodium acetate, sodium methylate, or dimethylamine. Elevated temperatures, for example of from 20°-120°C and preferably at about 75°C are employed.

Compounds of formula (X) are suitably obtained by reacting a compound of formula (XI)



(XI)

where R^1, R^2, R^3 and R^4 are as defined in relation to formula (I) and R^{86} is an alkyl group such as methyl; with a compound of formula (XII)

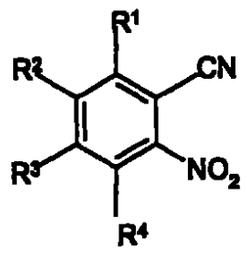
$$H_2N\text{-}R^{5'}$$

(XII)

where $R^{5'}$ is as defined in relation to formula (VIII). The reaction is suitably effected in an organic solvent such as methylene chloride, in the presence of a salt such as pyridinium hydrochloride. Moderate temperatures for example of from 0°-50°C and conveniently ambient temperature are employed.

Compounds of formula (XI) are suitably prepared by reacting a compound of formula (IX) as defined above, with a trialkylorthoformate such as trimethylorthoformate. The reaction is suitably effected at elevated temperature, for example of from 50°C to 120°C, and preferably at about 100°C, in the presence of a catalytic amount of an acid such as p-toluene sulphonic acid.

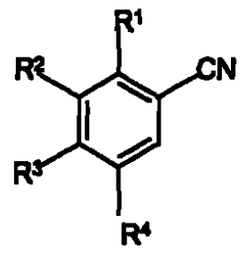
Compounds of formula (IX) are either known compounds or they can be prepared by conventional methods. In particular, compounds of formula (IX) may be prepared by reduction of the corresponding nitro compound of formula (XIII)



(XIII)

where R^1, R^2, R^3 and R^4 are as defined in relation to formula (I). Suitable reaction conditions are illustrated hereinafter.

Compounds of formula (XIII) may be obtained by nitration of a compound of formula (XIV)



(XIV)

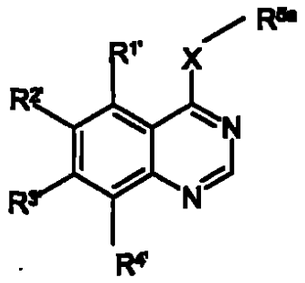
for example, using nitric acid as the nitrating agent. Again, suitable reaction conditions are illustrated hereinafter.

The nitrile of formula (XIV) may be derived by reaction of the corresponding formamide with hydroxylamine as illustrated hereinafter.

Compounds of Formula (I) and Formula (IA) are inhibitors of aurora 2 kinase. As a result, these compounds can be used to treat disease mediated by these agents, in particular proliferative disease.

According to a further aspect of the present invention there is provided a method for inhibiting aurora 2 kinase in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of Formula (I) or Formula (IA), or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

Certain compounds of formula (I) are novel and these form a further aspect of the invention. Thus the invention further comprises a compound of formula (IA)



(IA)

or a salt, ester or amide thereof;

where X is as defined in relation to formula (I);

$R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ are equivalent to R^1, R^2, R^3, R^4 as defined in relation to formula (I) and R^{5a} is an optionally substituted 5-membered heteroaromatic ring, subject to the following provisos:

(i) that where R^{5a} is a pyrazole group, it carries a substitutent of formula (k), (II) of (VI) above,

(ii) that where X is NH and R^{5a} is a substituted pyrazolone or tetrazolyl group, at least one of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ is other than hydrogen; or

(iii) that where X is O and R^{5a} is 1-methyl-4-nitro-1H-imidazol-5-yl, at least one of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ is other than hydrogen.

Preferably at least one of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ is other than hydrogen.

Suitably R^{5a} is selected from the groups of sub-formulae (a)-(j) as set out above.

Preferably R^{5a} is pyrrole, imidazole, triazole, thiazole, thiophene, or thiadiazole, any of which may be optionally substituted.

In particular, R^{5a} is substituted by at least one group of formula (k), (ll) of (VI) above.

Other preferred or particular groups and substitutents in formula (IA) are as set out for the equivalent groups in formula (I) above.

According to a further aspect of the invention there is provided a compound of the formula (IA) as defined herein, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, for use in a method of treatment of the human or animal body by therapy. In particular, the compounds are used in methods of treatment of proliferative disease such as cancer and in particular cancers such as colorectal or breast cancer where aurora 2 is upregulated.

The invention also provides a pharmaceutical composition comprising a compound of formula (IA) as defined herein, or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof, in combination with at pharmaceutically acceptable carrier. Preferred or particular compounds of formula (IA) for use in the compositions of the invention are as described above in relation to preferred compounds of formula (I).

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal track, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxyethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents

may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Suppository formulations may be prepared by mixing the active ingredient with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

Topical formulations, such as creams, ointments, gels and aqueous or oily solutions or suspensions, may generally be obtained by formulating an active ingredient with a conventional, topically acceptable, vehicle or diluent using conventional procedure well known in the art.

Compositions for administration by insufflation may be in the form of a finely divided powder containing particles of average diameter of, for example, 30μ or much less, the powder itself comprising either active ingredient alone or diluted with one or more physiologically acceptable carriers such as lactose. The powder for insufflation is then conveniently retained in a capsule containing, for example, 1 to 50mg of active ingredient for use with a turbo-inhaler device, such as is used for insufflation of the known agent sodium cromoglycate.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on Formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

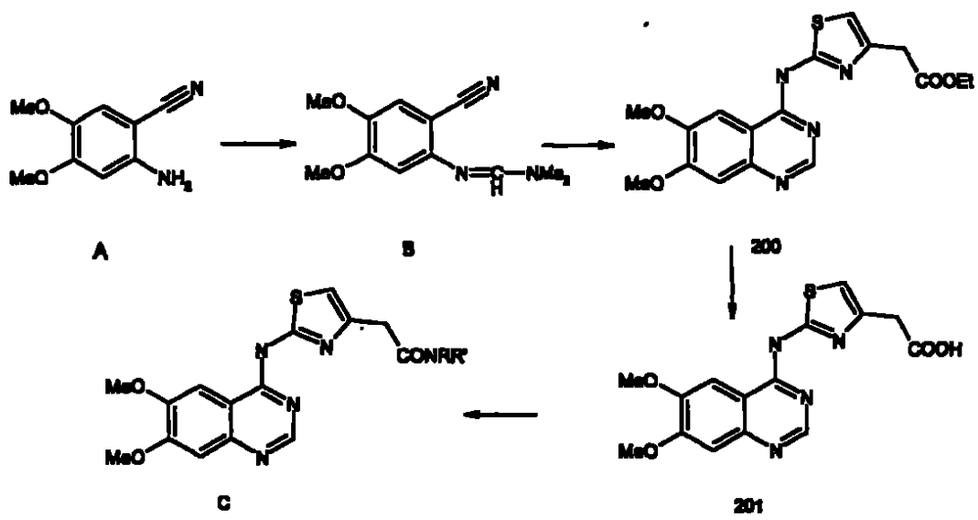
The size of the dose for therapeutic or prophylactic purposes of a compound of the Formula I will naturally vary according to the nature and severity of the conditions, the age and sex of the animal or patient and the route of administration, according to well known principles of medicine. As mentioned above, compounds of the Formula I are useful in treating diseases or medical conditions which are due alone or in part to the effects of aurora 2 kinase.

In using a compound of the Formula I for therapeutic or prophylactic purposes it will generally be administered so that a daily dose in the range, for example, 0.5 mg to 75 mg per kg body weight is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed. Thus, for example, for intravenous administration, a dose in the range, for example, 0.5 mg to 30 mg per kg body weight will generally be used. Similarly, for administration by inhalation, a dose in the range, for example, 0.5 mg to 25 mg per kg body weight will be used. Oral administration is however preferred.

A further aspect of the invention comprises a compound of Formula (I) or Formula (IA) as defined above, or a pharmaceutically acceptable salt or in vivo hydrolysable ester thereof, for use in the preparation of a medicament for the treatment of proliferative disease. Preferred compounds of Formula (I) or Formula (IA) for this purpose are as described above.

The following Examples illustrate the invention.

General Scheme 1



Compound B

The amino nitrile A (534 mg, 3 mmol) in benzene (15 ml) was reacted with N,N-dimethylformamide dimethyl acetal (535 mg, 4.5 mmol) at 90°C, in a Dean Stark equipped flask. After 4.5 hours reflux, the solution was concentrated, and the residual oil triturated with ether to give the title compound as a solid (680 mg, 90 %).

^{1}HNMR ($CDCl_3$) : 3.08 (s, 6H) ; 3.86 (s, 3H) ; 3.91 (s, 3H) ; 6.48 (s, 1H) ; 6.94 (s, 1H) ; 7.58 (s, 1H).

MS ES^+ : 234 $(M+H)^+$

Compound 200

A mixture of amidine B (1.4 g, 6 mmol), ethyl 2-amino-4-thiazoleacetate (1.4 g, 7.5 mmol) in acetic acid (14 ml) was heated at 130°C for 3 hours. The solvent was removed under vacuum, the residue was triturated in ethanol (5 ml) and a solution of $NaHCO_3$ (pH 8) for 10 minutes. The solid was recovered by filtration, washed with water, dissolved in CH_2Cl_2, and dried over $MgSO_4$. CH_2Cl_2 was evaporated, the residual oil treated with ether and pet. ether to give title compound (1.8 g, 80 %).

^{1}H NMR (DMSO-d_6) : 1.2 (t, 3H) ; 3.74 (s, 2H) ; 3.95 (s, 6H) ; 4.1 (q, 2H) ; 7.02 (s, 1H) ; 7.26 (s, 1H) ; 8.14 (s, 1H) ; 8.68 (s, 1H).

Compound 201

Ester 200 (1.8 g, 4.8 mmol) was reacted with 2N NaOH (4.8 ml, 9.6 mmol) in ethanol (20 ml) at room temperature for 2 hours. The mixture was cooled to room temperture, acidified with EtOH, HCl (2N) to pH 3. Stirring was carried on for 15 minutes, and a yellow solid of title compound was recovered by filtration (1.7 g, 100 %).

^{1}HNMR (DMSO-d_6) : 3.71 (s, 2H) ; 3.96 (s, 3H) ; 3.97 (s, 3H) ; 7.11 (s, 1H) ; 7.28 (s, 1H) ; 8.3 (brs, 1H) ; 8.88 (s, 1H).

Synthesis of amide 5, general procedure

The acid 201 (86.5 mg, 0.25 mmol) in DMF (1 ml) was reacted with various amines (2.6 mmol) in presence of O-(7-azabenzotriazol-1yl) N,N,N',N',-tetramethyluronium hexafluorophosphate (98 mg, 0.26 mmol), DIEA (33 mg, 0.26 mmol) at room temperature for 0.5 hour. A solution of $NaHCO_3$ (1 ml) and water (7 ml) was added to the mixture. The mixture was left overnight, and the precipitated solid was then recovered by filtration, washed with water and dried under vacuum in presence of P_2O_5, to give compounds of formula C as listed below.

Example 1.

Using the reaction described in the General Scheme 1, starting with 4-aminomethyl pyridine (27 mg, 0.25 mmol) yielded Compound No. 1 in Table 1 (50 mg, 46 %).

^{1}HNMR (DMSO-d_6) : 3.64 (s, 2H) ; 3.95 (s, 3H) ; 3.96 (s, 3H) ; 4.32 (d, 2H) ; 6.98 (s, 1H) ; 7.26 (m, 3H) ; 8.15 (s, 1H) ; 8.49 (m, 3H) ; 8.68 (s, 1H).

Example 2.

An analogous reaction to that described in the General Scheme 1, starting with morpholine (23 mg, 0.26 mmol) yielded Compound No 2 in Table 1 (70 mg, 67 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.55 (br m, 8H) ; 3.88 (s, 2H) ; 3.97 (s, 3H) ; 4.0 (s, 3H) ; 7.15 (s, 1H) ; 7.27 (s, 1H) ; 7.92 (s, 1H) ; 9.07 (s, 1H).

Example 3.

An analogous reaction to that described in the General Scheme 1, starting with 4-fluoroaniline (29 mg, 0.26 mmol) yielded the Compound No. 3 in Table 1 (75 mg, 68 %).

^{1}H NMR (DMSO-d_6) : 3.74 (s, 2H) ; 3.93 (s, 6H) ; 7.00 (s, 1H) ; 7.15 (t, 2H) ; 7.25 (s, 1H) ; 7.64 (m, 2H) ; 8.12 (s, 1H) ; 8.67 (s, 1H) ; 10.20 (s, 1H).

MS ES$^+$: 440 $(M,H)^+$

Example 4.

An analogous reaction to that described in the General Scheme 1, starting with N,N-dimethyl-1,4-phenylenediamine (35 mg, 0.26 mmol) yielded Compound 4 in Table 1 (65 mg, 56 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.2 (s, 6H) ; 3.9 (s, 2H) ; 3.97 (s, 3H) ; 4.0 (s, 3H) ; 7.27 (s, 1H) ; 7.3 (s, 1H) ; 7.65 (d, 2H) ; 7.8 (d, 2H) ; 7.99 (s, 1H).

MS ES$^+$: 465 $(M,H)^+$

Example 5.

An analogous reaction to that described in the General Scheme 1, starting with 4-methoxy-aniline (32 mg, 0.26 mmol) yielded Compound 5 in Table 1 (80 mg, 71 %).

^{1}HNMR (DMSO-d_6) : 3.71 (s, 5H) ; 3.93 (s, 3H) ; 3.94 (s, 3H) ; 6.88 (d, 2H) ; 6.99 (s, 1H) ; 7.25 (s, 1H) ; 7.53 (d, 2H) ; 8.13 (s, 1H) ; 8.67 (s, 1H) ; 9.99 (s, 1H).

MS ES$^+$: 452 $(M,H)^+$

Example 6.

An analogous reaction to that described in the General Scheme 1, starting with 5-methoxy-2-methylaniline (36 mg, 0.26 mmol) yielded Compound 6 in Table 1 (87 mg, 75 %).

^{1}HNMR (DMSO-d_6) : 2.13 (s, 3H) ; 3.69 (s, 3H) ; 3.81 (s, 2H) ; 3.96 (s, 6H) ; 6.65 (m, 1H) ; 7.05 (m, 1H) ; 7.09 (d, 1H) ; 7.21 (s, 1H) ; 7.26 (s, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H) ; 9.3 (s, 1H).

MS ES$^+$: 466 $(M_+H)^+$

Example 7.

An analogous reaction to that described in the General Scheme 1, starting with aminoacetaldehyde dimethyl acetal (27 mg, 0.26 mmol) yielded Compound 7 in Table 1 (80 mg, 74 %).

^{1}HNMR (DMSO-d_6) : 3.2 (t, 2H) ; 3.29 (s, 3H) ; 3.31 (s, 3H) ; 3.55 (s, 2H) ; 3.94 (s, 6H) ; 4.37 (t, 1H) ; 6.92 (s, 1H) ; 7.26 (s, 1H) ; 8.02 (t, 1H) ; 8.14 (s, 1H) ; 8.67 (s, 1H).

MS ES$^+$: 434 $(M_+H)^+$

Example 8.

An analogous reaction to that described in the General Scheme 1, starting with 3-trifluoromethylaniline (42 mg, 0.26 mmol) yielded Compound 8 in Table 1 (72 mg, 59 %).

^{1}HNMR (DMSO-d_6) : 3.80 (s, 2H) ; 3.93 (s, 3H) ; 3.94 (s, 3H) ; 7.04 (s, 1H) ; 7.26 (s, 1H) ; 7.41 (d, 1H) ; 7.55 (t, 1H) ; 7.81 (d, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H) ; 10.50 (s, 1H).

MS ES$^+$: 490 $(M_+H)^+$

Example 9.

An analogous reaction to that described in General Scheme 1, starting with N-methylpiperazine (26 mg, 0.26 mmol) yielded Compound 9 in Table 1(65 mg, 61 %).

^{1}HNMR (DMSO-d_6) : 2.73 and 2.77 (two t, 4H) ; 2.86 and 3.10 (two s, 3H) ; 3.56 and 3.74 (two t, 4H) ; 3.79 and 3.84 (two s, 2H) ; 3.95 (s, 6H) ; 6.95 (m, 1H) ; 7.26 (s, 1H) ; 8.14 (s, 1H) ; 8.68 (s, 1H).

MS ES$^+$: 429 $(M_+H)^+$

Example 10.

An analogous reaction to that described in General Scheme 1, starting with 2-methoxyethylamine (20 mg, 0.26 mmol) yielded Compound 10 in Table 1(68 mg, 67 %).
^{1}HNMR (DMSO-d_6) : 3.25 (s, 3H) ; 3.3 (m, 6H) ; 3.54 (s, 2H) ; 3.94 (s, 6H) ; 6.92 (s, 1H) ; 7.26 (s, 1H) ; 8.0 (t, 1H) ; 8.14 (s, 1H) ; 8.67 (s, 1H).
MS ES$^+$: 404 $(M+H)^+$

Example 11.

An analogous reaction to that described in General Scheme 1, starting with 2-(2-aminoethyl)-N-methylpyrrole (32 mg, 0.26 mmol) yielded Compound 11 in Table 1(93 mg, 82 %).
^{1}HNMR (DMSO-d_6) : 3.3 (m, 4H) ; 3.5 (s, 2H) ; 3.94 (s, 6H) ; 5.78 (s, 1H) ; 5.84 (m, 1H) ; 6.58 (s, 1H) ; 6.89 (s, 1H) ; 7.24 (s, 1H) ; 8.01 (t, 1H) ; 8.13 (s, 1H) ; 8.66 (s, 1H).
MS ES$^+$: 453 $(M+H)^+$

Example 12.

An analogous reaction to that described in the General Scheme 1, starting with 3-(methylamino)propionitrile (22 mg, 0.26 mmol) yielded Compound 12 in Table 1(60 mg, 58 %).
^{1}HNMR (DMSO-d_6) : 2.15 (s, 3H) ; 3.45 (m, 4H) ; 3.77 (s, 2H) ; 3.96 (s, 6H) ; 6.91 (s, 1H) ; 7.25 (s, 1H) ; 8.14 (s, 1H) ; 8.67 (s, 1H).
MS ES$^+$: 413 $(M+H)^+$

Example 13.

An analogous reaction to that described in General Scheme 1, starting with 4-fluorobenzylamine (33 mg, 0.26 mmol) yielded Compound 13 in Table 1(81 mg, 81 %).
^{1}HNMR (DMSO-d_6) : 3.59 (s, 2H) ; 3.95 (m, 6H) ; 4.27 (d, 2H) ; 6.94 (s, 1H) ; 7.15 (m, 2H) ; 7.26 (s, 1H) ; 7.31 (m, 2H) ; 7.95 (s, 1H) ; 8.14 (s, 1H) ; 8.41 (t, 1H) ; 8.67 (s, 1H).
MS ES$^+$: 454 $(M+H)^+$

Example 14.

An analogous reaction to that described in General Scheme 1, starting with 4-hydroxypiperidine (26 mg, 0.26 mmol) yielded Compound 14 in Table 1(86 mg, 80 %).

^{1}HNMR (DMSO-d_6) : 1.21 (m, 2H) ; 1.65 (m, 2H) ; 3.02 (m, 1H) ; 3.16 (m, 1H) ; 3.65 (m, 1H) ; 3.78 (m, 3H) ; 4.71 (d, 1H) ; 6.91 (s, 1H) ; 7.26 (s, 1H) ; 8.14 (s, 1H) ; 9.67 (s, 1H).
MS ES$^+$: 430 $(M+H)^+$

Example 15.

An analogous reaction to that described in General Scheme 1, starting with 3-aminoacetophenone (35 mg, 0.26 mmol) yielded Compound 15 in Table 1(92 mg, 79 %).
^{1}HNMR (DMSO-d_6) : 2.59 (s, 3H) ; 3.78 (s, 2H) ; 3.90 (s, 3H) ; 3.93 (s, 3H) ; 7.02 (s, 1H) ; 7.26 (s, 1H) ; 7.47 (t, 1H) ; 7.67 (d, 1H) ; 7.89 (d, 1H) ; 8.12 (s, 1H) ; 8.2 (s, 1H) ; 8.68 (s, 1H) ; 10.36 (s, 1H).
MS ES$^+$: 464 $(M+H)^+$.

Example 16.

An analogous reaction to that described in General Scheme 1, starting with 3,5-difluoroaniline (34 mg, 0.26 mmol) yielded Compound 16 in Table 1(71 mg, 64 %).
^{1}HNMR (DMSO-d_6, TFA) : 3.90 (s, 2H) ; 3.93 (s, 3H) ; 3.97 (s, 3H) ; 6.89 (m, 1H) ; 7.27 (s, 1H) ; 7.29 (s, 1H) ; 7.35 (m, 2H) ; 7.96 (m, 1H) ; 9.10 (s, 1H).
MS ES$^+$: 458 $(M+H)^+$

Example 17.

An analogous reaction to that described in General Scheme 1, starting with 3-cyanoaniline (31 mg, 0.26 mmol) yielded Compound 17 in Table 1(90 mg, 84 %).
MS ES$^+$: 447 $(M+H)^+$

Example 18.

An analogous reaction to that described in General Scheme 1, starting with 2-fluoroaniline (29 mg, 0.26 mmol) yielded Compound 18 in Table 1(86 mg, 82 %).
MS ES$^+$: 440 $(M+H)^+$

Example 19.

An analogous reaction to that described in General Scheme 1, starting with 3-(1-hydroxyethyl)aniline (36 mg, 0.26 mmol) yielded Compound 19 in Table 1(92 mg, 82 %).
MS ES$^+$: 466 $(M+H)^+$

Example 20.

An analogous reaction to that described in General Scheme 1, starting with 2,3-difluoroaniline (34 mg, 0.26 mmol) yielded Compound 20 in Table 1(51 mg, 47 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.98 (s, 3H) ; 4.01 (s, 3H) ; 4.03 (s, 2H) ; 7.19 (m, 2H) ; 7.27 (s, 1H) ; 7.29 (s, 1H) ; 7.73 (m, 1H) ; 7.99 (s, 1H) ; 9.11 (s, 1H).

MS ES$^+$: 458 $(M+H)^+$

Example 21.

An analogous reaction to that described in General Scheme 1, starting with 2-methyl-4-fluoroaniline (33 mg, 0.26 mmol) yielded Compound 21 in Table 1(94 mg, 86 %).

MS ES$^+$: 454 $(M+H)^+$

Example 22.

An analogous reaction to that described in General Scheme 1, starting with 2-fluoro-3-chloroaniline (38 mg, 0.26 mmol) yielded Compound 22 in Table 1(60 mg, 53 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.95 (s, 3H) ; 3.98 (s, 3H) ; 4.01 (s, 2H) ; 7.20 (m, 1H) ; 7.24 (s, 1H) ; 7.26 (s, 1H) ; 7.31 (m, 1H) ; 7.88 (m, 1H) ; 7.96 (s, 1H) ; 9.08 (s, 1H).

MS ES$^+$: 474 $(M+H)^+$

Example 23.

An analogous reaction to that described in General Scheme 1, starting with 2,5-difluoroaniline (34 mg, 0.26 mmol) yielded Compound 23 in Table 1(52 mg, 48 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.97 (s, 3H) ; 4.00 (s, 2H) ; 4.01 (s, 3H) ; 6.97 (m, 1H) ; 7.26 (s, 1H) ; 7.29 (s, 1H) ; 7.33 (m, 1H) ; 7.94 (m, 1H) ; 7.98 (s, 1H) ; 9.11 (s, 1H).

MS ES$^+$: 458$(M+H)^+$

Example 24.

An analogous reaction to that described in General Scheme 1, starting with 3-aminobenzamide (36 mg, 0.26 mmol) yielded Compound 24 in Table 1(94 mg, 84 %).

MS ES$^+$: 465 $(M+H)^+$

Example 25.

An analogous reaction to that described in General Scheme 1, starting with 4-aminophenol (29 mg, 0.26 mmol) yielded Compound 25 in Table 1(89 mg, 84 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.81 (s, 2H) ; 3.97 (s, 3H) ; 4.00 (s, 3H) ; 6.71 (d, 2H) ; 7.23 (s, 1H) ; 7.27 (s, 1H) ; 7.40 (d, 2H) ; 7.95 (s, 1H) ; 9.09 (s, 1H).

MS ES$^+$: 438 $(M+H)^+$

Example 26.

An analogous reaction to that described in General Scheme 1, starting with 2-fluoro-5-methylaniline (33 mg, 0.26 mmol) yielded Compound 26 in Table 1(88 mg, 81 %).

MS ES$^+$: 454 $(M+H)^+$

Example 27.

An analogous reaction to that described in General Scheme 1, starting with 2-bromo-4-fluoroaniline (50 mg, 0.26 mmol) yielded Compound 27 in Table 1(68 mg, 55 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.89 (s, 2H) ; 3.94 (s, 3H) ; 3.97 (s, 3H) ; 7.21 (m, 1H) ; 7.25 (s, 1H) ; 7.6 (s, 1H) ; 7.61 (m, 1H) ; 7.92 (m, 1H) ; 7.95 (s, 1H) ; 9.07 (s, 1H).

MS ES$^+$: 518, 520 $(M+H)^+$

Example 28.

An analogous reaction to that described in General Scheme 1, starting with 3,4-difluoroaniline (34 mg, 0.26 mmol) yielded Compound 28 in Table 1(81 mg, 74 %).

MS ES$^+$: 458 $(M+H)^+$

Example 29.

An analogous reaction to that described in General Scheme 1, starting with isonipecotamide (34 mg, 0.26 mmol) yielded Compound 29 in Table 1(96 mg, 88 %).

MS ES$^+$: 457 $(M+H)^+$

Example 30.

An analogous reaction to that described in General Scheme 1, starting with 4-trifluoromethoxyaniline (47 mg, 0.26 mmol) yielded Compound 30 in Table 1(105 mg, 87 %).
MS ES$^+$: 506 $(M+H)^+$

Example 31.

An analogous reaction to that described in General Scheme 1, starting with 5-amino-2-methoxypyridine (33 mg, 0.26 mmol) yielded Compound 31 in Table 1(86 mg, 79 %).
MS ES$^+$: 453 $(M+H)^+$

Example 32.

An analogous reaction to that described in General Scheme 1, starting with 2,4-difluoroaniline (34 mg, 0.26 mmol) yielded Compound 32 in Table 1(81 mg, 74 %).
MS ES$^+$: 458 $(M+H)^+$

Example 33.

An analogous reaction to that described in General Scheme 1, starting with 4-aminoresorcinol hydrochloride (43 mg, 0.26 mmol) yielded Compound 33 in Table 1(84 mg, 77 %).
MS ES$^+$: 454 $(M+H)^+$

Example 34.

An analogous reaction to that described in General Scheme 1, starting with 3-aminopyridine (25 mg, 0.26 mmol) yielded Compound 34 in Table 1(101 mg, 100 %).
MS ES$^+$: 423$(M+H)^+$

Example 35.

An analogous reaction to that described in General Scheme 1, starting with 4-chloroaniline (34 mg, 0.26 mmol) yielded Compound 35 in Table 1(109 mg, 100 %).
MS ES$^+$: 456, 458 $(M+H)^+$.

Example 36.

An analogous reaction to that described in General Scheme 1, starting with pyrrolidine (19 mg, 0.26 mmol) yielded Compound 36 in Table 1(33 mg, 35 %).

MS ES$^+$: 400 $(M+H)^+$

Example 37.

An analogous reaction to that described in General Scheme 1, starting with 3-methoxyaniline (33 mg, 0.26 mmol) yielded Compound 37 in Table 1(94 mg, 87 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.72 (s, 3H) ; 3.87 (s, 2H) ; 3.96 (s, 3H) ; 4.0 (s, 3H) ; 6.64 (m, 1H) ; 7.14 (d, 1H) ; 7.21 (d, 1H) ; 7.22 (s, 1H) ; 7.24 (s, 1H) ; 7.27 (s, 1H) ; 7.95 (s, 1H) ; 9.09 (s, 1H).

MS ES$^+$: 452 $(M+H)^+$

Example 38.

An analogous reaction to that described in General Scheme 1, starting with 3-hydroxy-4-methoxyaniline (37 mg, 0.26 mmol) yielded Compound 38 in Table 1(95 mg, 85 %).

MS ES$^+$: 468 $(M+H)^+$

Example 39.

An analogous reaction to that described in General Scheme 1, starting with 3-nitroaniline (36 mg, 0.26 mmol) yielded Compound 39 in Table 1(87 mg, 78 %).

MS ES$^+$: 467 $(M+H)^+$

Example 40.

An analogous reaction to that described in General Scheme 1, starting with 1-methyl-3-nitroaniline (40 mg, 0.26 mmol) yielded Compound 40 in Table 1(50 mg, 44 %).

MS ES$^+$: 481 $(M+H)^+$

Example 41.

An analogous reaction to that described in General Scheme 1, starting with 2-anilinoethanol (36 mg, 0.26 mmol) yielded Compound 41 in Table 1(45 mg, 41 %).

MS ES$^+$: 466 $(M+H)^+$

Example 42.

An analogous reaction to that described in General Scheme 1, starting with 4-trifluoromethylaniline (43 mg, 0.26 mmol) yielded Compound 42 in Table 1(86 mg, 73 %).
MS ES$^+$: 490 $(M+H)^+$

Example 43.

An analogous reaction to that described in General Scheme 1, starting with 3-amino-6-chloropyridine (33 mg, 0.26 mmol) yielded Compound 43 in Table 1(90 mg, 82 %).
^{1}HNMR (DMSO-d_6, TFA) : 3.92 (s, 2H) ; 3.96 (s, 3H) ; 4.0 (s, 3H) ; 7.27 (s, 1H) ; 7.28 (s, 1H) ; 7.46 (d, 1H) ; 7.98 (s, 1H) ; 8.1 (d, 1H) ; 8.65 (d, 1H) ; 9.1 (s, 1H).
MS ES$^+$: 457,459 $(M+H)^+$

Example 44.

An analogous reaction to that described in General Scheme 1, starting with 2-methoxy-5-chloroaniline (42 mg, 0.26 mmol) yielded Compound 44 in Table 1(90 mg, 77 %).
MS ES$^+$: 486, 488 $(M+H)^+$

Example 45.

An analogous reaction to that described in General Scheme 1, starting with 2-methylaminoethanol (20 mg, 0.26 mmol) yielded Compound 45 in Table 1(83 mg, 86 %).
MS ES$^+$: 404 $(M+H)^+$

Example 46.

An analogous reaction to that described in General Scheme 1, starting with 4-aminopyridine (25 mg, 0.26 mmol) yielded Compound 46 in Table 1(101 mg, 100 %).
MS ES$^+$: 423 $(M+H)^+$

Example 47.

An analogous reaction to that described in General Scheme 1, starting with 3-methyl-4-bromoaniline (49 mg, 0.26 mmol) yielded Compound 47 in Table 1(120 mg, 97 %).
MS ES$^+$: 516, 517 $(M+H)^+$

Example 48.

An analogous reaction to that described in General Scheme 1, starting with 2-chloro-5-methoxyaniline (42 mg, 0.26 mmol) yielded Compound 48 in Table 1(65 mg, 56 %).

^{1}HNMR (DMSO-d_6, TFA) : 3.73 (s, 2H) ; 3.98 (m, 9H) ; 6.78 (m, 1H) ; 7.28 (s, 2H) ; 7.39 (d, 1H) ; 7.50 (d, 1H) ; 7.98 (s, 1H) ; 9.10 (s, 1H).

MS ES$^+$: 486, 488 $(M_4H)^+$

Example 49.

An analogous reaction to that described in General Scheme 1, starting with 4-aminotoluene (28 mg, 0.26 mmol) yielded Compound 49 in Table 1(89 mg, 85 %).

MS ES$^+$: 436 $(M_4H)^+$

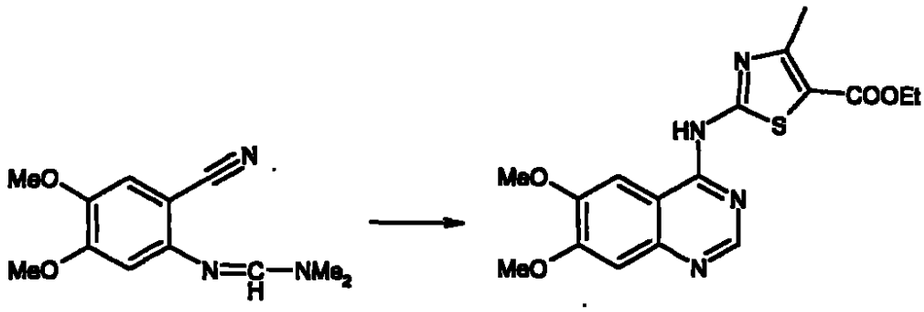
Example 50.

An analogous reaction to that described in General Scheme 1, starting with R(-)-2-pyrrolidinemethanol (27 mg, 0.26 mmol) yielded Compound 50 in Table 1(81 mg, 78 %).

MS ES$^+$: 430 $(M_4H)^+$

Example 50A.

Preparation of Compound 202

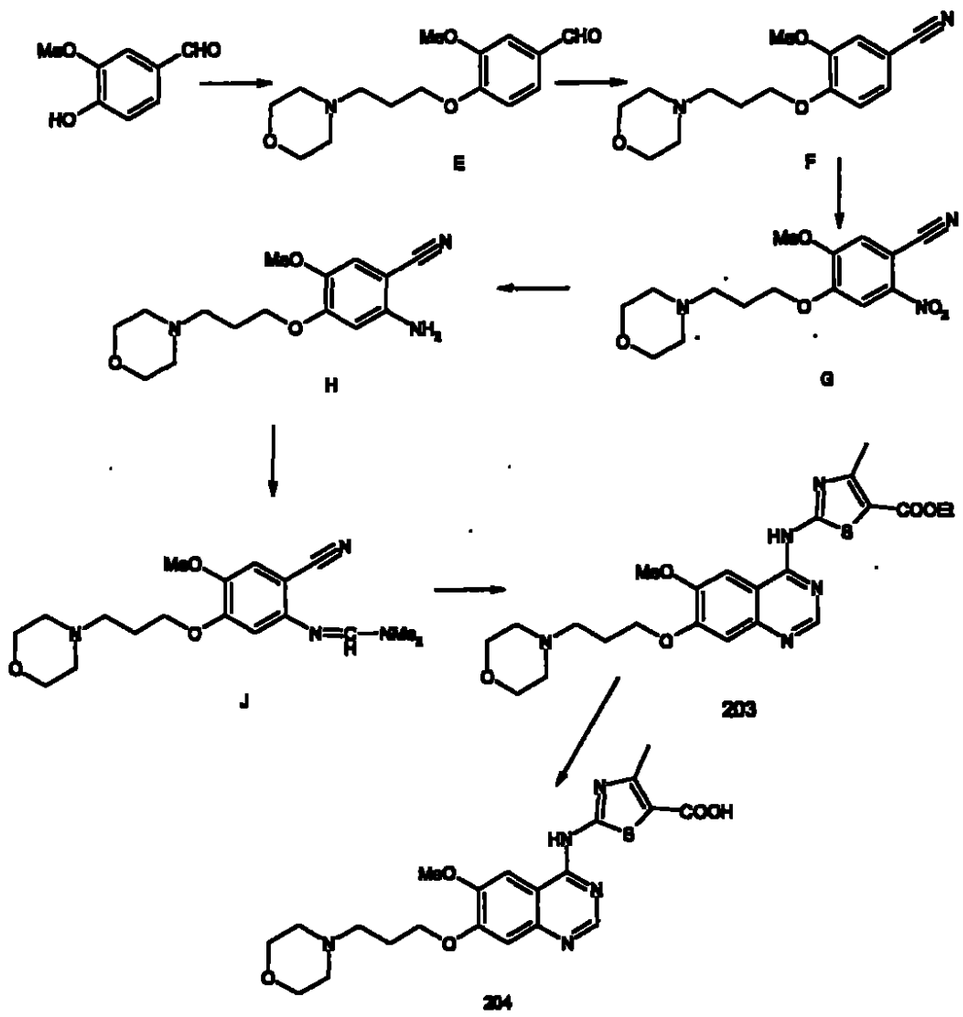


Amidine B (117 mg, 0.5 mmol) in acetic acid (12 ml) was reacted with ethyl-2-amino-4-methylthiazol-5-carboxylate (112 mg, 0.6 mmol) at 130°C for 3 hours. The solvent was evaporated, the residue was taken up into ethanol, and stirred for 10 minutes with a solution of $NaHCO_3$. The solid was recovered by filtration, washed with water, ether and dried under vacuum, to give title compound as a yellow solid (157 mg, 84 %).

^{1}HNMR (DMSO-d_6) : 1.31 (t, 3H) ; 2.6 (s, 3H) ; 3.96 (s, 6H) ; 4.27 (q, 2H) ; 7.28 (s, 1H) ; 8.11 (s, 1H) ; 8.77 (s, 1H).

MS ES$^+$: 375 $(M_4H)^+$

General Scheme 2



Compound E

Vanilline (30.4 g, 0.2 mol) was solubilized in DMF (200 ml) in presence of K_2CO_3 at 50°C. N-(3-chloropropyl)morpholine was slowly added over 30 minutes to this mixture, which was heated over night at 80°C. Formed KCl was removed by filtration, the solvent was evaporated, and the residual orange oil dissolved in AcOEt, washed with water 2x, dried over $MgSO_4$, filtered and concentrated. The residual oil crystallises to give title compound as a white solid (45.6 g, 82 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.22 (m, 2H) ; 3.13 (t, 2H) ; 3.32 (t, 2H) ; 3.52 (d, 2H) ; 3.67 (t, 2H) ; 3.84 (s, 3H) ; 4.02 (d, 2H) ; 4.18 (t, 2H) ; 7.20 (d, 1H) ; 7.43 (d, 1H) ; 7.58 (d, 1H) ; 9.90 (s, 1H).

MS ES$^+$: 280 $(M,H)^+$

Compound F

The aldehyde E (5.6 g, 20 mmol) was added to a solution of sodium acetate (3.3 g, 40 mmol) and hydroxylamine hydrochloride (2.8 g, 40 mmol) in acetic acid (25 ml). The mixture was refluxed for 18 hours, cooled, diluted with water and extracted with methylene chloride, dried over $MgSO_4$, filtered, concentrated, to give title compound (5.1 g, 93 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.19 (m, 2H) ; 3.12 (t, 2H) ; 3.29 (t, 2H) ; 3.50 (d, 2H) ; 3.67 (t, 2H) ; 3.81 (s, 3H) ; 4.01 (d, 2H) ; 4.15 (t, 2H) ; 7.12 (d, 1H) ; 7.39 (s, 1H) ; 7.41 (d, 1H).

MS ES$^+$: 277 $(M,H)^+$

Compound G

The nitrile F (37.2 g, 135 mmol) in acetic acid (100 ml) was added to a solution of nitric acid (d = 1.42) 180 ml, at such a rate to maintain the temperature below 30°C. The mixture was stirred at room temperature over night. A solution of potassium hydroxide (10N, 370 ml) was then added slowly to the solution at 0° leading to a final pH of 11-12. The reaction was extracted with CH_2Cl_2, the organic phases were dried over MgSO4, filtered, evaporated to give a yellow solid which was washed with ether, dried to give title compound (22 g, 50 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.2 (m, 2H) ; 3.13 (t, 2H) ; 3.3 (t, 2H) ; 3.53 (d, 2H) ; 3.67 (t, 2H) ; 3.99 (s, 3H) ; 4.01 (d, 2H) ; 4.31 (t, 2H) ; 7.74 (s, 1H) ; 7.90 (s, 1H).

Compound H

Compound G (21 g, 65 mmol) in solution in CH_2Cl_2 (250 ml), was reacted with sodium hydrosulfite (92 g, 458 mmol) in solution in water (250 ml) in presence of tetrabutyl ammonium chloride (12.7 g, 45.8 mmol) at room temperature, over night. Sodium hydroxide (2N) was then added, and the reaction mixture was extracted with CH_2Cl_2, the organic phase was washed with water, dried over $MgSO_4$, filtered, evaporated. The residue was purified by silica gel chromatography, eluent : AcOEt / CH_2Cl_2 : 50/50 followed by MeOH / AcOEt / CH_2Cl_2 5/45/50 to 20/30/50 to give title compound (12.5 g, 66 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.2 (m, 2H) ; 3.13 (t, 2H) ; 3.31 (t, 2H) ; 3.53 (d, 2H) ; 3.68 (t, 2H) ; 3.71 (s, 3H) ; 4.05 (m, 4H) ; 6.56 (s, 1H) ; 7.02 (s, 1H).

MS ES$^+$: 292$(M_+H)^+$

Compound J

The amino nitrile H (2.91 g, 10 mmol) in solution in toluene (50 ml) was reacted with N,N-dimethylformamide dimethyl acetal (1.79 g, 15 mmol), at 105°C for 5 hours, in a Dean Stark equipped flask. The solvent was evaporated, the residue triturated with ether to give title compound (3.4 g, 98 %).

^{1}HNMR (DMSO-d_6) : 1.87 (m, 2H) ; 2.36 (m, 6H) ; 2.95 (s, 3H) ; 3.04 (s, 3H) ; 3.56 (t, 4H) ; 3.72 (s, 3H) ; 4.06 (t, 2H) ; 6.72 (s, 1H) ; 7.07 (s, 1H) ; 7.89 (s, 1H).

MS ES$^+$: 347 $(M_+H)^+$

Compound 203

Amidine J (173 mg, 0.5 mmol) was dissolved in AcOH (1.7 ml) in presence of ethyl-2-amino-4-methyl thiazole-5-carboxylate (112 mg, 0.6 mmol) and heated at 130°C for 3 hours. The solvent was removed by evaporation, and the residual solid was stirred in ethanol and a diluted solution of $NaHCO_3$ for 10 minutes. The solid was washed with water, dried over P_2O_5 under vacuum, to give a yellow powder of title compound (170 mg, 70 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.32 (t, 3H) ; 2.30 (m, 2H) ; 2.68 (s, 3H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (m, 4H) ; 7.38 (s, 1H) ; 8.01 (s, 1H) ; 9.26 (s, 1H).

MS ES$^+$: 488 $(M_+H)^+$

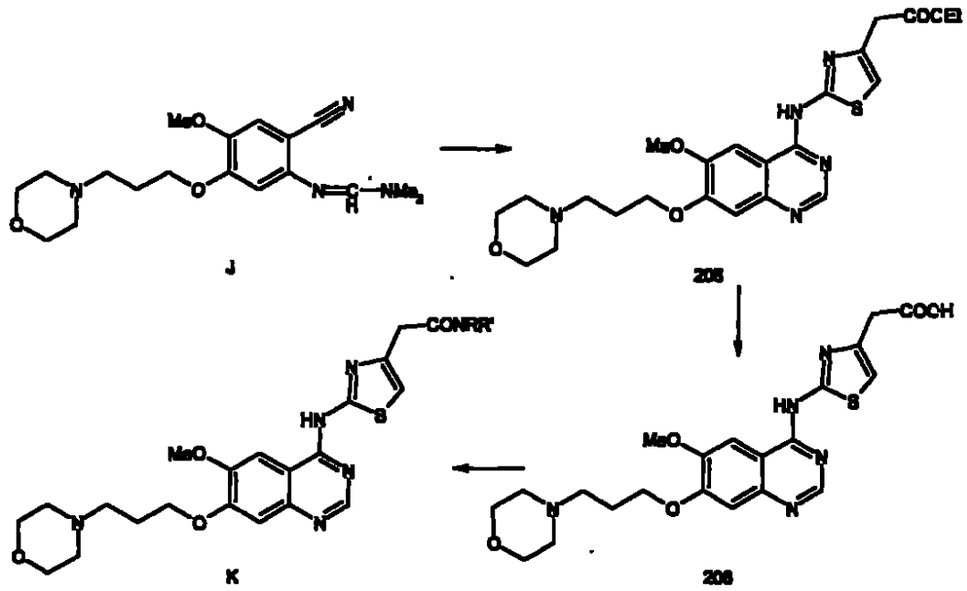
Compound 204

The ester 203 (122 mg, 0.25 mmol) was suspended in ethanol (5 ml) and reacted with sodium hydroxide (10N, 0.5 ml) at 80°C for 1 hour. The reaction mixture was cooled, acidified (pH 3.5), the yellow precipitate was filtered, washed with water, dried under vacuum, to give title compound (100 mg, 87 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.32 (m, 2H) ; 2.62 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.57 (d, 2H) ; 3.71 (t, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 7.35 (s, 1H) ; 7.98 (s, 1H) ; 9.23 (s, 1H).

MS ES$^+$: 460 $(M_+H)^+$

General Scheme 3



Compound 205

Amidine J (2.08 g, 6 mmol) was reacted with ethyl 2-amino-4-thiazolacetate (1.34 g, 7.2 mmol) in acetic acid (2 ml) at 130°C for 4 hours, under argon. The solvent was evaporated, the residual oil was triturated in ether / petr. ether, and the solid filtered. This solid was suspended in water at pH 9 ($NaHCO_3$) and extracted with CH_2Cl_2, dried, evaporated, to give title compound (2 g, 68 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.87 (s, 2H) ; 4.0 (s, 3H) ; 4.04 (d, 2H) ; 4.15 (q, 2H) ; 4.31 (t, 2H) ; 7.28 (s, 1H) ; 7.34 (s, 1H) ; 8.06 (s, 1H) ; 9.15 (s, 1H).

MS ES$^+$: 488 $(M+H)^+$

Compound 206

Ester 205 (2 g, 4.1 mmol) was suspended in ethanol (20 ml). 2N sodium hydroxide (4.1 ml, 8.2 mmol) was added to the suspension which was stirred for 3 hours at room temperature. HCl 2N was added to the solution, the yellow precipitate was filtered, washed with water, ethanol, ether and dried under vacuum, to give title compound (1.98 g, 99 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.55 (d, 2H) ; 3.71 (t, 2H) ; 3.79 (s, 2H) ; 4.0 (s, 3H) ; 4.03 (d, 2H) ; 4.31 (t, 2H) ; 7.25 (s, 1H) ; 7.34 (s, 1H) ; 8.01 (s, 1H) ; 9.12 (s, 1H).

MS ES$^+$: 460 $(M,H)^+$

Synthesis of amides K, general procedure

The acid 206 (83 mg, 0.17 mmol) in DMF (0.8 ml) was reacted with amine (0.17 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (78 mg, 0.204 mmol), DIEA (52 mg, 0.4 mmol), for 6 hours at room temperature. The reaction mixture was then treated with a solution of $NaHCO_3$ (6 ml) with stirring for 2 hours, washed with water, cooled to 5°C, and the solid filtered, triturated with ether, dried under vacuum over P2O5 to give title compounds.

Example 51.

An analogous reaction to that described in General Scheme 3, starting with aniline (19 mg, 0.2 mmol) yielded Compound 51 in Table 2 (73 mg, 81 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.29 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.88 (s, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.09 (t, 1H) ; 7.27 (s, 1H) ; 7.33 (m, 3H) ; 7.63 (d, 2H) ; 7.99 (s, 1H) ; 9.12 (s, 1H).

MS ES$^+$: 535 $(M,H)^+$.

Example 52.

An analogous reaction to that described in General Scheme 3, starting with 4-fluoroaniline (23 mg, 0.2 mmol) yielded Compound 52 in Table 2(79 mg, 84 %).

^{1}HNMR (DMSO-d_6-TFA) : 2.29 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.67 (t, 2H) ; 3.87 (s, 2H) ; 3.98 (s, 3H) ; 4.02 (d, 2H) ; 4.3 (t, 2H) ; 7.17 (t, 2H) ; 7.27 (s, 1H) ; 7.32 (s, 1H) ; 7.63 (m, 2H) ; 7.99 (s, 1H) ; 9.11 (s, 1H).

MS ES$^+$: 553 $(M,H)^+$.

Example 53.

An analogous reaction to that described in General Scheme 3, starting with 4-dimethylaminoaniline (28 mg, 0.2 mmol) yielded Compound 53 in Table 2(52 mg, 53 %).

^{1}HNMR (DMSO-d6-TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.19 (s, 6H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.30 (t, 2H) ; 7.28 (s, 1H) ; 7.33 (s, 1H) ; 7.64 (d, 1H) ; 7.77 (d, 1H) ; 8.01 (s, 1H) ; 9.12 (s, 1H).

MS ES$^+$: 578 $(M_4H)^+$

Example 54.

An analogous reaction to that described in General Scheme 3, starting with 4-chloroaniline (26 mg, 0.2 mmol) yielded Compound 54 in Table 2(72 mg, 75 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.31 (m, 2H) ; 3.14 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.89 (s, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.27 (s, 1H) ; 7.32 (s, 1H) ; 7.38 (d, 1H) ; 7.65 (d, 1H) ; 8.0 (s, 1H) ; 9.12 (s, 1H).

MS ES$^-$: 567, 569 $(M^-H)^-$.

Example 55.

An analogous reaction to that described in General Scheme 3, starting with 3-amino-6-chloropyridine (26 mg, 0.2 mmol) yielded Compound 55 in Table 2(80 mg, 83 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.28 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.93 (s, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.3 (t, 2H) ; 7.29 (s, 1H) ; 7.33 (s, 1H) ; 7.49 (d, 1H) ; 8.01 (s, 1H) ; 8.09 (d, 1H) ; 8.66 (d, 1H) ; 9.13 (s, 1H).

MS ES$^+$: 570, 572 $(M_4H)^+$.

Example 56.

An analogous reaction to that described in General Scheme 3, starting with morpholine (18 mg, 0.2 mmol) yielded Compound 56 in Table 2(14 mg, 16 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.6 (m, 12H) ; 3.9 (s, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.17 (s, 1H) ; 7.3 (s, 1H) ; 7.95 (s, 1H) ; 9.09 (s, 1H).

MS ES$^+$: 529 $(M_4H)^+$

Example 57.

An analogous reaction to that described in General Scheme 3, starting with pyrrolidine (14 mg, 0.2 mmol) yielded Compound 57 in Table 2(73 mg, 84 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.82 (m, 2H) ; 1.93 (m, 2H) ; 2.28 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (m, 4H) ; 3.55 (m, 4H) ; 3.68 (t, 2H) ; 3.71 (s, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.3 (t, 2H) ; 7.17 (s, 1H) ; 7.3 (s, 1H) ; 7.94 (s, 1H) ; 9.08 (s, 1H).

MS ES$^+$: 513 $(M+H)^+$

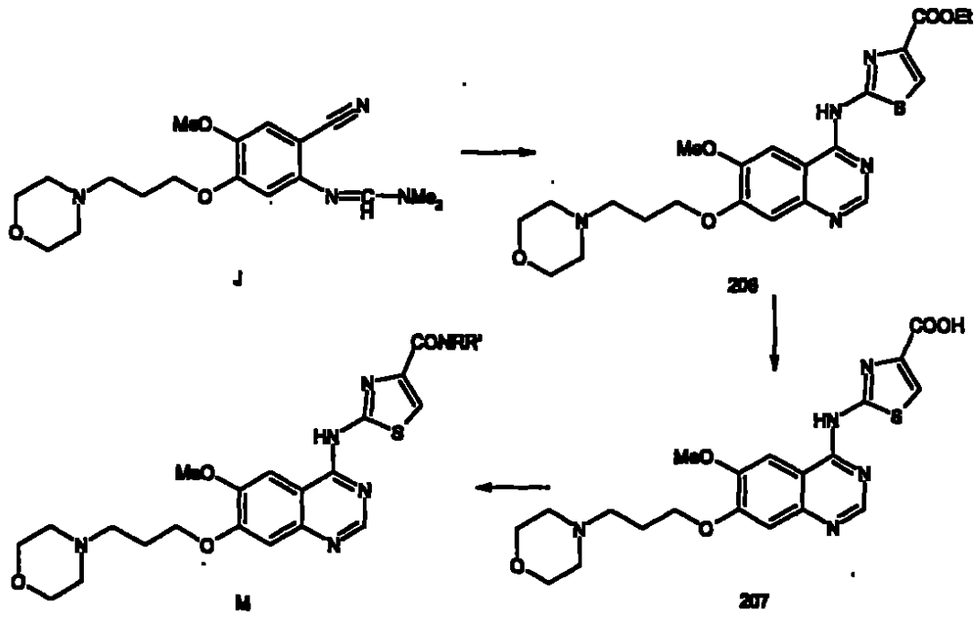
Example 58.

An analogous reaction to that described in General Scheme 3, starting with cyclohexylamine (20 mg, 0.2 mmol) yielded Compound 58 in Table 2 (80 mg, 87 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.25 (m, 4H) ; 1.75 (m, 4H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.56 (d, 2H) ; 3.6 (s, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.3 (t, 2H) ; 7.15 (s, 1H) ; 7.97 (s, 1H) ; 9.09 (s, 1H);

MS ES$^+$: 541 $(M+H)^+$

General Scheme 4



Compound 206

The amidine J (1.38 g, 4 mmol) in acetic acid (14 ml) was reacted with ethyl 2-amino-4-thiazolcarboxylate (0.72 g, 4.2 mmol) at 130°C for 6 hours. The solvent was evaporated, the residue dissolved in ethanol, and stirred with a saturated solution of $NaHCO_3$. The mixture

was extracted with CH_2Cl_2, dried, and purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH 98/2 → 90/10, to give title compound (0.738 g, 52 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.34 (t, 3H) ; 2.28 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (s, 3H) ; 4.04 (d, 2H) ; 4.34 (m, 4H) ; 7.45 (s, 1H) ; 8.33 (s, 1H) ; 8.44 (s, 1H) ; 9.26 (s, 1H).

MS ES$^+$: 474 $(M+H)^+$

Compound 207

Ester 206 (946 mg, 2 mmol) in suspension in ethanol (20 ml) was treated with sodium hydroxide (6N, 4 ml) at 75°C for 45 minutes. The reaction mixture was then cooled to room temperature, acidified (pH 3) with 6N HCl. The precipitate was filtered, washed with ethanol, triturated with ether, dried under vacuum, to give title compound (795 mg, 80 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.34 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.76 (t, 2H) ; 4.03 (m, 5H) ; 4.35 (t, 2H) ; 7.48 (s, 1H) ; 8.26 (s, 1H) ; 8.41 (s, 1H) ; 9.29 (s, 1H).

Synthesis of amides of general structure M, general procedure

The acid 207 (79 mg, 0.16 mmol) in DMF (1 ml) was reacted with amine (0.19 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (73 mg, 0.19 mmol), DIEA (52 mg, 0.4 mmol), for 1 hour at room temperature. The reaction mixture was then treated with a solution of $NaHCO_3$ (5 ml) with stirring for 0.5 hour, and the solid filtered, dried under vacuum over P_2O_5. For the compounds which did not precipitate, the solution was concentrated to dryness, the residues were washed with methylene chloride / methanol, filtered. Alumine was added to the methylene chloride / methanol solution and the solvent evaporated. Purification of the compounds was carried out by chromatography over alumine, eluent CH_2Cl_2 ; CH_2Cl_2 / MeOH : 95/5, to give title compounds.

Example 59.

An analogous reaction to that described in General Scheme 4, starting with aniline (18 mg, 0.19 mmol) yielded Compound 59 in Table 3(50 mg, 60 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.34 (t, 2H) ; 7.14 (t, 1H) ; 7.39 (t, 2H) ; 7.45 (s, 1H) ; 7.8 (d, 2H) ; 8.29 (s, 1H) ; 8.41 (s, 1H) ; 9.29 (s, 1H).

MS ES$^+$: 521 $(M+H)^+$.

Example 60.

An analogous reaction to that described in General Scheme 4, starting with 4-fluoroaniline (21 mg, 0.19 mmol) yielded Compound 60 in Table 3(70 mg, 82 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.33 (t, 2H) ; 3.56 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (d, 2H) ; 4.04 (s, 3H) ; 4.35 (t, 2H) ; 7.22 (t, 2H) ; 7.45 (s, 1H) ; 7.83 (m, 2H) ; 8.28 (s, 1H) ; 8.4 (s, 1H) ; 9.27 (s, 1H).

MS ES$^+$: 539 $(M+H)^+$

Example 61.

An analogous reaction to that described in General Scheme 4, starting with 4-chloroaniline (24 mg, 0.19 mmol) yielded Compound 61 in Table 3(70 mg, 79 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.68 (t, 2H) ; 4.04 (m, 5H) ; 4.35 (t, 2H) ; 7.45 (m, 3H) ; 7.84 (d, 2H) ; 8.29 (s, 1H) ; 8.4 (s, 1H) ; 9.27 (s, 1H).

MS ES$^+$: 555, 557 $(M+H)^+$

Example 62.

An analogous reaction to that described in General Scheme 4, starting with cyclohexylamine (19 mg, 0.19 mmol) yielded Compound 62 in Table 3(60 mg, 72 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.32 (m, 5H) ; 1.62 (m, 1H) ; 1.73 (m, 2H) ; 1.87 (m, 2H) ; 2.33 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.75 (m, 1H) ; 4.03 (s, 3H) ; 4.05 (d, 2H) ; 4.33 (t, 2H) ; 7.42 (s, 1H) ; 8.07 (s, 1H) ; 8.32 (s, 1H) ; 9.24 (s, 1H).

MS ES$^+$: 527 $(M+H)^+$

Example 63.

An analogous reaction to that described in General Scheme 4, starting with 3-(methylamino)-propionitrile (16 mg, 0.19 mmol) yielded Compound 63 in Table 3(40 mg, 49 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 2.88 5m, 3H) ; 3.14 (m, 4H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.71 (t, 2H) ; 3.75 (m, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.44 (s, 1H) ; 7.85 (s, 1H) ; 8.37 (s, 1H) ; 9.27 (s, 1H).

MS ES$^+$: 512 $(M+H)^+$

Example 64.

An analogous reaction to that described in General Scheme 4, starting with 4-hydroxypiperidine (19 mg, 0.19 mmol) yielded Compound 64 in Table 3(45 mg, 54 M).
^{1}HNMR (DMSOd_6, TFA) : 1.36 (m, 2H) ; 1.78 (m, 2H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.29 (m, 2H) ; 3.37 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.77 (m, 2H) ; 3.84 (m, 1H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.42 (s, 1H) ; 7.75 (s, 1H) ; 8.35 (s, 1H) ; 9.27 (s, 1H).
MS ES$^+$: 529 $(M,H)^+$.

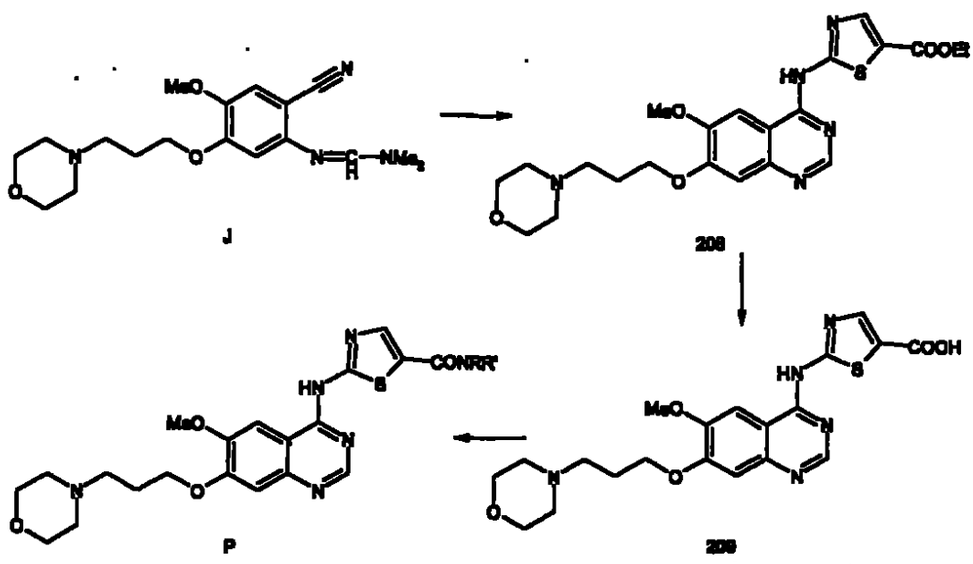
Example 65.

An analogous reaction to that described in General Scheme 4, starting with 4-aminopyridine (18 mg, 0.19 mmol) yielded Compound 65 in Table 3(35 mg, 42 %).
^{1}HNMR (DMSO-d_6, TFA) : 2.29 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (m, 5H) ; 4.34 (t, 2H) ; 7.48 (s, 1H) ; 8.41 (d, 2H) ; 8.43 (s, 1H) ; 8.52 (s, 1H) ; 8.81 (d, 2H) ; 9.24 (s, 1H).
MS ES$^+$: 522 $(M,H)^+$

Example 66.

An analogous reaction to that described in General Scheme 4, starting with 2-chloroaniline (24 mg, 0.19 mmol) yielded Compound 66 in Table 3 (25 mg, 28 %).
^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (d, 2H) ; 4.05 (s, 3H) ; 4.35 (t, 2H) ; 7.24 (t, 1H) ; 7.42 (t, 1H) ; 7.47 (s, 1H) ; 7.6 (d, 1H) $(M,H)^+$.

General Scheme 5



Compound 208

The amidine J (1.52 g, 4.4 mmol) in AcOH (15 ml) was reacted with ethyl 2-amino-5-thiazolcarboxylate (757 mg, 4.4 mmol) at 130°C under argon for 3 hours. The solvent was evaporated, the residual oil was dissolved in methylene chloride and purified by silica gel chromatography, eluent CH_2Cl_2, CH_2Cl_2 / MeOH : 95/5, to give title compound as a yellow solid (1.44 g, 70 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.33 (t, 3H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.35 (m, 4H) ; 7.41 (s, 1H) ; 8.14 (s, 1H) ; 8.44 (s, 1H) ; 9.3 (s, 1H).

MS ES$^+$: 474 $(M+H)^+$

Compound 209

Ester 208 (1.6 g, 3.4 mmol) in suspension in ethanol (32 ml) was reacted with sodium hydroxide (6N, 6 ml) at 75°C for 1 hour. The cooled solution was acidified with HCl (6N) to pH 4. The solid was filtered, washed with EtOH, ether, dried, to give a yellow solid (1.65 g, 86 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.28 (m, 2H) ; 3.12 (t, 2H) ; 3.32 (t, 2H) ; 3.51 (d, 2H) ; 3.66 (t, 2H) ; 3.97 (s, 3H) ; 3.99 (d, 2H) ; 4.31 (t, 2H) ; 7.37 (s, 1H) ; 8.06 (s, 1H) ; 8.32 (s, 1H) ; 9.24 (s, 1H).

MS ES$^+$: 446 $(M+H)^+$

Synthesis of amides of general structure P, general procedure

The acid 209 (95 mg, 0.17 mmol) in DMF, 1 ml was reacted with amine (0.2 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (91 mg, 0.24 mmol), DIEA (110 mg, 0.85 mmol) for 14 hours at room temperature and 5 hours at 50°C. The reaction mixture was then treated with a solution of $NaHCO_3$ (1 ml) with stirring for 0.5 hour, and concentrated. The residue was washed with methylene chloride / methanol (1/1, 25 ml). Alumine was added to the organic phase, which was then evaporated. Purification of the compound was carried out by chromatography over alumine, eluent CH_2Cl_2, CH_2Cl_2 / MeOH / 95/5, to give title compounds.

Example 67.

An analogous reaction to that described in General Scheme 5, starting with aniline (19 mg, 0.2 mmol) yielded Compound 67 in Table 4 (30 mg, 34 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.14 (t, 1H) ; 7.39 (m, 3H) ; 7.73 (d, 2H) ; 8.05 (s, 1H) ; 8.61 (s, 1H) ; 9.28 (s, 1H).

MS ES^+ : 521 $(M+H)^+$

Example 68.

An analogous reaction to that described in General Scheme 5, starting with 4-fluoroaniline (23 mg, 0.2 mmol) yielded Compound 68 in Table 4(58 mg, 64 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.20 (t, 1H) ; 7.38 (s, 1H) ; 7.73 (m, 1H) ; 8.05 (s, 1H) ; 8.57 (s, 1H) ; 9.28 (s, 1H).

MS ES^+ : 539 $(M+H)^+$

Example 69.

An analogous reaction to that described in General Scheme 5, starting with 4-chloroaniline (26 mg, 0.2 mmol) yielded Compound 69 in Table 4(32 mg, 34 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.32 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 7.39 (s, 1H) ; 7.44 (d, 2H) ; 7.76 (d, 2H) . 8.06 (s, 1H) ; 8.6 (s, 1H) ; 9.29 (s, 1H).

MS ES^+ : 555, 557 $(M+H)^+$

Example 70.

An analogous reaction to that described in General Scheme 5, starting with allylamine (12 mg, 0.2 mmol) yielded Compound 70 in Table 4(32 mg, 39 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.7 (t, 2H) ; 3.92 (d, 2H) ; 4.0 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 5.16 (d, 1H) ; 5.25 (d, 1H) ; 5.9 (m, 1H) ; 7.38 (s, 1H) ; 8.02 (s, 1H) ; 8.36 (s, 1H) ; 9.24 (s, 1H).

MS ES$^+$: 485 $(M+H)^+$

Example 71.

An analogous reaction to that described in General Scheme 5, starting with 3-(methylamino)-propionitrile (17 mg, 0.2 mmol) yielded Compound 71 in Table 4(32 mg, 39 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 2.89 (m, 3H) ; 3.15 (t, 2H) ; 3.34 (m, 4H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.8 (m, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 7.38 (s, 1H) ; 8.07 (s, 1H) ; 8.22 (s, 1H) ; 9.25 (s, 1H).

MS ES$^+$: 512 $(M+H)^+$.

Example 72.

An analogous reaction to that described in General Scheme 5, starting with 4-hydroxypiperidine (20 mg, 0.2 mmol) yielded Compound 72 in Table 4(12 mg, 13 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.45 (m, 2H) ; 1.82 (m, 2H) ; 2.31 (m, 2H) ; 3.15 (m, 4H) ; 3.35 (t, 2H) ; 3.4 (m, 2H) ; 3.54 (d, 2H) ; 3.7 (t, 2H) ; 3.79 (m, 1H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.38 (s, 1H) ; 8.06 (s, 1H) ; 8.09 (s, 1H) ; 9.23 (s, 1H).

MS ES$^+$: 529 $(M+H)^+$

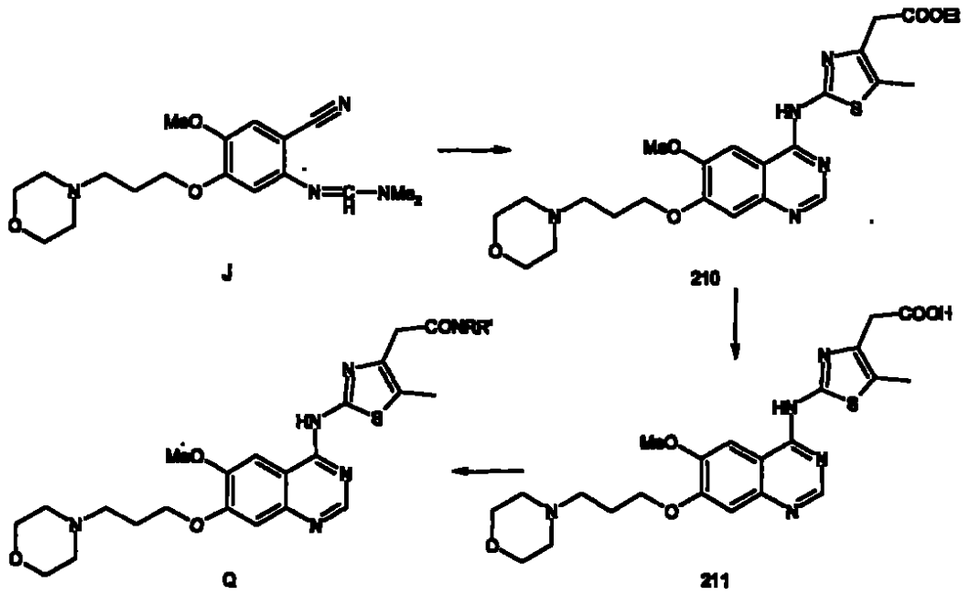
Example 73.

An analogous reaction to that described in General Scheme 5, starting with 4-aminopyridine (19 mg, 0.2 mmol) yielded Compound 73 in Table 4 (50 mg, 57 %).

^{1}HNMR (DMSO-d_6-TFA) : 2.29 (m, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.7 (t, 2H) ; 4.02 (s, 3H) ; 4.03 (d, 2H) ; 4.34 (t, 2H) ; 7.46 (s, 1H) ; 8.15 (s, 1H) ; 8.27 (d, 2H) ; 8.78 (s, 1H) ; 8.8 (d, 2H) ; 9.31 (s, 1H).

MS ES$^+$: 522 $(M+H)^+$

General Scheme 6



Compound 210

Amidine J (450 mg, 1.3 mmol) was reacted with methyl 2-amino-5-methyl-4-thiazolacetate (242 mg, 1.3 mmol) in acetic acid (5 ml) at 130°C for 3 hours, under argon. The solvent was evaporated, ethylacetate and water were added to the residual oil, the pH adjusted to 9 with a saturated solution of sodium bicarbonate and the mixture extracted with ethylacetate. The organic phase was washed with a saturated solution of sodium chloride, dried over magnesium sulphate, filtered, concentrated. The residual oil was purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH : 98/2 to 95/5 to give title compound (380 mg, 60 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 2.35 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.68 (s, 3H) ; 3.83 (s, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.31 (s, 1H) ; 7.96 (s, 1H) ; 9.06 (s, 1H).

MS ES^+ : 488 $(M+H)^+$

Compound 211

Ester 210 (360 mg, 0.74 mmol) in ethanol (10 ml) was reacted with sodium hydroxide (6N, 1 ml) at room temperature for 1 hour. HCl (6N) was then added to the solution cooled to 0°C, and the pH adjusted to 3-4. The solid was recovered by filtration, washed with ethanol, ether, dried under vacuum, to give title compound as a dihydrochloride (550 mg, 83 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.34 (m, 5H) ; 3.13 (t, 2H) ; 3.32 (t, 2H) ; 3.52 (d, 2H) ; 3.74 (s, 2H) ; 3.78 (t, 2H) ; 3.98 (s, 3H) ; 4.01 (d, 2H) ; 4.31 (t, 2H) ; 7.37 (s, 1H) ; 7.91 (s, 1H) ; 9.03 (s, 1H).

MS ES$^+$: 474 $(M+H)^+$

Synthesis of amides of general structure O, general procedure

The acid 211 (87 mg, 0.13 mmol) in DMF (1 ml) was reacted with amine (0.169 mmol) in presence of O-(7-azabensotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (69 mg, 0.182 mmol), diisopropylethylamine (84 mg, 0.65 mmol) over night, at room temperature. The reaction mixture was diluted with water (5 ml) and a concentrated solution of sodium bicarbonate (1 ml). The solid was filtered, washed with water, ethanol, ether, and dried under vacuum, to give title compounds. For the compounds which did not precipitate, the solution was concentrated to dryness, the residues were washed with methylene chloride, methanol, filtered. Alumine was added to the methylene chloride / methanol solution, and the solvent was evaporated. Purification of the compounds was carried out by chromatography over alumine, eluent CH_2Cl_2 / MeOH : 98/2 to 95/5, to give title compounds.

Example 74.

An analogous reaction to that described in General Scheme 6, starting with aniline (16 mg, 0.17 mmol) yielded Compound 74 in Table 17 (50 mg, 70 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.28 (m, 2H) ; 2.37 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.56 (d, 2H) ; 3.68 (t, 2H) ; 3.84 (s, 2H) ; 3.96 (s, 3H) ; 4.03 (d, 2H) ; 4.28 (t, 2H) ; 7.07 (t, 1H) ; 7.29 (s, 1H) ; 7.3 (t, 2H) ; 7.61 (d, 2H) ; 7.89 (s, 1H) ; 9.02 (s, 1H).

MS ES$^+$: 549 $(M+H)^+$

Example 75.

An analogous reaction to that described in General Scheme 6, starting with 4-fluoroaniline (19 mg, 0.17 mmol) yielded Compound 75 in Table 17 (50 mg, 67 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 2.38 (s, 3H) ; 3.16 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.84 (s, 2H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.16 (t, 2H) ; 7.29 (s, 1H) ; 7.64 (m, 2H) ; 7.9 (s, 1H) ; 9.03 (s, 1H).

MS ES$^+$: 567 $(M+H)^+$.

Example 76.

An analogous reaction to that described in General Scheme 6, starting with 4-chloroaniline (22 mg, 0.17 mmol) yielded Compound 76 in Table 17(45 mg, 59 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.28 (m, 2H) ; 2.37 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.85 (s, 2H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.37 (d, 2H) ; 7.65 (d, 2H) ; 7.9 (s, 1H) ; 9.03 (s, 1H).

MS ES$^+$: 583 $(M_+H)^+$

Example 77.

An analogous reaction to that described in General Scheme 6, starting with 4-hydroxypiperidine (17 mg, 0.17 mmol) yielded Compound 77 in Table 17(45 mg, 62 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.42 (m, 2H) ; 1.82 (m, 2H) ; 2.31 (m, 5H) ; 3.08 (m, 1H) ; 3.16 (t, 2H) ; 3.27 (m, 1H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.78 (m, 2H) ; 3.83 (s, 2H) ; 3.92 (m, 1H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.28 (s, 1H) ; 7.85 (s, 1H) ; 9.0 (s, 1H).

MS ES$^+$: 557 $(M_+H)^+$.

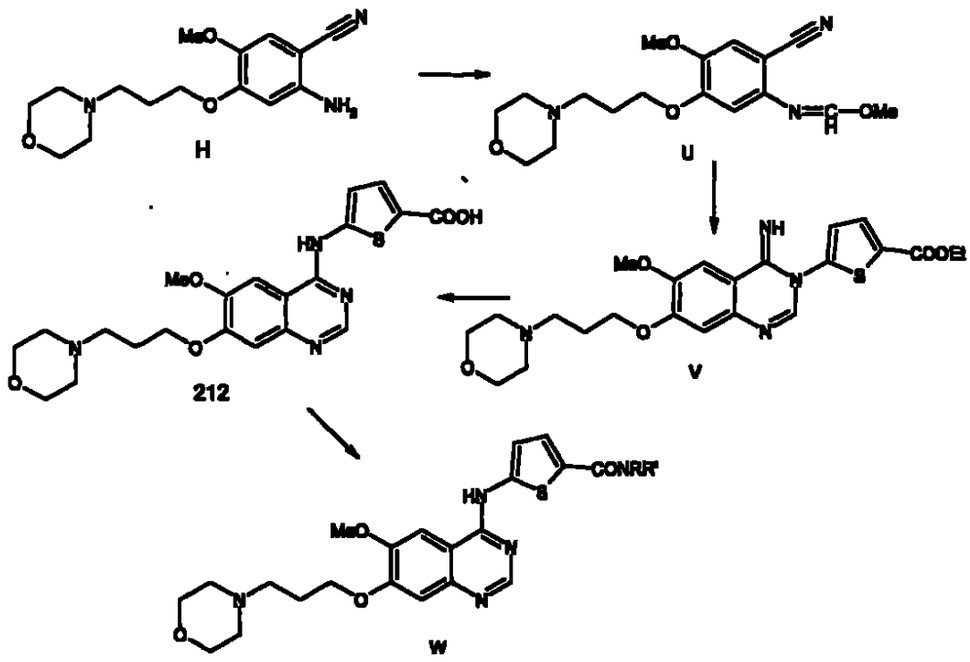
Example 78.

An analogous reaction to that described in General Scheme 6, starting with 4-aminopyridine (16 mg, 0.17 mmol) yielded Compound 78 in Table 17(35 mg, 49 %).

^{1}HNMR (DMSO-d6, TFA) : 2.29 (m, 2H) ; 2.39 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.96 (s, 3H) ; 4.02 (d, 2H) ; 4.04 (s, 2H) ; 4.29 (t, 2H) ; 7.33 (s, 1H) ; 7.92 (s, 1H) ; 8.1 (d, 2H) ; 8.76 (d, 2H) ; 9.06 (s, 1H).

MS ES$^+$: 550 $(M_+H)^+$.

General Scheme 7



Compound U

The amino nitrile H (2.91 g, 10 mmol) was reacted with trimethylorthoformate (10 ml) in presence of p-toluene-sulfonic acid (38 mg, 2 mmol) at 80°C for 6 hours. The solvent was evaporated, the residue crystallised from ether to give title compound (3.01 g, 90.4 %).

^{1}HNMR (DMSO-d_6) : 1.9 (t, 2H) ; 2.4 (m, 6H) ; 3.58 (t, 4H) ; 3.78 (s, 3H) ; 3.85 (s; 3H) ; 4.08 (t, 2H) ; 6.88 (s, 1H) ; 7.28 (s, 1H) ; 8.2 (s, 1H).

MS ES$^+$: 334 $(M+H)^+$

Compound V

Imidate U (0.25 g, 0.75 mmol) in CH_2Cl_2 (5 ml) was reacted with ethyl 2-amino-5-thiophenecarboxylate (0.13 g, 0.79 mmol) in presence of pyridinium hydrochloride (0.09 g, 0.75 mmol), at room temperature over night. Ethyl acetate was then added, and the solid was recovered by filtration, washed with ethyl acetate, dried under vacuum, to give product (0.23 g, 65 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.33 (t, 3H) ; 2.28 (m, 2H) ; 3.12 (t, 2H) ; 3.32 (t, 2H) ; 3.53 (d, 2H) ; 3.73 (t, 2H) ; 3.96 (s, 3H) ; 4.02 (d, 2H) ; 4.37 (m, 4H) ; 7.45 (s, 1H) ; 7.67 (d, 1H) ; 7.95 (d, 1H) ; 8.12 (s, 1H) ; 8.52 (s, 1H).

MS ES$^+$: 473 $(M,H)^+$

Compound 212

Ester V (1.1 g, 2.3 mmol) in methanol (20 ml) was treated with sodium hydroxide (2N, 20 ml) at 75°C for 4 hours, and at room temperature over night. Methanol was evaporated, and the remaining aqueous solution was kept for 24 hours at 5°C. The solid was filtered, washed with water, MeOH / CH_2Cl_2 : 1/1, dried under vacuum to give title compound (0.9 g, 87 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.31 (m, 2H) ; 3.14 (t, 2H) ; 3.33 (t, 2H) ; 3.53 (d, 2H) ; 3.76 (t, 2H) ; 4.01 (d, 2H) ; 4.07 (s, 3H) ; 4.33 (t, 2H) ; 7.44 (s, 1H) ; 7.54 (d, 1H) ; 7.68 (d, 1H) ; 8.54 (s, 1H) ; 9.22 (s, 1H).

MS ES$^+$: 445 $(M,H)^+$

Synthesis of amides of general structure W, general procedure

Acid 212 (80 mg, 0.18 mmol) in DMF (1.5 ml) was reacted with amine (0.216 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (80 mg, 0.21 mmol), DIEA (80 µl, 0.46 mmol), for 3 hours at room temperature. The reaction mixture was then treated with a solution of $NaHCO_3$ (2 ml) with stirring for 0.5 hour, the solid filtered, washed with water, ether, dried under vacuum over P_2O_5, to give title compound.

Example 79.

An analogous reaction to that described in General Scheme 7, starting with aniline (17 µl, 0.186 mmol) yielded Compound 79 in Table 18 (80 mg, 86 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.32 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.53 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (d, 2H) ; 4.03 (s, 3H) ; 4.3 (t, 2H) ; 7.7 (t, 1H) ; 7.32 (m, 4H) ; 7.73 (d, 2H) ; 7.98 (d, 1H) ; 8.18 (s, 1H) ; 9.22 (s, 1H).

MS ES$^+$: 520 $(M,H)^+$

Example 80.

An analogous reaction to that described in General Scheme 7, starting with 4-fluoroaniline (24 mg, 0.216 mmol) yielded Compound 80 in Table 18 (62 mg, 64 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.05 (m, 5H) ; 4.33 (t, 2H) ; 7.21 (t, 2H) ; 7.33 (d, 1H) ; 7.4 (s, 1H) ; 7.77 (m, 2H) ; 7.98 (d, 1H) ; 8.2 (s, 1H) ; 9.25 (s, 1H).

MS ES$^+$: 538 $(M+H)^+$.

Example 81.

An analogous reaction to that described in General Scheme 7, starting with 3-aminophenol (24 mg, 0.216 mmol) yielded Compound 81 in Table 18 (60 mg, 66 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.7 (t, 2H) ; 4.04 (d, 2H) ; 4.06 (s, 3H) ; 4.33 (t, 2H) ; 6.53 (m, 1H) ; 7.13 (m, 2H) ; 7.3 (d, 1H) ; 7.36 (d, 1H) ; 7.4 (s, 1H) ; 7.96 (s, 1H) ; 8.0 (d, 1H) ; 8.26 (s, 1H) ; 9.25 (s, 1H).

MS ES$^+$: 536 $(M+H)^+$.

Example 82.

An analogous reaction to that described in General Scheme 7, starting with 4-aminopyridine (20 mg, 0.216 mmol) yielded Compound 82 in Table 18 (16 mg, 19 %).

^{1}HNMR (DMSO-d6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.32 (t, 2H) ; 7.01 (d, 1H) ; 7.03 (s, 1H) ; 8.18 (d, 1H) ; 8.22 (s, 1H) ; 8.3 (d, 2H) ; 8.76 (d, 2H) ; 9.3 (s, 1H).

MS ES$^+$: 521 $(M+H)^+$.

Example 83.

An analogous reaction to that described in General Scheme 7, starting with 4-amino-1-butanol (19 mg, 0.216 mmol) yielded Compound 83 in Table 18 (22 mg, 28 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.46 (m, 2H) ; 1.58 (m, 2H) ; 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.26 (t, 2H) ; 3.36 (t, 2H) ; 3.44 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (m, 5H) ; 4.32 (t, 2H) ; 7.26 (d, 1H) ; 7.39 (s, 1H) ; 7.7 (d, 1H) ; 8.19 (s, 1H) ; 9.21 (s, 1H).

MS ES$^+$: 516 $(M+H)^+$

Example 84.

An analogous reaction to that described in General Scheme 7, starting with 3-aminobenzamide (29 mg, 0.216 mmol) yielded Compound 84 in Table 18 (60 mg, 77 %).
^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.67 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.32 (t, 2H>) ; 7.34 (d, 1H) ; 7.39 (s, 1H) ; 7.42 (t, 1H) ; 7.62 (d, 1H) ; 7.96 (d, 1H) ; 8.05 (d, 1H) ; 8.21 (m, 2H) ; 9.27 (s, 1H).
MS ES$^+$: 563 $(M+H)^+$.

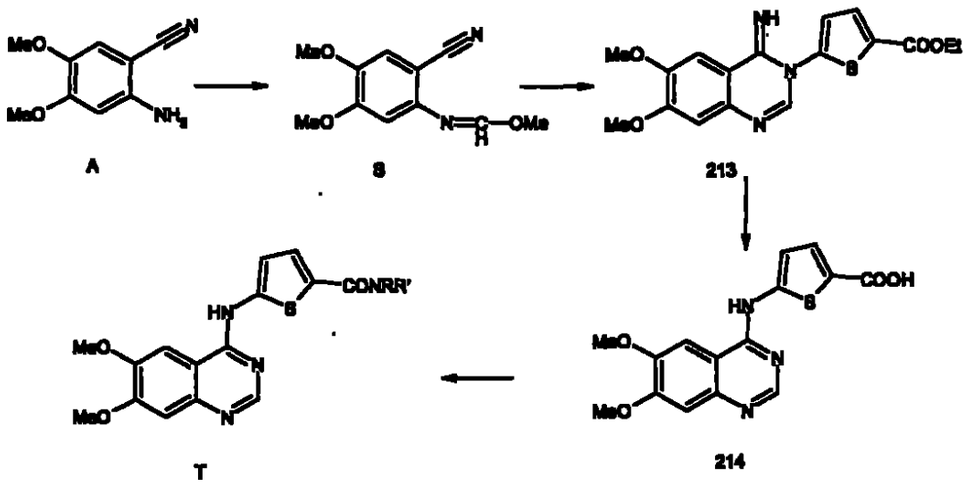
Example 85.

An analogous reaction to that described in General Scheme 7, starting with allylamine (12 mg, 0.216 mmol) yielded title Compound 85 in Table 18 (20 mg,, 43 %).
^{1}HNMR (DMSO-d6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.91 (d, 2H) ; 4.04 (m, 5H) ; 4.32 (t, 2H) ; 5.12 (d, 1H) ; 5.2 (d, 1H) ; 5.91 (m, 1H) ; 7.26 (d, 1H) ; 7.38 (s, 1H) ; 7.75 (d, 1H) ; 8.19 (s, 1H) ; 9.22 (s, 1H).
MS ES$^+$: 484 $(M+H)^+$.

Example 86.

An analogous reaction to that described in General Scheme 7, starting with Methyl-4-aminobutyrate (25 mg, 0.216 mmol) yielded Compound 86 in Table 18 (18 mg, 23 %).
^{1}HNMR : 1.8 (t, 2H) ; 2.3 (m, 2H) ; 2.39 (t, 2H) ; 3.16 (t, 2H) ; 3.28 (t, 2H) ; 3.35 (t, 2H) ; 3.56 (d, 2H) ; 3.6 (s, 3H) ; 3.67 (t, 2H) ; 4.04 (m, 5H) ; 4.32 (t, 2H) ; 7.26 (d, 1H) ; 7.38 (s, 1H) ; 7.69 (d, 1H) ; 8.19 (s, 1H) ; 9.22 (s, 1H).
MS ES$^+$: 544 $(M+H)^+$.

General Scheme 8



Compound S

Aminonitrile A (1.78 g, 10 mmol) was treated with trimethylorthoformate (10 ml) and a catalytic amount of p-toluene sulfonic acid at 100°C for 1 hour. The mixture was cooled to room temperature, ethyl acetate was added, and the insoluble solid removed by filtration, the solvent was then evaporated, the residue triturated with ether to give title compound as a yellow solid (1.56 g, 71 %).

^{1}HNMR (DMSO-d_6) : 3.77 (s, 3H) ; 3.83 (s, 3H) ; 3.84 (s, 3H) ; 6.87 (s, 1H) ; 7.26 (s, 1H) ; 8.19 (s, 1H).

MS ES$^+$: 221 $(M,H)^+$.

Compound 213

Imidate S (0.165 g, 0.75 mmol) was reacted with ethyl 2-amino-5-thiophenecarboxylate (0.13 g, 0.79 mmol) in methylene chloride (4 ml) in presence of pyridinium hydrochloride (88 mg, 0.75 mmol) at room temperature for 4 hours. The solvent was evaporated, and the residue was purified by silica gel chromatography, eluent : AcOEt / CH2Cl2, 1/1 ; followed by MeOH / AcOEt / CH2Cl2, 1/4/5, to give title compound (0.135 g , 50 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.33 (t, 3H) ; 3.95 (s, 3H) ; 4.03 (s, 3H) ; 4.38 (q, 2H) ; 7.43 (s, 1H) ; 7.67 (d, 1H) ; 7.95 (d, 1H) ; 8.05 (s, 1H) ; 8.52 (s, 1H).

MS ES$^+$: 360 $(M,H)^+$

Compound 214

The ester 213 (72 mg, 0.2 mmol) in methanol (2 ml) was treated with sodium hydroxide (2N, 2 ml) at 75°C for 1.5 hour. The reaction mixture was cooled to room temperature, and the pH adjusted to 3 by addition of HCl 2N. The solid was recovered by filtration, washed with water, dried under vacuum in presence of P_2O_5, to give title compound (83 mg, 100 %).

^{1}HNMR (DMSO-d_6, TFA) : 4.02 (s, 3H) ; 4.04 (s, 3H) ; 7.38 (s, 1H) ; 7.42 (d, 1H) ; 7.68 (d, 1H) ; 8.35 (s, 1H) ; 9.21 (s, 1H).

MS ES$^+$: 332 $(M,H)^+$.

Example 87.

Synthesis of compound of General formula T where NRR' = NHPh (Compound 87)

Quinazoline 214 (45 mg, 0.108 mmol) in DMF (1 ml) was reacted with aniline (12 µl, 0.13 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (50 mg, 0.13 mmol), DIEA (75 µl, 0.43 mmol) for 1.5 hour at room temperature. A saturated solution of sodium bicarbonate (2 ml) was added to the mixture which was stirred for 0.5 hour. The solid was filtered, washed with water, and purified by chromatography over alumine, eluent AcOEt / CH_2Cl_2 : 1/1 to MeOH / AcOEt / CH_2Cl_2 : 1/4/5, to give title compound (15 mg, 34 %).

^{1}HNMR (DMSO-d_6) : 3.97 (s, 3H) ; 4.01 (s, 3H) ; 7.05 (d, 1H) ; 7.09 (t, 1H) ; 7.29 (s, 1H) ; 7.36 (t, 2H) ; 7.74 (d, 2H) ; 7.91 (d, 1H) ; 7.92 (s, 1H) ; 8.72 (s, 1H).

MS ES$^+$: 406 $(M,H)^+$

Example 88.

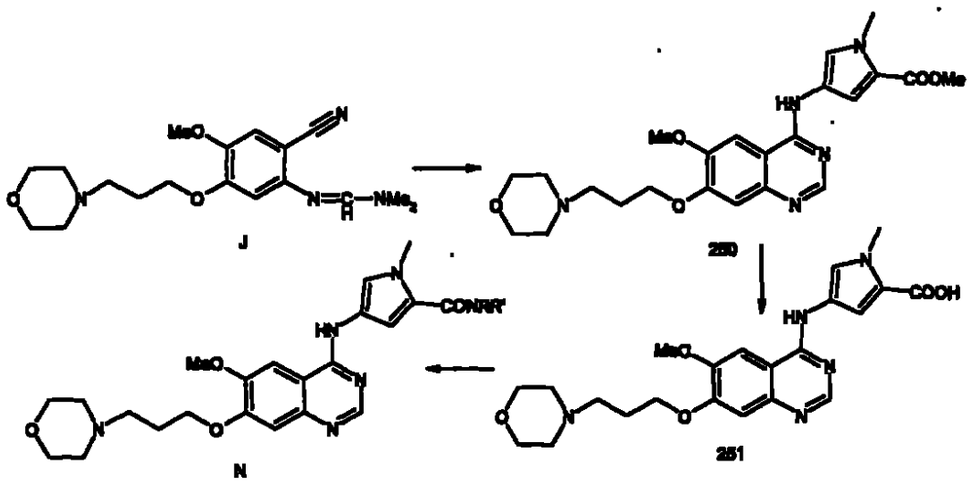
Synthesis of Compound 88 of General formula T where NRR' is NHPh(4-F)

An analogous reaction to that described in the Example 87, starting with quinazoline 213 (60 mg, 0.14 mmol), 4-fluoroaniline (17 µl, 0.17 mmol) yielded title compound (15 mg, 24 %).

^{1}HNMR (DMSO-d_6, TFA) : 4.04 (s, 3H) ; 4.06 (s, 3H) ; 7.18 (t, 2H) ; 7.32 (d, 1H) ; 7.35 (s, 1H) ; 7.75 (t, 2H) ; 7.98 (d, 1H) ; 8.17 (s, 1H) ; 9.23 (s, 1H).

MS ES$^+$: 425 $(M,H)^+$.

General Scheme 9



Example 89. Preparation of Compound 250 in Table 9

Amidine J (1.04 g, 3 mmol) in acetic acid (10 ml) was reacted with methyl 4-amino-1-methyl-2-pyrrolecarboxylate hydrochloride (686 mg, 3.6 mmol) and dimethylamine in methanol (1.25 M 2.9 ml, 3.6 mmol) at 130°C for 5.5 hours. The solvent was evaporated, water and an aqueous solution of sodium bicarbonate were added to the residue, the precipitate was filtered, dried under vacuum over P_2O_5. The solid was redissolved in a large volume of tetrahydrofuran, methylene chloride, methanol, the solution was concentrated, the solid filtered, washed with ether, dried, to give title compound (1.18 g, 86 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.8 (s, 3H) ; 3.95 (s, 3H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.26 (d, 1H) ; 7.32 (s, 1H) ; 7.69 (d, 1H) ; 8.06 (s, 1H) ; 8.94 (s, 1H).

MS ES$^+$: 456 $[M,H]^+$

Example 90. Preparation of Compound 251 in Table 9

Ester 250 (1.34 g, 3 mmol) was treated with sodium hydroxide (6N, 3 ml) in ethanol (25 ml) at 75° for 2 hours. The solution was then cooled to room temperature, acidified to pH 3 with HCl (6N), the precipitate was recovered by filtration, washed with ethanol, ether, dried under vacuum to give title compound (636 mg, 42 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (m, 5H) ; 4.3 (t, 2H) ; 7.19 (s, 1H) ; 7.32 (s, 1H) ; 7.62 (s, 1H) ; 8.17 (s, 1H) ; 8.93 (s, 1H).

MS ES$^+$: 428 $[M,H]^+$

Example 91. Synthesis of amides N, general procedure

Acid 251 (79 mg, 0.15 mmol) in DMF (1 ml) was reacted with O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (62 mg, 0.165 mmol), the appropriate amine (1.65 mmol) and DIEA (68 mg, 0.525 mmol) at room temperature for 1.5 hour. The reaction mixture was then diluted with water (4 ml) and an aqueous solution of sodium bicarbonate (1 ml). The solid was recovered by filtration, redissolved in tetrahydrofuran, methylene chloride, and concentrated, the precipitated solid was recovered, washed with ether, dried under vacuum, to give title compound.

Example 92. Preparation of Compound 252 in Table 9

Compound of example 1 was obtained by reaction of the N-hydroxybenzotriazol ester of 3 (56 mg, 0.1 mmol) with aniline (11 mg, 0.12 mmol) in DMF (1 ml) at 105°C for 3 hours. Water was added to the cooled reaction mixture, which was extracted with ethylacetate, the organic phase was washed with water, dried over $MgSO_4$, filtered and concentrated to give title compound (12 mg, 23 %). The N-hydroxybenzotriazol ester was obtained as described in the general procedure of Example 91.

^{1}HNMR (DMSOd_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.08 (t, 1H) ; 7.33 (m, 3H) ; 7.4 (s, 1H) ; 7.63 (s, 1H) ; 7.74 (d, 2H) ; 8.1 (s, 1H) ; 8.93 (s, 1H).

MS ES+ : 517 $[M,H]^+$

Example 93. Preparation of Compound 253 in Table 9

An analogous reaction to that described in Example 92, but starting with 4-fluoroaniline (22 mg, 0.195 mmol) yielded title compound (40 mg, 57 %).

^{1}H NMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.72 (t, 2H) ; 3.97 (s, 3H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.3 (t, 2H) ; 7.18 (t, 2H) ; 7.34 (s, 1H) ; 7.4 (d, 1H) ; 7.63 (d, 1H) ; 7.76 (m, 1H) ; 8.11 (s, 1H) ; 8.94 (s, 1H).

MS ES$^+$: 535 $[M+H]^+$

Example 94. Preparation of Compound 254 in Table 9

An analogous reaction to that described in Example 92, but starting with cyclohexylamine (16 mg, 0.17 mmol) yielded title compound (60 mg, 76 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.14 (m, 1H) ; 1.3 (m, 4H) ; 1.62 (m, 1H) ; 1.8 (m, 4H) ; 2.29 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (m, 3H) ; 3.9 (s, 3H) ; 4.0 (s, 3H) ; 4.03 (d, 2H) ; 4.28 (t, 2H) ; 7.14 (d, 1H) ; 7.31 (s, 1H) ; 7.49 (d, 1H) ; 8.07 (s, 1H) ; 8.9 (s, 1H).

MS ES$^+$: 523 $[M+H]^+$

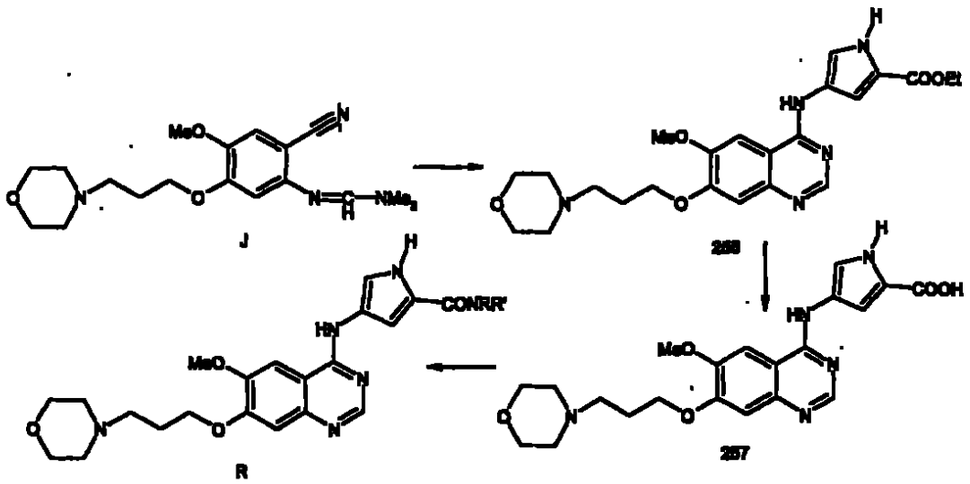
Example 95. Preparation of Compound 255 in Table 9

An analogous reaction to that described in the Example 92, but starting with N,N-dimethyl-1,4-phenylenediamine (23 mg, 0.17 mmol) yielded title compound (61 mg, 73 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.21 (s, 6H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.97 (s, 3H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.35 (s, 1H) ; 7.45 (d, 1H) ; 7.66 (m, 3H) ; 7.93 (d, 2H) ; 8.1 (s, 1H) ; 8.93 (s, 1H).

MS ES$^+$: 560 $[M+H]^+$

General Scheme 10



Example 96. Preparation of Compound 256 in Table 9

Amidine J (1.38 g, 4 mmol) in acetic acid (14 ml) was reacted with ethyl 4-amino-2-pyrrolecarboxylate (0.702 g, 4.56 mmol) at 130°C for 5 hours. The solution was concentrated,

the solid recovered by filtration and washed with ether. This solid was then treated with a diluted solution of sodium bicarbonate, filtered, washed with water and dried under vacuum over P_2O_5 to give title compound (1.34 g, 73 %).

^{1}H NMR (DMSO-d_6) : 1.3 (t, 3H) ; 1.95 (t, 2H) ; 2.38 (m, 4H) ; 2.44 (t, 2H) ; 3.58 (m, 4H) ; 3.94 (s, 3H) ; 4.16 (d, 2H) ; 4.23 (q, 2H) ; 7.05 (d, 1H) ; 7.14 (s, 1H) ; 7.59 (d, 1H) ; 7.75 (s, 1H) ; 8.46 (s, 1H) ; 9.53 (s, 1H) ; 11.72 (s, 1H).

MS ES$^+$: 456 $[M+H]^+$

Example 96. Preparation of Compound 257 in Table 9

Ester 256 (1.34 g, 3 mmol) in ethanol (25 ml) was treated with sodium hydroxide (6N, 3 ml) at 75°C for 2 hours. The solution was cooled, and acidified with hydrochloric acid (6N) to pH 3. The precipitate was filtered, washed with ethanol, ether, dried under vacuum over P_2O_5, to give title compound (0.63 g, 42 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (s, 3H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.19 (d, 1H) ; 7.32 (s, 1H) ; 7.62 (d, 1H) ; 8.17 (s, 1H) ; 8.93 (s, 1H).

MS ES$^+$: 428 $[M+H]^+$

Example 97. Preparation of Compound 258 in Table 9

Acid 256 (75 mg, 0.15 mmol) in DMF (0.7 ml) was reacted with O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (68 mg, 0.18 mmol), aniline (17 mg, 0.18 mmol) and DIEA (62 mg, 0.48 mmol) at room temperature over night. The reaction mixture was then diluted with a saturated solution of sodium bicarbonate (5 ml), and stirred for 1 hour. The solid was filtered, washed with water, dried under vacuum over P_2O_5, to give title compound (30 mg, 40 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.54 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.31 (t, 2H) ; 7.08 (t, 1H) ; 7.35 (m, 3H) ; 7.46 (d, 1H) ; 7.56 (d, 1H) ; 7.77 (d, 1H) ; 8.1 (s, 1H) ; 8.93 (s, 1H).

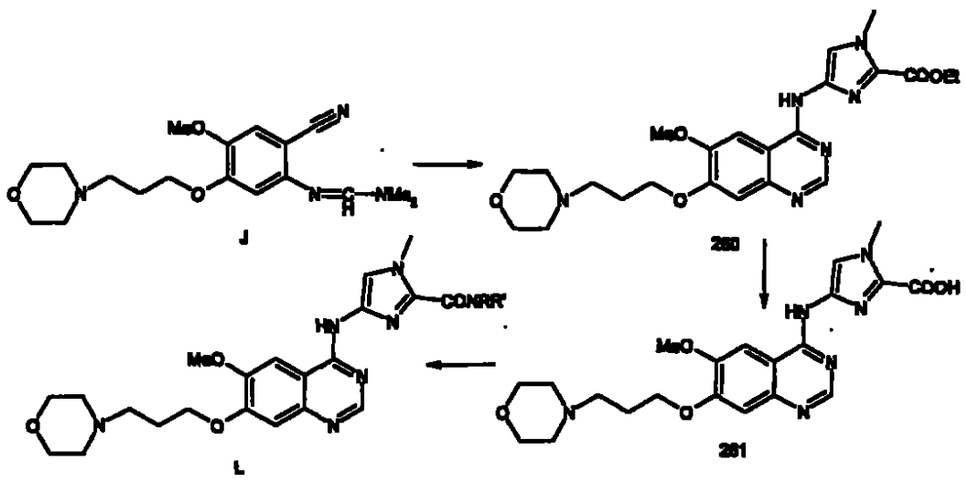
MS ES$^+$: 503 $[M+H]^+$

Example 98. Preparation of Compound 259 in Table 9

An analogous reaction to that described for the Example 97, but starting with cyclohexylamine (18 mg, 0.18 mmol) yielded title compound (30 mg, 39 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.13 (m, 1H) ; 1.3 (m, 4H) ; 1.63 (m, 1H) ; 1.8 (m, 4H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.76 (m, 1H) ; 4.0 (s, 1H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.2 (d, 1H) ; 7.3 (s, 1H) ; 7.43 (d, 1H) ; 8.0 (s, 1H) ; 8.9 (s, 1H).
MS ES$^+$: 509 $[M+H]^+$

General Scheme 11



Example 99. Preparation of Compound 260 in Table 10

Amidine J (1.04 g, 3 mmol) in acetic acid (10 ml) was reacted with ethyl 4-amino-1-methyl-2-imidazolecarboxylate hydrochloric acid (0.74 g, 3.6 mmol) in presence of dimethylamine / MeOH (1.25N, 2.9 ml, 3.6 mmol) at 130°C for 3 hours. The solvent was evaporated, the residue triturated with ether and filtered. The solid was suspended in water, the pH adjusted to 9 with an aqueous solution of sodium bicarbonate, the suspension was filtered, washed with water, dried under vacuum over P_2O_5, to give title compound (1.1 g, 78 %).
^{1}HNMR (DMSO-d_6) : 1.32 (t, 3H) ; 1.96 (m, 2H) ; 2.37 (m, 4H) ; 2.44 (t, 2H) ; 3.58 (m, 4H) ; 3.94 (s, 3H) ; 4.0 (s, 3H) ; 4.17 (t, 2H) ; 4.28 (q, 2H) ; 7.16 (s, 1H) ; 7.99 (s, 1H) ; 8.07 (s, 1H) ; 8.53 (s, 1H) ; 10.55 (s, 1H).

Example 100. Preparation of Compound 261 in Table 10

Ester 260 (1.1 g, 2.34 mmol) in ethanol (23 ml) was reacted with sodium hydroxyde (6N, 2.3 ml) at 80°C for 2.5 hours. The mixture was cooled, and acidified with hydrochloric acid (6N) to pH 3. The suspension was recovered by centrifugation, washed with ethanol, ether, dried under vacuum over P_2O_5, to give title compound (930 mg, 73 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.76 (t, 2H) ; 4.01 (s, 3H) ; 4.05 (m, 5H) ; 4.32 (t, 2H) ; 7.41 (s, 1H) ; 8.03 (s, 1H) ; 8.38 (s, 1H) ; 9.0 (s, 1H).

MS ES$^+$: 443 $[M+H]^+$

Example 101. Preparation of Compounds of General Structure I.

Acid 261 (88 mg, 0.16 mmol) in DMF (1 ml) was reacted with O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate (73 mg, 0.19 mmol), the appropriate amine (0.18 mmol) and DIEA (82 mg, 0.4 mmol) at room temperature for 3 hours. The solution was then diluted with a saturated solution of sodium bicarbonate (4 ml) and stirred at room temperature for 3 hours. The precipitate was filtered, washed with water, dried under vacuum over P_2O_5, to give title compound.

Example 102. Preparation of Compound 262 in Table 10

An analogous reaction to that described in Example 101, but starting with aniline (17 mg, 0.18 mmol) yielded title compound (37 mg, 44 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (m, 5H) ; 4.06 (s, 3H) ; 4.31 (t, 2H) ; 7.13 (t, 1H) ; 7.38 (m, 3H) ; 7.78 (d, 2H) ; 7.99 (s, 1H) ; 8.27 (s, 1H) ; 9.01 (s, 1H).

MS ES$^+$: 518 $[M+H]^+$

Example 103. Preparation of Compound 263 in Table 10

An analogous reaction to that described in Example 101, but starting with 4-fluoroaniline (20 mg, 0.18 mmol) yielded title compound (84 mg, 97 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.1 (s, 3H) ; 4.31 (t, 2H) ; 7.21 (t, 2H) ; 7.39 (s, 1H) ; 7.82 (m, 2H) ; 7.98 (s, 1H) ; 8.32 (s, 1H) ; 9.01 (s, 1H).

MS ES$^+$: 536 $[M+H]^+$

Example 104. Preparation of Compound 264 in Table 10

An analogous reaction to that described in Example 101, but starting with N,N-dimethyl-1,4-phenylenediamine (24 mg, 0.18 mmol) yielded title compound (80 mg, 88 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.21 (s, 6H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (m, 5H) ; 4.1 (s, 3H) ; 4.31 (t, 2H) ; 7.4 (s, 1H) ; 7.66 (d, 2H) ; 7.98 (d, 2H) ; 8.01 (s, 1H) ; 8.32 (s, 1H) ; 9.01 (s, 1H).

MS ES$^+$: 561 $[M+H]^+$

Example 105. reparation of Compound 265 in Table 10

An analogous reaction to that described in Example 101, but starting with 4-chloroaniline (23 mg, 0.18 mmol) yielded title compound (55 mg, 62 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.1 (s, 3H) ; 4.32 (t, 2H) ; 7.39 (s, 1H) ; 7.43 (d, 2H) ; 7.84 (d, 2H) ; 7.99 (s, 1H) ; 8.32 (s, 1H) ; 9.01 (s, 1H).

MS ES$^+$: 552, 554 $[M+H]^+$

Example 106. Preparation of Compound 266 in Table 10

An analogous reaction to that described in Example 101, but starting with pyrrolidine (13 mg, 0.18 mmol) yielded title compound (50 mg, 62 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.85 (m, 4H) ; 2.28 (m, 2H) ; 3.15 (t, 2H) ; 3.32 (t, 2H) ; 3.5 (m, 4H) ; 3.66 (t, 2H) ; 3.89 (m, 5H) ; 3.98 (m, 5H) ; 4.27 (t, 2H) ; 7.33 (s, 1H) ; 7.85 (s, 1H) ; 8.29 (s, 1H) ; 8.96 (s, 1H).

MS ES$^+$: 496 $[M+H]^+$

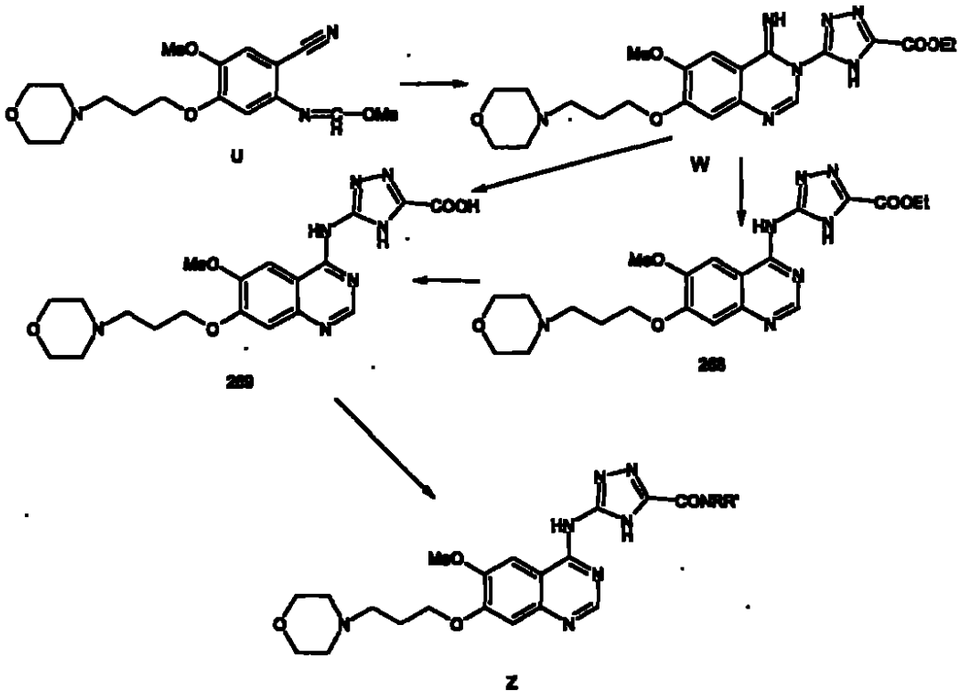
Example 107. Preparation of Compound 267 in Table 10

An analogous reaction to that described in Example 101, but starting with cyclohexylamine (18 mg, 0.18 mmol) yielded title compound (54 mg, 64 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.19 (m, 1H) ; 1.35 (m, 4H) ; 1.61 (m, 1H) ; 1.71 (m, 2H) ; 1.85 (m, 2H) ; 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.69 (t, 2H) ; 3.75 (m, 1H) ; 4.01 (s, 3H) ; 4.04 (m, 5H) ; 4.3 (t, 2H) ; 7.37 (s, 1H) ; 7.9 (s, 1H) ; 8.29 (s, 1H) ; 8.99 (s, 1H).

MS ES$^+$: 524 $[M+H]^+$

General Scheme 12



Example 108.

Step (a) Preparation of Intermediates of General formula W

Imidate U (2 g, 6 mmol) in dimethylformamide (40 ml) was reacted with ethyl 5-amino-4H-1,2,4-triazole-3-carboxylate hydrochloric acid (1.16 g, 6 mmol) in presence of sodium hydride (60 %, 504 mg, 12.6 mmol) at 110°C for 7 hours, under argon. The mixture was then cooled to room temperature, and acetic acid (1.03 ml, 18 mmol) was added, the solvent was evaporated under vacuum, the residue purified by silica gel chromatography, eluent : CH_2Cl_2 / MeOH, 90/10 to give title compound (1.07 g, 39 %).

^{1}H NMR (DMSO-d_6, TFA) : 1.39 (t, 3H) ; 2.28 (m, 2H) ; 3.15 (t, 2H) ; 3.32 (t, 2H) ; 3.56 (d, 2H) ; 3.68 (t, 2H) ; 3.98 (s, 3H) ; 4.05 (d, 2H) ; 4.37 (t, 2H) ; 4.52 (q, 2H) ; 7.49 (s, 1H) ; 8.12 (s, 1H) ; 8.71 (s, 1H).

MS ES$^+$: 458 $[M+H]^+$

Step (b) : Preparation of Compound 268 in Table 11

Triazole ester W (80 mg, 0.17 mmol) in dimethylformamide (3 ml) was treated with dimethylamine acetate (0.52 mmol) at 70°C for 20 minutes. The mixture was cooled, the

solvent evaporated, and the residue purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH / NH3, 90/10/1 to give title product (60 mg, 75 %).

^{1}H NMR (DMSO-d_6, TFA) : 1.34 (t, 3H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.0 (s, 3H) ; 4.04 (d, 2H) ; 4.36 (m, 4H) ; 7.48 (s, 1H) ; 8.26 (s, 1H) ; 9.01 (s, 1H).

MS ES$^+$: 458 $[M,H]^+$

Example 109. Preparation of Compound 269 in Table 11

Triazole ester 268 (900 mg, 1.97 mmol) in methanol (20 ml), was treated with sodium hydroxyde (2N, 20 ml) at 80°C for 1.5 hour. The mixture was cooled, and acidified to pH 2.5 with hydrochloric acid (6N), the solid was recovered by filtration dried under vacuum over P_2O_5 to give title compound (843 mg, 100 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.37 (m, 2H) ; 3.12 (t, 2H) ; 3.3 (t, 2H) ; 3.5 (d, 2H) ; 3.87 (t, 2H) ; 3.97 (d, 2H) ; 4.01 (s, 3H) ; 4.35 (t, 2H) ; 7.63 (s, 1H) ; 8.32 (s, 1H) ; 8.97 (s, 1H).

MS ES$^+$: 430 $(M,H)^+$.

Example 110. Preparation of Compound 270 in Table 11

Acid 269 (120 mg, 0.28 mmol) in DMF (2 ml) was reacted with aniline (0.025 ml, 0.28 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N',-tetramethyluronium hexafluorophosphate (106 mg, 0.28 mmol) and DIEA (0.12 ml, 0.7 mmol) at room temperature for 4 hours. The solvent was evaporated, the residue dissolved in methylene chloride / methanol, and treated with a methanolic solution of dimethylamine (2M, 1 ml) at room temperature over night. The solvent was evaporated, and the residue purified by flash silica gel chromatography, eluent CH_2Cl_2 / MeOH, 90/10 to give title compound (12 mg, 9 %).

^{1}H NMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.18 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 7.16 (t, 1H) ; 7.39 (t, 2H) ; 7.45 (s, 1H) ; 7.83 (d, 2H) ; 8.2 (s, 1H) ; 8.95 (s, 1H).

MS ES$^+$: 505 $[M,H]^+$

Example 111. Preparation of Compound 271 in Table 11

An analogous reaction to that described in Example 110, but starting with 4-fluoroaniline (0.13 ml, 1.4 mmol) yielded title compound (44 mg, 18 %).

^{1}H NMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.0 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.23 (t, 2H) ; 7.44 (s, 1H) ; 7.86 (m, 1H) ; 8.18 (s, 1H) ; 8.93 (s, 1H).

MS ES$^+$: 523 $[M_+H]^+$

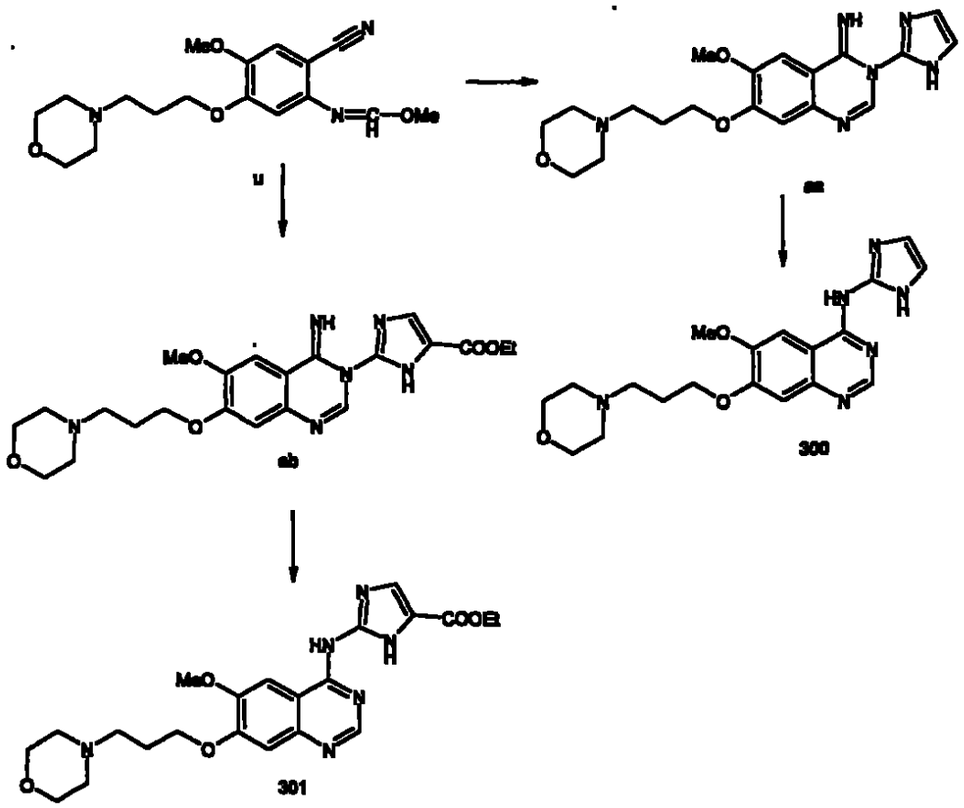
Example 112. Preparation of Compound 272 in Table 11

An analogous reaction to that described in Example 110 but starting with allylamine (0.13 ml, 1.75 mmol) yielded the title compound (26 mg, 10 %).

^{1}H NMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.34 ((, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.94 (d, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 5.13 (d, 1H) ; 5.18 (d, 1H) ; 5.92 (m, 1H) ; 7.41 (s, 1H) ; 8.17 (s, 1H) ; 8.91 (s, 1H).

MS ES$^+$: 469 $[M_+H]^+$

General Scheme 13



Example 113. Preparation of Compound 300 in Table 12

Step 1 Preparation of Compound aa

Imidate u, (200 mg, 0.6 mmol) in DMF (4 ml) was condensed with 2-aminoimidazole, sulfate (160 mg, 0.6 mmol) in presence of sodium hydride (60 %, 50 mg, 1.26 mmol) at 90°C for 2 hours. The mixture was cooled, acetic acid (0.01 ml, 1.8 mmol) was added, the solvent was evaporated, and the residue purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH, 90/10 to give title compound (112 mg, 48 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.33 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.36 (t, 2H) ; 7.41 (s, 2H) ; 7.47 (s, 1H) ; 8.13 (s, 1H) ; 8.66 (s, 1H).

MS ES$^+$: 385 $[M+H]^+$

Step 2: Preparation of Compound 300

Imidazole aa (105 mg, 0.273 mmol) in DMF (2 ml) was heated at 80°C for 0.3 hour in presence of dimethylamine acetate (0.819 mmol), the solvent was evaporated, and the residue was purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH sat. NH_3, 90/10 to give title compound (78 mg, 74 %).

^{1}HNMR (DMSO) : 1.96 (m, 2H) ; 2.39 (m, 4H) ; 2.46 (t, 2H) ; 3.6 (m, 4H) ; 3.9 (s, 3H) ; 4.18 (t, 2H) . 6.9 (s, 2H) ; 7.14 (s, 1H) ; 7.84 (s, 1H) ; 8.39 (s, 1H).

MS ES$^+$: 385 $[M+H]^+$

Example 114 Preparation of Compound 301 in Table 12

Step 1: Preparation of Compound ab

Imidate u (250 mg, 0.751 mmol) in DMF (4 ml) was reacted with ethyl 2-aminoimidazole-4-carboxylate (117 mg, 0.751 mmol) in presence of sodium hydride (60 %, 30 mg, 0.826 mmol) at 100° C for 3 hours. The mixture was cooled, acetic acid (0.13 ml, 2.25 mmol) was added, the solvent was evaporated, and the residue purified by silica gel chromatography to give title compound (125 mg, 36 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.32 (t, 3H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (q, 2H) ; 4.37 (t, 2H) ; 7.49 (s, 1H) ; 8.11 (s, 1H) ; 8.2 (s, 1H) ; 8.65 (s, 1H).

MS ES$^+$: 457 $[M+H]^+$

Step 2: Preparation of Compound 301 in Table 12

Imidazole 3 (122 mg, 0.268 mmol) in DMF (2 ml) was heated at 80°C for 0.3 hour in presence of dimethylamine acetate (0.802 mmol). The solvent was evaporated, and the residue was purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH sat. NH_3 95/5 to 90/10 to give title compound (105 mg, 86 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.32 (t, 3H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.94 (s, 3H) ; 4.03 (d, 2H) ; 4.27 (t, 2H) ; 4.33 (q, 2H) ; 7.27 (s, 1H) ; 7.84 (s, 1H) ; 7.92 (s, 1H) ; 8.76 (s, 1H).

MS ES$^+$: 457 $[M+H]^+$

Example 115. Preparation of compound 302 in Table 13

An analogous reaction to that described in general scheme 5, starting with 4-methoxyaniline (32 mg, 0.26 mmol) yielded compound 302 in Table 13 (24 mg, 21%).

MS ES$^+$: 551 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.76 (s, 3H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 6.96 (d, 2H) ; 7.38 (s, 1H) ; 7.62 (d, 2H) ; 8.04 (s, 1H) ; 8.55 (s, 1H) 9.27 (s, 1H).

Example 116. Preparation of compound 303 in Table 13

An analogous reaction to that described in general scheme 5, starting with 4-methylaniline (28 mg, 0.26 mmol) yielded compound 303 in Table 13 (23 mg, 22%).

MS ES$^+$: 535 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.29 (s, 3H) ; 2.33 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.19 (d, 2H) ; 7.38 (s, 1H) ; 7.60 (d, 2H) ; 8.05 (s, 1H) ; 8.58 (s, 1H) ; 9.28 (s, 1H).

Example 117. Preparation of compound 304 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-aminopyridine (24 mg, 0.26 mmol) yielded compound 304 in Table 13 (12 mg, 11%).

MS ES$^+$: 522 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.34 (t, 2H) ; 7.33 (m, 1H) ; 7.41 (s, 1H) ; 8.07 (m, 2H) ; 8.09 (s, 1H) ; 8.46 (d, 1H) ; 8.81 (s, 1H) ; 9.30 (s, 1H).

Example 118. Preparation of compound 305 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-aminobenzyl alcohol (32 mg, 0.26 mmol) yielded compound 305 in Table 13 (54 mg, 60%).

MS ES$^+$: 551 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.33 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 3.78 (s, 2H) ; 4.02 (s, 3H) ; 4.05 (d, 2H) ; 4.34 (t, 2H) ; 6.73 (d, 1H) ; 7.30 (m, 2H) ; 7.39 (s, 1H) ; 7.40 (m, 1H) ; 8.07 (s, 1H) ; 8.62 (s, 1H) ; 9.3 (s, 1H).

Example 119. Preparation of compound 306 in Table 13

An analogous reaction to that described in general scheme 5, starting with 4-methoxybenzylamine (36 mg, 0.26 mmol) yielded compound 306 in Table 13 (29 mg, 26%).

MS ES$^+$: 565 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.28 (t, 2H) ; 3.14 (t, 2H) ; 3.31 (t, 2H) ; 3.50 (d, 2H) ; 3.68 (t, 2H) ; 3.69 (s, 3H) ; 3.94 (s, 3H) ; 3.98 (d, 2H) ; 4.26 (t, 2H) ; 4.37 (s, 2H) ; 6.89 (m, 2H) ; 7.12 (m, 2H) ; 7.35 (s, 1H) ; 7.90 (s, 1H) ; 8.31 (s, 1H) ; 9.15 (s, 1H).

Example 120. Preparation of compound 307 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3-nitroaniline (36 mg, 0.26 mmol) yielded compound 307 in Table 13 (27 mg, 24%).

MS ES$^+$: 566 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.30 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.40 (s, 1H) ; 7.71 (t, 1H) ; 7.99 (d, 1H) ; 8.08 (s, 1H) ; 8.14 (d, 1H) ; 8.64 (s, 1H) ; 8.71 (s, 1H) ; 9.31 (s, 1H).

Example 121. Preparation of compound 308 in Table 13

An analogous reaction to that described in general scheme 5, starting with aminoacetonitrile (24 mg, 0.26 mmol) yielded compound 308 in Table 13 (29 mg, 30%).

MS ES$^+$: 484 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.00 (s, 3H) ; 4.02 (d, 2H) ; 4.32 (t, 2H) ; 4.37 (s, 2H) ; 7.39 (s, 1H) ; 8.06 (s, 1H) ; 8.36 (s, 1H) ; 9.27 (s, 1H).

Example 122. Preparation of compound 309 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-methyl-5-nitroaniline (40 mg, 0.26 mmol) yielded compound 309 in Table 13 (14 mg, 12%).

MS ES$^+$: 580 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.39 (s, 1H) ; 7.58 (d, 1H) ; 8.04 (d, 1H) ; 8.08 (s, 1H) ; 8.34 (d, 1H) ; 8.62 (s, 1H) ; 9.29 (s, 1H).

Example 123. Preparation of compound 310 in Table 13

An analogous reaction to that described in general scheme 5, starting with cyclopropylamine (15 mg, 0.26 mmol) yielded compound 310 in Table 13 (6 mg, 6%).

MS ES$^+$: 485 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 0.68 (m, 2H) ; 0.74 (m, 2H) ; 2.27 (t, 2H) ; 2.67 (m, 1H) ; 3.12 (t, 2H) ; 3.31 (t, 2H) ; 3.51 (d, 2H) ; 3.69 (t, 2H) ; 3.95 (s, 3H) ; 3.98 (d, 2H) ; 4.29 (t, 2H) ; 7.32 (s, 1H) ; 7.96 (s, 1H) ; 8.24 (s, 1H) ; 9.20 (s, 1H).

Example 124. Preparation of compound 311 in Table 13

An analogous reaction to that described in general scheme 5, starting with 4-nitrobenzylamine (49 mg, 0.26 mmol) yielded compound 311 in Table 13 (5 mg, 4%).

MS ES$^+$: 580 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 4.63 (s, 2H) ; 7.38 (s, 1H) ; 7.62 (d, 2H) ; 8.04 (s, 1H) ; 8.23 (d, 2H) ; 8.40 (s, 1H) ; 9.25 (s, 1H).

Example 125. Preparation of compound 312 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-anilinoethanol (36 mg, 0.26 mmol) yielded compound 312 in Table 13 (49 mg, 44%).

MS ES$^+$: 565 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.7 (m, 4H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 4.49 (t, 2H) ; 7.15 (t, 1H) ; 7.26 (d, 2H) ; 7.41 (t, 2H) ; 7.43 (s, 1H) ; 8.15 (s, 1H) ; 8.48 (s, 1H) ; 9.31 (s, 1H).

Example 126. Preparation of compound 313 in Table 13

An analogous reaction to that described in general scheme 5, starting with furfurylamine (25 mg, 0.26 mmol) yielded compound 313 in Table 13 (20 mg, 19%).

MS ES$^+$: 525 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (d, 2H) ; 4.32 (t, 2H) ; 4.48 (s, 2H) ; 6.33 (d, 1H) ; 6.41 (d, 1H) ; 7.37 (s, 1H) ; 7.59 (s, 1H) ; 8.01 (s, 1H) ; 8.37 (s, 1H) ; 9.24 (s, 1H).

Example 127. Preparation of compound 314 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3-chloroaniline (33 mg, 0.26 mmol) yielded compound 314 in Table 13 (21 mg, 19%).

MS ES$^+$: 555, 557 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.54 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.32 (t, 2H) ; 7.20 (d, 1H) ; 7.39 (s, 1H) ; 7.42 (t, 1H) ; 7.63 (d, 1H) ; 7.91 (s, 1H) ; 8.07 (s, 1H) ; 8.61 (s, 1H) ; 9.30 (s, 1H).

Example 128. Preparation of compound 315 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-methoxyaniline (32 mg, 0.26 mmol) yielded compound 315 in Table 13 (67 mg, 61%).

MS ES$^+$: 551 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.87 (s, 3H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 6.99 (t, 1H) ; 7.13 (d, 1H) ; 7.23 (t, 1H) ; 7.40 (s, 1H) ; 7.66 (d, 1H) ; 8.04 (s, 1H) ; 8.64 (s, 1H) ; 9.27 (s, 1H).

Example 139. Preparation of compound 316 in Table 13

An analogous reaction to that described in general scheme 5, starting with thiophene-2-methylamine (29 mg, 0.26 mmol) yielded compound 316 in Table 13 (25 mg, 23%).

MS ES^+ : 541 $(M+H)^+$

^1H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.01 (s, 3H) ; 4.04 (d, 2H) ; 4.34 (t, 2H) ; 4.67 (s, 2H) ; 6.99 (m, 1H) ; 7.08 (m, 1H) ; 7.39 (s, 1H) ; 7.41 (d, 1H) ; 8.04 (s, 1H) ; 8.36 (s, 1H) ; 9.27 (s, 1H).

Example 140. Preparation of compound 317 in Table 13

An analogous reaction to that described in general scheme 5, starting with neopentylamine (23 mg, 0.26 mmol) yielded compound 317 in Table 13 (31 mg, 30%).

MS ES^+ : 515 $(M+H)^+$

^1H NMR (DMSO-d6, TFA) : 0.91 (s, 9H) ; 2.31 (t, 2H) ; 3.10 (s, 2H) ; 3.17 (t, 2H) ; 3.35 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.35 (s, 1H) ; 8.00 (s, 1H) ; 8.45 (s, 1H) ; 9.23 (s, 1H).

Example 141. Preparation of compound 318 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2,6-difluorobenzylamine (37 mg, 0.26 mmol) yielded compound 318 in Table 13 (35 mg, 31%).

MS ES^+ : 571 $(M+H)^+$

^1H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.31 (t, 2H) ; 4.54 (s, 2H) ; 7.11 (t, 2H) ; 7.36 (s, 1H) ; 7.42 (m, 1H) ; 8.00 (s, 1H) ; 8.35 (s, 1H) ; 9.24 (s, 1H).

Example 142. Preparation of compound 319 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-methylallylamine (28 mg, 0.26 mmol) yielded compound 319 in Table 13 (16 mg, 16%).

MS ES^+ : 499 $(M+H)^+$

^1H NMR (DMSO-d6, TFA) : 1.72 (s, 3H) ; 2.31 (t, 1H) ; 3.15 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.72 (s, 2H) ; 3.99 (s, 3H) ; 4.02 (d, 2H) ; 4.31 (t, 2H) ; 4.82 (s, 1H) ; 4.86 (s, 1H) ; 7.36 (s, 1H) ; 8.01 (s, 1H) ; 8.37 (s, 1H) ; 9.23 (s, 1H).

Example 143. Preparation of compound 320 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-methyl-4-fluoroaniline (33 mg, 0.26 mmol) yielded compound 320 in Table 13 (47 mg, 43%).

MS ES$^+$: 553 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.26 (s, 3H) ; 2.31 (t, 1H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.33 (t, 2H) ; 7.07 (m, 1H) ; 7.18 (d, 1H) ; 7.36 (m, 1H) ; 7.38 (s, 1H) ; 8.06 (s, 1H) ; 8.53 (s, 1H) ; 9.27 (s, 1H).

Example 144. Preparation of compound 321 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-fluoro-5-methylaniline (33 mg, 0.26 mmol) yielded compound 321 in Table 13 (60 mg, 54%).

MS ES$^+$: 553 $(M+H)^+$

Example 145. Preparation of compound 322 in Table 13

An analogous reaction to that described in general scheme 5, starting with 4-fluorobenzylamine (33 mg, 0.26 mmol) yielded compound 322 in Table 13 (33 mg, 30%).

MS ES$^+$: 553 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 1H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (d, 2H) ; 4.33 (t, 2H) ; 4.47 (s, 2H) ; 7.15 (t, 2H) ; 7.36 (s, 1H) ; 7.37 (m, 2H) ; 8.02 (s, 1H) ; 8.36 (s, 1H) ; 9.24 (s, 1H).

Example 146. Preparation of compound 323 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3,4-difluorobenzylamine (37 mg, 0.26 mmol) yielded compound 323 in Table 13 (17 mg, 15%).

MS ES$^+$: 571 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 4.48 (s, 2H) ; 7.21 (m, 1H) ; 7.38 (s, 1H) ; 7.38 (m, 2H) ; 8.03 (s, 1H) ; 8.38 (s, 1H) ; 9.24 (s, 1H).

Example 147. Preparation of compound 324 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3-methylaniline (28 mg, 0.26 mmol) yielded compound 324 in Table 13 (57 mg, 53%).

MS ES$^+$: 535 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.32 (m, 5H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (s, 3H) ; 4.04 (d, 2H) ; 6.95 (d, 1H) ; 7.24 (t, 1H) ; 7.38 (s, 1H) ; 7.53 (m, 2H) ; 8.04 (s, 1H) ; 8.59 (s, 1H) ; 9.28 (s, 1H).

Example 148. Preparation of compound 325 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-(methylthio)aniline (36 mg, 0.26 mmol) yielded compound 325 in Table 13 (73 mg, 64%).

MS ES$^+$: 567 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 2.44 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.22 (t, 1H) ; 7.37 (m, 4H) ; 8.06 (s, 1H) ; 8.52 (s, 1H) ; 9.27 (s, 1H).

Example 149. Preparation of compound 326 in Table 13

An analogous reaction to that described in general scheme 5, starting with 5-aminoindole (34 mg, 0.26 mmol) yielded compound 326 in Table 13 (16 mg, 15%).

MS ES$^+$: 560 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.32 (t, 2H) ; 7.36 (m, 5H) ; 7.94 (s, 1H) ; 8.04 (s, 1H) ; 8.28 (s, 1H) ; 9.28 (s, 1H).

Example 150. Preparation of compound 327 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3-aminobenzonitrile (31 mg, 0.26 mmol) yielded compound 327 in Table 13 (30 mg, 28%).

MS ES$^+$: 546 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.67 (t, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.40 (s, 1H) ; 7.60 (m, 2H) ; 7.97 (m, 1H) ; 8.08 (s, 1H) ; 8.21 (s, 1H) ; 8.61 (s, 1H) ; 9.30 (s, 1H).

Example 151. Preparation of compound 328 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2,4-difluorobenzylamine (37 mg, 0.26 mmol) yielded compound 328 in Table 13 (27 mg, 24%).
MS ES$^+$: 571 $(M+H)^+$
^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 4.49 (s, 2H) ; 7.09 (m, 1H) ; 7.21 (m, 1H) ; 7.38 (s, 1H) ; 8.02 (s, 1H) ; 8.38 (s, 1H) ; 9.24 (s, 1H).

Example 152. Preparation of compound 329 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3-(2-aminoethyl)pyridine (32 mg, 0.26 mmol) yielded compound 329 in Table 13 (33 mg, 30%).
MS ES$^+$: 550 $(M+H)^+$
^{1}H NMR (DMSO-d6, TFA) : 2.33 (t, 2H) ; 3.11 (t, 2H) ; 3.18 (t, 2H) ; 3.35 (t, 2H) ; 3.57 (d, 2H) ; 3.66 (t, 2H) ; 3.68 (t, 2H) ; 4.01 (s, 3H) ; 4.05 (d, 2H) ; 4.34 (t, 2H) ; 7.41 (s, 1H) ; 8.05 (s, 1H) ; 8.08 (dd, 2H) ; 8.28 (s, 1H) ; 8.59 (d, 1H) ; 8.87 (d, 1H) ; 8.95 (s, 1H) ; 9.25 (s, 1H).

Example 153. Preparation of compound 330 in Table 13

An analogous reaction to that described in general scheme 5, starting with N-methylisobutylamine (23 mg, 0.26 mmol) yielded compound 330 in Table 13 (23 mg, 22%).
MS ES$^+$: 515 $(M+H)^+$
^{1}H NMR (DMSO-d6, TFA) : 0.88 (d, 6H) ; 2.02 (m, 1H) ; 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.27 (m, 5H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.37 (s, 1H) ; 8.03 (s, 1H) ; 8.18 (s, 1H) ; 9.23 (s, 1H).

Example 154. Preparation of compound 331 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-aminobenzylamine (32 mg, 0.26 mmol) yielded compound 331 in Table 13 (6 mg, 6%).
MS ES$^+$: 550 $(M+H)^+$
^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 4.47 (s, 2H) ; 7.41 (s, 1H) ; 7.46 (m, 4H) ; 8.06 (s, 1H) ; 8.42 (s, 1H) ; 9.24 (s, 1H).

Example 155. Preparation of compound 332 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3-methylbutylamine (23 mg, 0.26 mmol) yielded compound 332 in Table 13 (48 mg, 47%).

MS ES$^+$: 515 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 0.90 (d, 6H) ; 1.43 (q, 2H) ; 1.62 (m, 1H) ; 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.28 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (d, 2H) ; 4.31 (t, 2H) ; 7.35 (s, 1H) ; 8.00 (s, 1H) ; 8.31 (s, 1H) ; 9.23 (s, 1H).

Example 156. Preparation of compound 333 in Table 13

An analogous reaction to that described in general scheme 5, starting with 1-aminomethyl-1-cyclohexanol (43 mg, 0.26 mmol) yielded compound 333 in Table 13 (7 mg, 6%).

MS ES$^+$: 557 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 1.37 (m, 10H) ; 2.28 (t, 2H) ; 3.11 (t, 2H) ; 3.23 (s, 2H) ; 3.32 (t, 2H) ; 3.51 (d, 2H) ; 3.65 (t, 2H) ; 3.96 (s, 3H) ; 3.99 (d, 2H) ; 4.28 (t, 2H) ; 7.32 (s, 1H) ; 7.95 (s, 1H) ; 8.43 (s, 1H) ; 9.19 (s, 1H).

Example 157. Preparation of compound 334 in Table 13

An analogous reaction to that described in general scheme 5, starting with 2-aminomethylpyrazine (38 mg, 0.26 mmol) yielded compound 334 in Table 13 (25 mg, 24%).

MS ES$^+$: 537 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.33 (t, 2H) ; 3.13 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.05 (d, 2H) ; 4.30 (t, 2H) ; 4.65 (s, 2H) ; 7.38 (s, 1H) ; 8.03 (s, 1H) ; 8.40 (s, 1H) ; 8.57 (d, 1H) ; 8.62 (d, 1H) ; 8.70 (s, 1H) ; 9.24 (s, 1H).

Example 158. Preparation of compound 335 in Table 13

An analogous reaction to that described in general scheme 5, starting with 3-methoxyaniline (32 mg, 0.26 mmol) yielded compound 335 in Table 13 (60 mg, 54%).

MS ES$^+$: 551 $(M+H)^+$

^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.58 (d, 2H) ; 3.70 (t, 2H) ; 3.79 (s, 3H) ; 4.03 (s, 3H) ; 4.06 (d, 2H) ; 4.34 (t, 2H) ; 6.73 (d, 1H) ; 7.29 (d, 1H) ; 7.32 (d, 1H) ; 7.41 (m, 2H) ; 8.07 (s, 1H) ; 8.62 (s, 1H) ; 9.30 (s, 1H).

Example 159. Preparation of compound 336 in Table 13

An analogous reaction to that described in general scheme 5, starting with 4-chlorobenzylamine (19 mg, 0.26 mmol) yielded compound 336 in Table 13 (31 mg, 54%).
MS ES$^+$: 569, 571 $(M+H)^+$
^{1}H NMR (DMSO-d6, TFA) : 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 1H) ; 4.48 (s, 2H) ; 7.42 (m, 5H) ; 8.02 (s, 1H) ; 8.37 (s, 1H) ; 9.24 (s, 1H).

Example 160. Preparation of compound 337 in Table 14

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (78 mg, 0.17 mmol) in DMF (1 ml), was reacted with aniline (19 mg, 0.2 mmol) in presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (76 mg, 0.2 mmol) and DIEA (44 mg, 0.34 mmol) at 50°C over night. The reaction mixture was cooled, treated with $NaHCO_3$ (1 ml), concentrated. The yellow solid was recovered, dissolved in a mixture of CH_2Cl_2 / MeOH (60/40) 20 ml. Alumina (3 g) was added to the mixture, the solvent was evaporated, and the solid was added on top of an alumina column which was eluted with CH_2Cl_2 / MeOH (10/0 to 9/1) to give title compound (43 mg, 47 %).
MS ES$^+$: 535 $(M+H)^+$
^{1}HNMR (DMSOd_6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (m, 5H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.08 (t, 1H) ; 7.32 (m, 3H) ; 7.62 (m, 3H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).
4-(ethyl(2-amino-1,3-thiazole-5-yl)acetate)-6-methoxy-7-(3-morpholinopropoxy)quinazoline. Amidine J of scheme. 2 (4.5 g, 13 mmol) in acetic acid (45 ml) was reacted with ethyl (2-amino-1,3-thiazole-5-yl)acetate (2.54 g, 13.65 mmol) at reflux for 5.5 hour under argon. The mixture was concentrated, and the residue was purified over silicagel chromatography, eluant CH_2Cl_2 / MeOH, 95/5 to 90/10 to give title compound (4.5 g, 63 %).

^{1}HNMR (DMSOd_6) : 1.22 (t, 3H) ; 1.96 (t, 2H) ; 2.37 (m, 4H) ; 2.35 (t, 2H) ; 3.58 (m, 4H) ; 3.91 (s, 2H) ; 3.95 (s, 3H) ; 4.13 (q, 2H) ; 4.20 (t, 2H) ; 7.25 (s, 1H) ; 7.36 (s, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H).

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.

4-(ethyl(2-amino-1,3-thiazole-5-yl)acetate)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (4.38 g, 8 mmol) in ethanol (44 ml) was treated with sodium hydroxyde (2N, 10 ml) at 50°C for 4 hours. The mixture was cooled to room temperature and the pH adjusted to 3.5 with 2N HCl. The residue was dissolved in CH_2Cl_2 / MeOH, 60/40, DIEA (3 g, 24 mmoles) was added, the mixture was stirred for 10 minutes, filtered, and the solution was concentrated to give an oily residue. This residue was dissolved in ethanol, and the solvent was partially evaporated. A cristalin solid was recovered, suspended in ethanol, washed with ether and dried under vacuum to give title compound (3.7 g, 100 %).

^{1}HNMR (DMSOd_6, TFA) : 2.28 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.70 (t, 2H) ; 3.92 (s, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.30 (t, 2H) ; 7.32 (s, 1H) ; 7.60 (s, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 161. Preparation of compound 338 in Table 14

An analogous reaction to that described in example 36 but starting with 3-chloro-4-fluoroaniline (30 mg, 0.2 mmol) yielded the title compound (24 mg, 24 %).

MS ES$^+$: 587 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.34 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (m, 5H) ; 4.03 (d, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.65 (s, 1H) ; 7.85 (s, 1H) ; 7.97 (d, 1H) ; 9.09 (s, 1H).

Example 162. Preparation of compound 339 in Table 14

An analogous reaction to that described in example 36 but starting with 4-chloroaniline (26 mg, 0.2 mmol) yielded title compound (73 mg, 76 %).

MS ES$^+$: 569 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.89 (m, 5H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.39 (d, 2H) ; 7.64 (s, 1H) ; 7.65 (d, 2H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 163. Preparation of compound 340 in Table 14

An analogous reaction to that described in example 36 but starting with 3,4-difluoroaniline (26 mg, 0.2 mmol) yielded title compound (75 mg, 77 %).

MS ES$^+$: 571(M+H)$^+$

^{1}HNMR (DMSOd$_6$, TFA) 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.72 (t, 2H) ; 3.99 (m, 5H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.31 (s, 1H) ; 7.32 (m, 1H) ; 7.41 (q, 1H) ; 7.65 (s, 1H) ; 7.81 (m, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 164. Preparation of compound 341 in Table 14

An analogous reaction to that described in example 36 but starting with 3-methoxyaniline (25 mg, 0.2 mmol) yielded title compound (40 mg, 42 %).

MS ES$^+$: 565 (M+H)$^+$

^{1}HNMR (DMSOd$_6$, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.70 (t, 2H) ; 3.74 (s, 3H) ; 3.97 (s, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.31 (t, 2H) ; 6.68 (d, 1H) ; 7.15 (d, 1H) ; 7.23 (t, 1H) ; 7.29 (s, 1H) ; 7.33 (s, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 165. Preparation of compound 342 in Table 14

An analogous reaction to that described in example 36 but starting with 2-chloroaniline (26 mg, 0.2 mmol) yielded title compound (15 mg, 16 %).

MS ES$^+$: 569 (M+H)$^+$

^{1}HNMR (DMSOd$_6$, TFA) : 2.30 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.05 (m, 4H) ; 4.31 (t, 2H) ; 7.22 (t, 1H) ; 7.30 (s, 1H) ; 7.35 (t, 1H) ; 7.51 (d, 1H) ; 7.65 (s, 1H) ; 7.75 (d, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 166. Preparation of compound 343 in Table 14

An analogous reaction to that described in example 36 but starting with 4-methoxyaniline (26 mg, 0.21 mmol) yielded title compound (55 mg, 57 %).

MS ES$^+$: 565.6 (M+H)$^+$

^{1}HNMR (DMSOd$_6$, TFA) : 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.73 (t, 2H) ; 3.80 (s, 3H) ; 3.97 (s, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 6.93 (d, 2H) ; 7.09 (s, 1H) ; 7.33 (s, 1H) ; 7.56 (d, 2H) ; 7.66 (s, 1H) ; 7.94 (s, 1H) ; 9.12 (s, 1H).

Example 167. Preparation of compound 344 in Table 14

An analogous reaction to that described in example 36 but starting with 4-methylaniline (23 mg, 0.21 mmol) yielded title compound (51 mg, 54 %).

MS ES$^+$: 549.7 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.29 (s, 3H) ; 2.31 (t, 2H) ; 3.19 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 3.99 (s, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.16 (d, 2H) ; 7.33 (s, 1H) ; 7.54 (d, 2H) ; 7.67 (s, 1H) ; 7.94 (s, 1H) ; 9.12 (s, 1H).

Example 168. Preparation of compound 345 in Table 14

An analogous reaction to that described in example 36 but starting with 2-methylaniline (23 mg, 0.21 mmol) yielded title compound (42 mg, 45 %).

MS ES$^+$: 549.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.24 (s, 3H) ; 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.12 (t, 1H) ; 7.19 (t, 1H) ; 7.24 (d, 1H) ; 7.31 (s, 1H) ; 7.43 (t, 1H) ; 7.66 (s, 1H) ; 7.92 (s, 1H) ; 9.08 (s, 1H).

Example 169. Preparation of compound 346 in Table 14

An analogous reaction to that described in example 36 but starting with 2-aminopyridine (20 mg, 0.21 mmol) yielded title compound (12 mg, 13 %).

MS ES$^+$: 536.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (m, 5H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.34 (s, 1H) ; 7.37 (t, 1H) ; 7.68 (s, 1H) ; 7.93 (d, 1H) ; 7.94 (s, 1H) ; 8.10 (t, 1H) ; 8.42 (d, 1H) ; 9.10 (s, 1H).

Example 170. Preparation of compound 347 in Table 14

An analogous reaction to that described in example 36 but starting with 2-aminobenzylalcohol (26 mg, 0.21 mmol) yielded title compound (24 mg, 24 %).

MS ES$^+$: 565.7 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.97 (t, 2H) ; 2.41 (m, 6H) ; 3.59 (m, 4H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.21 (t, 2H) ; 4.50 (d, 2H) ; 5.27 (t, 1H) ; 7.18 (t, 1H) ; 7.25 (d, 1H) ; 7.26 (s, 1H) ; 7.42 (m, 2H) ; 7.52 (d, 1H) ; 8.67 (s, 1H) ; 9.59 (s, 1H).

Example 171. Preparation of compound 348 in Table 14

An analogous reaction to that described in example 36 but starting with 2-amino-3-methyl-1-butanol (22 mg, 0.21 mmol) yielded title compound (25 mg, 27 %).

MS ES$^+$: 545.7 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 0.87 (d, 3H) ; 0.89 (d, 3H) ; 1.86 (m, 1H) ; 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.44 (2s, 2H) ; 3.57 (d, 2H) ; 3.63 (q, 1H) ; 3.70 (t, 2H) ; 3.80 (d, 2H) ; 4.01 (t, 3H) ; 4.07 (d, 2H) ; 4.31 (t, 2H) ; 7.32 (s, 1H) ; 7.58 (s, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 172. Preparation of compound 349 in Table 14

An analogous reaction to that described in example 36 but starting with 2-anilinoethanol (29 mg, 0.21 mmol) yielded title compound (11 mg, 11 %).

MS ES$^+$: 579.7 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.38 (t, 2H) ; 3.40 (m, 2H) ; 3.50 (t, 2H) ; 3.54 (d, 2H) ; 3.67 (m, 2H) ; 3.75 (t, 2H) ; 3.98 (s, 3H) ; 4.07 (d, 2H) ; 4.31 (t, 2H) ; 7.30 (s, 1H) ; 7.40 (s, 1H) ; 7.45 (m, 2H) ; 7.52 (m, 3H) ; 7.89 (s, 1H) ; 9.08 (s, 1H).

Example 173. Preparation of compound 350 in Table 14

An analogous reaction to that described in example 36 but starting with 3-chloro-4-methylamine (30 mg, 0.21 mmol) yielded title compound (3 mg, 3 %).

MS ES$^+$: 583.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (m, 5H) ; 3.20 (t, 2H) ; 3.40 (t, 2H) ; 3.60 (d, 2H) ; 3.72 (t, 2H) ; 4.01 (s, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 7.32 (m, 2H) ; 7.42 (d, 1H) ; 7.68 (s, 1H) ; 7.87 (s, 1H) ; 7.95 (s, 1H) ; 9.13 (s, 1H).

Example 174. Preparation of compound 351 in Table 14

An analogous reaction to that described in example 36 but starting with 3-nitroaniline (29 mg, 0.21 mmol) yielded title compound (20 mg, 21 %).

MS ES$^+$: 580.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.33 (t, 2H) ; 3.20 (t, 2H) ; 3.39 (t, 2H) ; 3.60 (d, 2H) ; 3.73 (t, 2H) ; 4.02 (s, 3H) ; 4.06 (d, 2H) ; ';4.09 (s, 2H) ; 4.34 (t, 2H) ; 7.34 (s, 1H) ; 7.67 (d, 1H) ; 7.70 (s, 1H) ; 7.95 (s, 1H) ; 7.98 (m, 2H) ; 8.74 (s, 1H) ; 9.15 (s, 1H).

Example 175. Preparation of compound 352 in Table 14

An analogous reaction to that described in example 36 but starting with aminoacetonitrile (19 mg, 0.21 mmol) yielded title compound (28 mg, 31 %).

MS ES$^+$: 498.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 3.84 (s, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.21 (s, 2H) ; 4.31 (t, 2H) ; 7.31 (s, 1H) ; 7.60 (s, 1H) ; 9.10 (s, 1H).

Example 176. Preparation of compound 353 in Table 14

An analogous reaction to that described in example 36 but starting with 2-methyl-5-nitroaniline (32 mg, 0.21 mmol) yielded title compound (11 mg, 11 %).

MS ES$^+$: 594.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 2.44 (s, 3H) ; 3.19 (t, 2H) ; 3.40 (t, 2H) ; 3.59 (d, 2H) ; 3.73 (t, 2H) ; 4.03 (s, 3H) ; 4.07 (d, 2H) ; 4.16 (s, 2H) ; 4.34 (t, 2H) ; 7.34 (s, 1H) ; 7.57 (d, 1H) ; 7.71 (s, 1H) ; 7.95 (s, 1H) ; 8.01 (d, 1H) ; 8.58 (s, 1H) ; 9.13 (s, 1H).

Example 177. Preparation of compound 354 in Table 14

An analogous reaction to that described in example 36 but starting with 2-amino-5-chloropyridine (27 mg, 0.21 mmol) yielded title compound (13 mg, 13 %).

MS ES$^+$: 570.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.07 (s, 2H) ; 4.31 (t, 2H) ; 7.02 (d, 1H) ; 7.36 (s, 1H) ; 7.64 (s, 1H) ; 7.92 (s, 1H) ; 7.98 (dd, 1H) ; 8.21 (d, 1H) ; 9.1 (s, 1H).

Example 178. Preparation of compound 355 in Table 14

An analogous reaction to that described in example 36 but starting with 4-trifluoromethylaniline (34 mg, 0.21 mmol) yielded title compound (26 mg, 25 %);

MS ES$^+$: 603.7 $(M+H)^+$

^{1}H NMR ($DMSOd_6$, TFA): 2.30 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.72 (t, 2H) ; 3.99 (s, 3H) ; 4.05 (m, 4H) ; 4.31 (t, 2H) ; 7.31 (s, 1H) ; 7.66 (s, 1H) ; 7.70 (d, 2H) ; 7.84 (d, 2H) ; 7.92 (s, 1H) ; 9.10 (s, 1H).

Example 179. Preparation of compound 356 in Table 14

An analogous reaction to that described in example 36 but starting with 3-chloroaniline (27 mg, 0.21 mmol) yielded title compound (47 mg, 48 %).

MS ES$^+$: 569.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2 H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.04 (d, 2H) ; 4.31 (t, 2H) ; 7.14 (d, 1H) ; 7.30 (s, 1H) ; 7.37 (t, 1H) ; 7.47 (d, 1H) ; 7.65 (s,1H) ; 7.87 (s, 1H) ; 7.92 (s, 1H) ; 9.10 (s, 1H).

Example 180. Preparation of compound 357 in Table 14

An analogous reaction to that described in example 36 but starting with 2-methoxyaniline (26 mg, 0.21 mmol) yielded title compound (44 mg, 46 %).

MS ES$^+$: 565.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.33 (t, 2H) ; 3.20 (t, 2H) ; 3.40 (t, 2H) ; 3.60 (d, 2H) ; 3.73 (t, 2H) ; 3.91 (s, 3H) ; 4.03 (s, 3H) ; 4.08 (d, 2H) ; 4.11 (s, 2H) ; 4.34 (t, 2H) ; 6.96 (t, 1H) ; 7.12 (m, 2H) ; 7.34 (s, 1H) ; 7.66 (s, 1H) ; 7.95 (s, 1H) ; 8.01 (d, 1H) ; 9.12 (s, 1H).

Example 181. Preparation of compound 358 in Table 14

An analogous reaction to that described in example 36 but starting with 2-fluoroaniline (23 mg, 0.21 mmol) yielded title compound (43 mg, 46 %).

MS ES$^+$: 553.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (s, 3H) ; 4.05 (d, 2H) ; 4.08 (s, 2H) ; 4.31 (t, 2H) ; 7.19 (m, 2H) ; 7.28 (m, 1H) ; 7.31 (s, 1H) ; 7.64 (s, 1H) ; 7.93 (m, 2H) ; 9.06 (, 1H).

Example 182. Preparation of compound 359 in Table 14

An analogous reaction to that described in example 36 but starting with thiphene-2-methylamine (24 mg, 0.21 mmol) yielded title compound (50 mg, 53 %).

MS ES$^+$: 555.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 3.80 (s, 2H) ; 4.01 (s, 3H) ; 4.06 (d, 2H) ; 4.33 (t, 2H) ; 4.52 (s, 2H), 6.98 (dd, 1H) ; 7.02 (dd, 1H) ; 7.32 (s, 1H) ; 7.41 (dd, 1H) ; 7.60 (sq, 1H) ; 7.93 (s, 1H) ; 9.11 (s, 1H).

Example 187. Preparation of compound 364 in Table 14

An analogous reaction to that described in example 36 but starting with 2-methyl-4-fluoroaniline (26 mg, 0.21 mmol) yielded title compound (60 mg, 62 %).

MS ES$^+$: 567.7 $(M+H)^+$

^{1}H NMR (DMSOd$_6$, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (s, 3H) ; 4.01 (s, 2H) ; 4.04 (d, 2H) ; 4.31 (t, 2H) ; 7.02 (t, 1H) ; 7.10 (d, 1H) ; 7.31 (s, 1H) ; 7.41 (q, 1H) ; 7.66 (s, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 188. Preparation of compound 365 in Table 14

An analogous reaction to that described in example 36 but starting with 2,5-difluoroaniline (27 mg, 0.21 mmol) yielded title compound (14 mg, 14 %).

MS ES$^+$: 571.7 $(M+H)^+$.

^{1}H NMR (DMSOd$_6$, TFA): 2.31 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.01 (s, 3H) ; 4.06 (d, 2H) ; 4.12 (s, 2H) ; 4.33 (t, 2H) ; 7.00 (m, 1H) ; 7.33 (m, 2H) ; 7.65 (s, 1H) ; 7.95 (m, 2H) ; 9.11 (s, 1H).

Example 189. Preparation of compound 366 in Table 14

An analogous reaction to that described in example 36 but starting with 2-fluoro-4-chloroaniline (31 mg, 0.21 mmol) yielded title compound (12 mg, 12 %).

MS ES$^+$: 587.6 $(M+H)^+$

^{1}H NMR (DMSOd$_6$, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (m, 4H) ; 4.31 (t, 2H) ; 7.29 (d, 1H) ; 7.52 (dd, 1H) ; 7.64 (s, 1H) ; 7.97 (d, 1H) ; 9.09 (s, 1H).

Example 190. Preparation of compound 367 in Table 14

An analogous reaction to that described in example 36 but starting with 2-fluoro-4-methylaniline (26 mg, 0.21 mmol) yielded title compound (20 mg, 20 %).

MS ES$^+$: 567.7 $(M+H)^+$

^{1}H NMR (DMSOd$_6$, TFA): 2.31 (s, 3H) ; 2.32 (t, 2H) ; 3.20 (t, 2H) ; 3.39 (t, 2H) ; 3.59 (d, 2H) ; 3.73 (t, 2H) ; 4.03 (s, 3H) ; 4.07 (d, 2H) ; 4.09 (s, 2H) ; 4.34 (t, 2H) ; 7.02 (m, 1H) ; 7.18 (dd, 1H) ; 7.34 (s, 1H) ; 7.67 (s, 1H) ; 7.77 (d, 1H) ; 7.95 (s, 1H) ; 9.12 (s, 1H).

Example 183. Preparation of compound 360 in Table 14

An analogous reaction to that described in example 36 but starting with 2-amino-1-phenylethanol (29 mg, 0.21 mmol) yielded title compound (32 mg, 33 %).

MS ES$^+$: 579.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.18 (m, 3H) ; 3.36 (m, 3H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.74 (s, 2H) ; 3.99 (s, 3H) ; 4.05 (d, 2H) ; 4.30 (t, 2H) ; 4.66 (m, 1H) ; 7.3 (m, 6H) ; 7.53 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 184. Preparation of compound 361 in Table 14

An analogous reaction to that described in example 36 but starting with 3-(1-hydroxyethyl)aniline (29 mg, 0.21 mmol) yielded title compound (50 mg, 50 %).

MS ES$^+$: 579.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 1.34 (d, 3H) ; 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.00 (s, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 4.72 (q, 1H) ; 7.07 (d, 1H) ; 7.29 (t, 1H) ; 7.33 (s, 1H) ; 7.53 (d, 1H) ; 7.67 (s, 2H) ; 7.93 (s, 1H) ; 9.12 (s, 1H).

Example 185. Preparation of compound 362 in Table 14

An analogous reaction to that described in example 36 but starting with neopentylamine (18 mg, 0.21 mmol) yielded title compound (57 mg, 64 %).

MS ES$^+$: 529.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA) : 0.89 (s, 9H) ; 2.33 (t, 2H) ; 2.97 (s, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.59 (d, 2H) ; 3.80 (s, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.32 (t, 2H) ; 7.33 (s, 1H) ; 7.60 (s, 1H) ; 7.93 (s, 1H) ; 9.11 (s, 1H).

Example 186. Preparation of compound 363 in Table 14

An analogous reaction to that described in example 36 but starting with 3-fluoro-4-methoxyaniline (30 mg, 0.21 mmol) yielded title compound (64 mg, 65 %).

MS ES$^+$: 583.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 3.82 (s, 3H) ; 3.96 (s, 2H) ; 4.00 (s, 3H) ; 4.04 (d, 2H) ; 4.31 (t, 2H) ; 7.15 (t, 1H) ; 7.30 (d, 1H) ; 7.31 (s, 1H) ; 7.61 (s, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.10 (s, 1H).

Example 191. Preparation of compound 368 in Table 14

An analogous reaction to that described in example 36 but starting with 3-methylaniline (23 mg, 0.21 mmol) yielded title compound (45 mg, 48 %).

MS ES^+: 549.7 $(M+H)^+$

^1H NMR ($DMSOd_6$, TFA): 2.31 (m, 5H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.00 (s, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 6.93 (d, 1H) ; 7.24 (t, 1H) ; 7.33 (s, 1H) ; 7.43 (d, 1H) ; 7.51 (s, 1H) ; 7.67 (s, 1H) ; 7.94 (s, 1H) ; 9.12 (s, 1H).

Example 192. Preparation of compound 369 in Table 14

An analogous reaction to that described in example 36 but starting with 2-(methylthio)aniline (29 mg, 0.21 mmol) yielded title compound (13 mg, 13 %).

MS ES^+: 581.7 $(M+H)^+$

^1H NMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 2.46 (s, 3H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.59 (d, 2H) ; 3.72 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (s, 2H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 7.22 (t, 1H) ; 7.27 (t, 1H) ; 7.34 (s, 1H) ; 7.39 (d, 1H) ; 7.45 (d, 1H) ; 7.68 (s, 1H) ; 7.93 (s, 1H) ; 9.10 (s, 1H).

Example 193. Preparation of compound 370 in Table 14

An analogous reaction to that described in example 36 but starting with 5-aminoindole (28 mg, 0.21 mmol) yielded title compound (33 mg, 34 %).

MS ES^+: 574.7 $(M+H)^+$

^1H NMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.36 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 3.97 (s, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.31 (t, 2H) ; 7.32 (m, 6H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.10 (s, 1H).

Example 194. Preparation of compound 371 in Table 14

An analogous reaction to that described in example 36 but starting with 2,4-difluoroaniline (27 mg, 0.21 mmol) yielded title compound (28 mg, 29 %).

MS ES^+: 571.7 $(M+H)^+$

^1H NMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.59 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.08 (s, 2H) ; 4.34 (t, 2H) ; 7.12 (t, 1H) ; 7.34 (s, 1H) ; 7.36 (m, 1H) ; 7.89 (m, 1H) ; 7.95 (s, 1H) ; 9.12 (s, 1H).

Example 195. Preparation of compound 372 in Table 14

An analogous reaction to that described in example 36 but starting with 2-fluoro-4-methylaniline (26 mg, 0.21 mmol) yielded title compound (35 mg, 37 %).

MS ES$^+$: 567.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.33 (s, 5H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (s, 3H) ; 4.07 (s, 2H) ; 4.08 (d, 2H) ; 4.33 (t, 2H) ; 7.04 (d, 1H) ; 7.12 (d, 1H) ; 7.34 (s, 1H) ; 7.66 (s, 1H) ; 7.78 (t, 1H) ; 7.94 (s, 1H) ; 9.12 (s, 1H).

Example 196. Preparation of compound 373 in Table 14

An analogous reaction to that described in example 36 but starting with 3-cyanoaniline (25 mg, 0.21 mmol) yielded title compound (21 mg, 22 %).

MS ES$^+$: 560.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (s, 3H) ; 4.06 (s, 2H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 7.34 (s, 1H) ; 7.6 (m, 2H) ; 7.69 (s, 1H) ; 7.85 (m, 1H) ; 7.95 (s, 1H) ; 8.18 (s, 1H) ; 9.13 (s, 1H).

Example 197. Preparation of compound 374 in Table 14

An analogous reaction to that described in example 36 but starting with 2-methyl-5-fluoroaniline (26 mg, 0.21 mmol) yielded title compound (15 mg, 16 %).

MS ES$^+$: 567.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.27 (s, 3H) ; 2.32 (t, 2H) ; 3.20 (t, 2H) ; 3.39 (t, 2H) ; 3.59 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.09 (s, 2H) ; 4.33 (t, 2H) ; 6.96 (t, 1H) ; 7.29 (t, 1H) ; 7.34 (s, 1H) ; 7.48 (d, 1H) ; 7.69 (s, 1H) ; 7.95 (s, 1H) ; 9.12 (s, 1H).

Example 198. Preparation of compound 375 in Table 14

An analogous reaction to that described in example 36 but starting with 2-methyl-5-chloroaniline (30 mg, 0.21 mmol) yielded title compound (20 mg, 21 %).

MS ES$^+$: 583.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA) : 2.26 (s, 3H) ; 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.71 (t, 2H) ; 4.01 (s, 3H) ; 4.05 (d, 2H) ; 4.07 (s, 2H) ; 4.32 (t, 2H) ; 7.16 (dd, 1H) ; 7.27 (d, 1H) ; 7.31 (s, 1H) ; 7.65 (d, 1H) ; 7.65 (s, 1H) ; 7.93 (s, 1H) ; 9.10 (s, 1H).

Example 199. Preparation of compound 376 in Table 15

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-((1-methyl-piperidine-4-yl)methoxy)quinazoline (89 mg, 0.2 mmol) in DMF (1.5 ml), was reacted with aniline (22 mg, 0.24 mmol) in presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (99 mg, 0.26 mmol) and DIEA (50 mg, 0.4 mmol) at 60°C over night. After cooling to room temperature the reaction mixture was diluted with dichloromethane, and purified by silicagel chromatography, eluting successively with CH_2Cl_2, CH_2Cl_2 / MeOH 90/10, and CH_2Cl_2 / MeOH sat. NH_3 90/10 to give title compound (50 mg, 42 %).

MS ES^+: 519.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.58 (m, 2H) ; 2.02 (m, 2H) ; 2.13 (m, 1H) ; 2.80 (s, 3H) ; 3.03 (t, 2H) ; 3.52 (d, 2H) ; 3.98 (s, 2H) ; 3.98 (s, 3H) ; 4.10 (d, 2H) ; 7.06 (t, 1H) ; 7.29 (s, 1H) ; 7.33 (t, 2H) ; 7.60 (d, 2H) ; 7.61 (s, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

The NMR spectrum of example 75 in presence of acid shows the existence of 2 forms in a ratio of approximately 9 : 1. Signals due to the minor form are seen at 1.95 (m) 3.23 (m) 3.32 (m) 4.28 (d) 9.38 (m). All other examples, up to example 101, similarly display 2 forms, in subsequent examples, only the major form is being described.

4-benzyloxy-3-methoxybenzonitrile.

4-benzyloxy-3-methoxybenzaldehyde (4.84 g, 20 mmol) in acetic acid (25 ml) and sodium acetate (3.3 g, 40 mmol) was reacted with hydroxylamine hydrochloride (2.8 g, 40 mmol) at reflux for 6 hours. The mixture was cooled, diluted with water, extracted with methylene chloride, dried over $MgSO_4$, concentrated to give title compound (4.8 g, 100 %).

^{1}HNMR ($DMSOd_6$): 3.83 (s, 3H) ; 5.20 (s, 2H) ; 7.21 (d, 1H) ; 7.40 (m, 7H).

2-nitro-4-benzyloxy-5-methoxybenzonitrile

4-benzyloxy-3-methoxybenzonitrile (4.78 g, 20 mmol) in acetic acid (10 ml) was slowly added to nitric acid (25 ml) at 20°C to 30°C. The mixture was stirred at room temperature for 6 hours, basified (pH 10-11) with cooling (KOH 10N), extracted with methylene chloride, dried over $MgSO_4$ evaporated. The solid was recristallysed in hot EtOAc, a yellow solid of title compound was obtained (3.62 g, 64 %).

MS ES^+: 285 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 3.97 (s, 3H) ; 5.33 (s, 2H) ; 7.40 (m, 5H) ; 7.71 (s, 1H) ; 8.01 (s, 1H).

2-nitro-4-hydroxy-5-methoxybenzonitrile

2-nitro-4-benzyloxy-5-methoxybenzonitrile (3 g, 10.6 mmol) was treated with trifluoroacetic acid (30 ml) at reflux for 0.5 hour. The solvent was evaporated, the residue triturated with ether to give a yellow solid of title compound (1.27 g, 62 %).

^{1}HNMR ($DMSOd_6$) : 3.95 (s, 3H) ; 7.63 (s, 1H) ; 7.70 (s, 1H).

2-nitro-4-((1-tert-butyloxycarbonylpiperidin-4-yl)methoxy)-5-methoxybenzonitrile

2-nitro-4-hydroxy-5-methoxybenzonitrile (388 mg, 2 mmol) in DMF (5 ml) and acetonitrile (5 ml) was reacted with 4-(4-tolylsulphonyloxymethyl)-1-tert-butyloxycarbonyl-piperidine (738. mg, 2 mmol) and K_2CO_3 (414 mg, 3 mmol) at 110°C for 3.5 hours. The mixture was diluted with water, extracted with ethylacetate, washed HCl (2N), dried over $MgSO_4$, evaporated to give title compound (630 mg, 80 %).

^{1}HNMR ($CDCl_3$): 1.31 (m, 2H) ; 1.47 (s, 9H) ; 1.85 (m, 2H) ; 2.07 (m, 1H) ; 2.77 (m, 2H) ; 3.96 (d, 2H) ; 3.99 (s, 3H) ; 4.19 (m, 2H) ; 7.19 (s, 1H) ; 7.75 (s, 1H).

2-nitro-4-(1-piperidin-4-ylmethoxy)-5-methoxybenzonitrile.

2-nitro-4-((1-tert-butyloxycarbonylpiperidin-4-yl)methoxy)-5-methoxybenzonitrile (1.17 g, 3 mmol) in CH_2Cl_2 (12 ml) was treated with TFA (2.4 ml) for 1 hour at room temperature. The solvent was evaporated, the residue was taken up in a mixture of CH_2Cl_2 and concentrated sodium bicarbonate, extracted with CH_2Cl_2. The organic phase was dried over MgSO4, concentrated to give title compound as a solid (770 mg, 88 %).

^{1}HNMR ($CDCl_3$): 1.33 (m, 2H) ; 1.86 (d, 2H) ; 2.03 (m, 1H) ; 2.71 (t, 2H) ; 3.15 (d, 2H) ; 3.96 (d, 2H) ; 3.99 (s, 3H) ; 7.18 (s, 1H) ; 7.76 (s, 1H).

2-nitro-4-(1-methylpiperidin-4-ylmethoxy)-5-methoxybenzonitrile.

2-nitro-4-(1-piperidin-4-ylmethoxy)-5-methoxybenzonitrile (771 mg, 2.65 mmol) in CH_2Cl_2 (8 ml) and MeOH (4 ml) was reacted for 0.5 hour with formaldehyde (13.3 M, 300 µl, 4 mmol), acetic acid (191 mg, 3.18 mmol) and $NaBH(OAc)_3$ (674 mg, 3.18 mmol) slowly added over 15 minutes. The solution was evaporated, the oily residue was taken up in a mixture of Na_2CO_3 and ethylacetate, extracted with ethylacetate. The organic phase was dried over $MgSO_4$, evaporated to give title compound as a yellow solid (698 mg, 86 %).

^{1}HNMR ($CDCl_3$) : 4.7 (m, 2H) ; 1.88 (d, 2H) ; 1.90 (m, 1H) ; 2.0 (m, 2H) ; 2.3 (s, 3H) ; 2.91 (d, 2H) ; 2.95 (d, 2H) ; 2.99 (s, 3H) ; 7.18 (s, 1H) ; 7.76 (s, 1H).

2-amino-4-(1-methylpiperidin-4-ylmethoxy)-5-methoxybenzonitrile

2-nitro-4-(1-methylpiperidin-4-ylmethoxy)-5-methoxybenzonitrile (1.1 g, 3.6 mmol) in THF (20 ml) in presence of benzyltrimethylammonium chloride (334 mg, 1.8 mmol) was treated by a slow addition of $Na_2S_2O_4$ (3.1 g, 18 mmol) in water (20 ml). After 0.5h , HCl (6N, 20ml)

was added to the mixture, which was stirred at 60°C for 5 h. The mixture was cooled to room temperature, extracted with ethylacetate. The aqueous phase was made basic with Na_2CO_3 (solid), and extracted with ethylacetate. The organic phase was dried over $MgSO_4$, concentrated, to give a yellow solid (748 mg, 75 %) of title compound.

^{1}HNMR ($DMSOd_6$): 1.29 (m, 2H) ; 1.70 (m, 3H) ; 1.85 (t, 2H) ; 2.14 (s, 3H) ; 2.76 (d, 2H) ; 3.64 (s, 3H) ; 3.75 (d, 2H) ; 5.57 (s, 2H) ; 6.40 (s, 1H) ; 6.87 (s, 1H).

N'-(2-cyano-4-methoxy-5-(1-methylpiperidin-4-ylmethoxy)phenyl)-N,N-dimethylimidoformamide.

2-amino-4-(1-methylpiperidin-4-ylmethoxy)-5-methoxy-benzonitrile (710 mg, 2.58 mmol) was reacted with DMF DMA (414 mg, 3.5 mmol) in toluene (15 ml) at reflux for 5 hours. The solution was concentrated, the oily residue triturated with ether to give a yellow solid of title compound (680 mg, 80 %).

^{1}HNMR ($DMSOd_6$): 1.28 (m, 2H) ; 1.72 (m, 3H) ; 1.85 (t, 2H) ; 2.14 (s, 3H) ; 2.76 (d, 2H) ; 2.95 (s, 3H) ; 3.05 (s, 3H) ; 3.72 (s, 3H) ; 3.86 (d, 2H) ; 6.71 (s, 1H) ; 7.07 (s, 1H) ; 7.89 (s, 1H).

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline.

N'-(2-cyano-4-methoxy-5-(1-methylpiperidin-4-ylmethoxy)phenyl)-N,N-diemethylimidoformamide (627 mg, 1.9 mmol) was reacted with methyl-2-amino-1,3-thiazol-5-acetate (360 mg, 2.1 mmol) in acetic acid (6.3 ml) at reflux for 4.5 hour under nitrogen. The mixture was concentrated, and the oily residue purified by silicagel chromatography, Eluant : CH_2Cl_2 / MeOH 90/10 and CH_2Cl_2 / MeOH sat. NH_3 90/10 to give title compound (552 mg, 63 %).

^{1}HNMR ($DMSOd_6$): 1.35 (m, 2H) ; 1.76 (m, 3H) ; 1.87 (t, 2H) ; 2.16 (d, 2H) ; 2.78 (d, 2H) ; 3.67 (s, 3H) ; 3.93 (s, 2H) ; 3.96 (s, 3H) ; 4.01 (d, 2H) ; 7.24 (s, 1H) ; 7.36 (s, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H).

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6-methoxy-7-((1-methylpiperidin-4-yl)methoxy)quinazoline (137 mg, 0.3 mmol) in ethanol (1.4 ml) was treated with NaOH (2N, 3.75 ml, 7.5 mmol) at room temperature for 0.5 hour. HCl (2N) was added to adjust the pH to 3. The solution was evaporated, the solid solubilized in CH_2Cl_2 (6 ml) MeOH (4 ml) DIEA

(excess) was added. The insoluble was filtered, the filtrate was concentrated, ethanol was added, the solid filtered, washed with ether, to give title compound (102 mg, 77 %).

MS ES$^+$: 444.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.61 (m, 2H) ; 2.03 (d, 2H) ; 2.16 (m, 1H) ; 2.80 (s, 3H) ; 3.03 (t, 2H) ; 3.5 (d, 2H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.10 (d, 2H) ; 7.32 (s, 1H) ; 7.59 (s, 1H) ; 7.89 (s, 1H) ; 9.07 (s, 1H).

Example 200. Preparation of compound 377 in Table 15

An analogous reaction to that described in example 75 but starting with 3-chloro-4-fluoroaniline (44 mg, 0.3 mmol) yielded compound 76 in table 3 (63 mg, 60 %)

MS ES$^+$: 571 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.64 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.8 (s, 3H) ; 3.04 (t, 2H) ; 3.51 (d, 2H) ; 3.99 (s, 3H) ; 4.0 (s, 2H) ; 4.11 (d, 2H) ; 7.34 (s, 1H) ; 7.39 (t, 1H) ; 7.5 (m, 1H) ; 7.65 (s, 1H) ; 7.91 (dd, 1H) ; 9.09 (s, 1H).

Example 201. Preparation of compound 378 in Table 15

An analogous reaction to that described in example 75 but starting with 2-aminopyridine (40 mg, 0.42 mmol) yielded compound 77 in table 3 (100 mg, 53 %)

MS ES$^+$: 520 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.65 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.78 (s, 3H) ; 3.02 (t, 2H) ; 3.48 (d, 2H) ; 3.99 (s, 3H) ; 4.1 (d, 2H) ; 4.14 (s, 2H) ; 7.32 (m, 1H) ; 7.39 (s, 1H) ; 7.66 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (d, 1H) ; 8.16 (t, 1H) ; 8.4 (d, 1H) ; 9.079 (s, 1H).

Example 202. Preparation of compound 379 in Table 15

An analogous reaction to that described in example 75 but starting with 3,4-difluoroaniline (54 mg, 0.42 mmol) yielded compound 78 in table 3 (120 mg, 72 %)

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.63 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.79 (s, 3H) ; 3.03 (t, 2H) ; 3.49 (d, 2H) ; 3.99 (s, 3H) ; 4.0 (s, 2H) ; 4.10 (d, 2H) ; 7.35 (s, 1H) ; 7.39 (m, 2H) ; 7.64 (s, 1H) ; 7.82 (dd., 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 203. Preparation of compound 380 in Table 15

An analogous reaction to that described in example 75 but starting with 2-chloroaniline (54 mg, 0.42 mmol) yielded compound 79 in table 3 (29 mg, 16 %)

MS ES^+: 553 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.62 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 1H) ; 2.81 (s, 3H) ; 3.04 (t, 2H) ; 3.51 (d, 2H) ; 4.0 (s, 3H) ; 4.08 (s, 2H) ; 4.11 (d, 2H) ; 7.24 (t, 1H) ; 7.31 (s, 1H) ; 7.34 (dd, 1H) ; 7.53 (d, 1H) ; 7.66 (s, 1H) ; 7.75 (d, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 204. Preparation of compound 381 in Table 15

An analogous reaction to that described in example 75 but starting with 4-methylaniline (45 mg, 0.42 mmol) yielded compound 80 in table 3 (155 mg, 85 %)

MS ES^+: 533 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.65 (m, 2H) ; 2.02 (m, 2H) ; 2.16 (m, 1H) ; 2.27 (s, 3H) ; 2.8 (s, 3H) ; 3.05 (t, 2H) ; 3.50 (d, 2H) ; 3.97 (s, 2H) ; 3.99 (s, 3H) ; 4.11 (d, 2H) ; 7.14 (d, 2H) ; 7.34 (s, 1H) ; 7.52 (d, 2H) ; 7.63 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 205. Preparation of compound 382 in Table 15

An analogous reaction to that described in example 75 but starting with 2-methylaniline (45 mg, 0.42 mmol) yielded compound 81 in table 3 (126 mg, 69 %)

MS ES^+: 533 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.62 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.24 (s, 3H) ; 2.8 (s, 3H) ; 3.04 (t, 2H) ; 3.51 (d, 2H) ; 3.99 (s, 3H) ; 4.02 (s, 2H) ; 4.10 (d, 2H) ; 7.11 (t, 1H) ; 7.19 (t, 1H) ; 7.24 (d, 1H) ; 7.33 (s, 1H) ; 7.43 (d, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.07 (s, 1H).

Example 206. Preparation of compound 383 in Table 15

An analogous reaction to that described in example 75 but starting with 4-chloroaniline (54 mg, 0.42 mmol) yielded compound 82 in table 3 (128 mg, 68 %)

MS ES^+: 553 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.65 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.79 (s, 3H) ; 3.04 (t, 2H) ; 3.50 (d, 2H) ; 3.99 (s, 3H) ; 4.0 (s, 2H) ; 4.1 (d, 2H) ; 7.36 (s, 1H) ; 7.38 (d, 2H) ; 7.64 (s, 1H) ; 7.68 (d, 2H) ; 7.9 (s, 1H) ; 9.08 (s, 1H).

Example 207. Preparation of compound 384 in Table 15

An analogous reaction to that described in example 75 but starting with 4-fluoroaniline (47 mg, 0.42 mmol) yielded compound 83 in table 3 (136 mg, 84 %)

MS ES^+: 537 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.62 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.79 (s, 3H) ; 3.03 (t, 2H) ; 3.50 (d, 2H) ; 3.97 (s, 2H) ; 3.98 (s, 3H) ; 4.1 (d, 2H) ; 7.16 (t, 2H) ; 7.34 (s, 1H) ; 7.63 (s, 1H) ; 7.65 (m, 2H) ; 7.9 (s, 1H) ; 9.07 (s, 1H).

Example 208. Preparation of compound 385 in Table 15

An analogous reaction to that described in example 75 but starting with 2-amino-6-methylpyrimidine (45 mg, 0.42 mmol) yielded compound 84 in table 3 (91 mg, 57 %)

MS ES^+: 534 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.61 (m, 2H) ; 2.05 (m, 2H) ; 2.15 (m, 1H) ; 2.50 (s, 3H) ; 2.8 (s, 3H) ; 3.03 (t, 2H) ; 3.52 (d, 2H) ; 4.02 (s, 3H) ; 4.1 (s, 2H) ; 4.11 (d, 2H) ; 7.15 (m, 1H) ; 7.33 (s, 1H) ; 7.65 (s, 1H) ; 7.8 (m, 2H) ; 7.91 (s, 1H) ; 9.07 (s, 1H).

Example 209. Preparation of compound 386 in Table 15

An analogous reaction to that described in example 75 but starting with 3-methoxyaniline (52 mg, 0.42 mmol) yielded compound 85 in table 3 (125 mg, 67 %)

MS ES^+: 549 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.63 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.8 (s, 3H) ; 3.04 (t, 2H) ; 3.52 (d, 2H) ; 3.75 (s, 3H) ; 3.98 (s, 2H) ; 3.99 (s, 3H) ; 4.11 (d, 2H) ; 6.68 (m, 1H) ; 7.17 (d, 1H) ; 7.24 (t, 1H) ; 7.33 (s, 1H) ; 7.35 (d, 1H) ; 7.64 (s, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 210. Preparation of compound 387 in Table 15

An analogous reaction to that described in example 75 but starting with 2-amino-5-chloropyridine (54 mg, 0.42 mmol) yielded compound 86 in table 3 (22 mg, 11 %)

MS ES^+: 554$(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.61 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 1H) ; 2.8 (s, 3H) ; 3.03 (t, 2H) ; 3.5 (d, 2H) ; 3.98 (s, 3H) ; 4.07 (s, 2H) ; 4.11 (d, 2H) ; 7.30 (s, 1H) ; 7.63 (s, 1H) ; 7.9 (s, 1H) ; 7.93 (dd, 1H) ; 8.12 (d, 1H) ; 8.41 (d, 1H).

Example 211 Preparation of compound 388 in Table 15

An analogous reaction to that described in example 75 but starting with 3-chloroaniline (54 mg, 0.42 mmol) yielded compound 87 in Table 2 (130 mg, 69 %).

MS ES$^+$: 553 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.62 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.78 (s, 3H) ; 3.02 (t, 2H) ; 3.49 (d, 2H) ; 3.97 (s, 3H) ; 3.99 (s, 2H) ; 4.08 (d, 2H) ; 7.13 (d, 1H) ; 7.3 (s, 1H) ; 7.38 (t, 1H) ; 7.64 (s, 1H) ; 7.86 (s, 1H) ; 7.90 (s, 1H) ; 9.07 (s, 1H).

Example 212. Preparation of compound 389 in Table 15

An analogous reaction to that described in example 75 but starting with 2-fluoroaniline (47 mg, 0.42 mmol) yielded compound 88 in Table 3 (116 mg, 63 %).

MS ES$^+$: 537 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.64 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.79 (s, 3H) ; 3.03 (t, 2H) ; 3.50 (d, 2H) ; 3.99 (s, 3H) ; 4.07 (s, 2H) ; 4.10 (d, 2H) ; 7.19 (m, 2H) ; 7.25 (m, 1H) ; 7.35 (s, 1H) ; 7.63 (s, 1H) ; 7.90 (s, 1H) ; 7.91 (m, 1H) ; 9.07 (s, 1H).

Example 213. Preparation of compound 390 in Table 15

Analogous reaction to that described in example 75 but starting with 3-dluoro-4-methoxyaniline (59 mg, 0.42 mmol) yielded compound 89 in Table 3 (151 mg, 85 %).

MS ES$^+$: 567 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.62 (m, 2H) ; 2.01 (m, 2H) ; 2.15 (m, 1H) ; 2.79 (s, 3H) ; 3.03 (t, 2H) ; 3.51 (d, 2H) ; 3.81 (s, 3H) ; 3.96 (s, 2H) ; 3.98 (s, 3H) ; 4.10 (d, 2H) ; 7.14 (t, 1H) ; 7.28 (d, 1H) ; 7.34 (s, 1H) ; 7.59 (dd, 1H) ; 7.6 (s, 1H) ; 7.90 (s, 1H) ; 9.07 (s, 1H).

Example 214. Preparation of compound 391 in Table 15

An analogous reaction to that described in example 75 but starting with 2-methyl-4-fluoroaniline (53 mg, 0.42 mmol) yielded compound 90 in Table 3 (151 mg, 81 %).

MS ES$^+$: 551 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.62 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.33 (s, 3H) ; 2.79 (s, 3H) ; 2.93 (t, 2H) ; 3.48 (d, 2H) ; 3.97 (s, 3H) ; 3.99 (s, 2H) , 4.09 (d, 2H) ; 7.01 (dt, 1H) ; 7.1 (dd, 1H) ; 7.37 (s, 1H) ; 7.39 (m, 1H) ; 7.64 (s, 1H) ; 7.89 (s, 1H) ; 9.05 (s, 1H).

Example 215. Preparation of compound 392 in Table 15

An analogous reaction to that described in example 75 but starting with 2-amino-4-methylpyridine (45 mg, 0.42 mmol) yielded compound 91 in Table 3 (119 mg, 66 %).

MS ES$^+$: 534 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.66 (m, 2H) ; 2.05 (m, 2H) ; 2.15 (m, 1H) ; 2.77 (s, 3H) ; 3.03 (t, 2H) ; 3.48 (d, 2H) ; 3.97 (s, 3H) ; 4.09 (d, 2H) ; 4.21 (s, 2H) ; 7.35 (m, 1H) ; 7.45 (s, 1H) ; 7.69 (s, 1H) ; 7.70 (s, 1H) ; 7.90 (s, 1H) ; 8.31 (d, 1H) ; 9.06 (s, 1H).

Example 216. Preparation of compound 393 in Table 15

An analogous reaction to that described in example 75 but starting with 2,5-difluoroaniline (54 mg, 0.42 mmol) yielded compound 92 in Table 3 (42 mg, 22 %).

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.60 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.81 (s, 3H) ; 3.04 (t, 2H) ; 3.52 (d, 2H) ; 3.99 (s, 3H) ; 4.10 (s, 2H) ; 4.11 (d, 2H) ; 7.02 (m, 2H) ; 7.32 (s, 1H) ; 7.34 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.92 (m, 1H) ; 9.08 (s, 1H).

Example 217. Preparation of compound 394 in Table 15

An analogous reaction to that described in example 75 but starting with 2-fluoro-4-chloroaniline (61 mg, 0.42 mmol) yielded compound 93 in Table 3 (97 mg, 50 %).

MS ES$^+$: 571 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.63 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.77 (s, 3H) ; 3.03 (t, 2H) ; 3.48 (d, 2H) ; 3.98 (s, 3H) ; 4.07 (s, 2H) ; 4.09 (d, 2H) ; 7.26 (d, 1H) ; 7.38 (s, 1H) ; 7.5 (dd, 1H) ; 7.62 (s, 1H) ; 7.89 (s, 1H) ; 7.96 (t, 1H) ; 9.06 (s, 1H).

Example 218. Preparation of compound 395 in Table 15

An analogous reaction to that described in example 75 but starting with 2-fluoro-5-methylaniline (53 mg, 0.42 mmol) yielded compound 94 in Table 3 (119 mg, 63 %).

MS ES$^+$: 551 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.63 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 1H) ; 2.28 (s, 3H) ; 2.77 (s, 3H) ; 3.03 (t, 2H) ; 3.49 (d, 2H) ; 3.98 (s, 3H) ; 4.05 (s, 2H) ; 4.09 (d, 2H) ; 6.98 (m, 1H) ; 7.15 (dd, 1H) ; 7.38 (s, 1H) ; 7.62 (s, 1H) ; 7.72 (m, 1H) ; 7.89 (s, 1H) ; 9.06 (s, 1H).

Example 219. Preparation of compound 396 in Table 15

An analogous reaction to that described in example 75 but starting with 3-methylaniline (45 mg, 0.42 mmol) yielded compound 95 in Table 3 (144g, 79 %).

MS ES^+: 533 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.64 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.3 (s, 3H) ; 2.79 (s, 3H) ; 3.04 (t, 2H) ; 3.51 (d, 2H) ; 3.98 (s, 2H) ; 3.99 (3H) ; 4.10 (d, 2H) ; 6.90 (d, 1H) ; 7.21 (t, 1H) ; 7.36 (s, 1H) ; 7.42 (d, 1H) ; 7.49 (s, 1H) ; 7.63 (s, 1H) ; 7.9 (s, 1H) ; 9.07 (s, 1H).

Example 220. Preparation of compound 397 in Table 15

An analogous reaction to that described in example 75 but starting with 2,4-difluoroaniline (54 mg, 0.42 mmol) yielded compound 96 in Table 3 (121 mg, 74 %).

MS ES^+: 555 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.63 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 1H) ; 2.78 (s, 3H) ; 3.03 (t, 2H) ; 3.5 (d, 2H) ; 3.98 (s, 3H) ; 4.04 (s, 2H) ; 4.1 (d, 2H) ; 7.08 (m, 1H) ; 7.33 (m, 1H) ; 7.36 (s, 1H) ; 7.63 (s, 1H) ; 7.86 (m, 1H) ; 7.90 (s, 1H) ; 9.07 (s, 1H).

Example 221. Preparation of compound 398 in Table 15

An analogous reaction to that described in example 75 but starting with 2-fluoro-4-methylaniline (53 mg, 0.42 mmol) yielded compound 97 in Table 3 (147 mg, 79 %).

MS ES^+: 551 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.63 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.3 (s, 3H) ; 2.79 (s, 3H) ; 3.04 (t, 2H) ; 3.51 (d, 2H) ; 3.99 (s, 3H) ; 4.04 (s, 2H) ; 4.1 (d, 2H) ; 6.99 (d, 1H) ; 7.10 (d, 1H) ; 7.35 (s, 1H) ; 7.62 (s, 1H) ; 7.75 (t, 1H) ; 7.90 (s, 1H) ; 9.07 (s, 1H).

Example 222. Preparation of compound 399 in Table 15

An analogous reaction to that described in example 75 but starting with 3-cyanoaniline (50 mg, 0.42 mmol) yielded compound 98 in Table 3 (118 mg, 71 %).

MS ES^+: 544 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.66 (m, 2H) ; 2.07 (m, 2H) ; 2.17 (m, 1H) ; 2.81 (s, 3H) ; 3.06 (t, 2H) ; 3.53 (d, 2H) ; 4.0 (s, 3H) ; 4.05 (s, 2H) ; 4.11 (d, 2H) ; 7.36 (s, 1H) ; 7.54 (m, 2H) ; 7.65 (s, 1H) ; 7.86 (dd, 1H) ; 7.92 (s, 1H) ; 8.18 (s, 1H) ; 9.09 (s, 1H).

Example 223. Preparation of compound 400 in Table 15

An analogous reaction to that described in example 75 but starting with 2-methyl-5-fluoroaniline (53 mg, 0.42 mmol) yielded compound 99 in Table 3 (107 mg, 57 %).
MS ES$^+$: 551 $(M+H)^+$
^{1}HNMR ($DMSOd_6$, TFA): 1.65 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.24 (s, 3H) ; 2.76 (s, 3H) ; 3.02 (t, 2H) ; 3.47 (d, 2H) ; 3.98 (s, 3H) ; 4.07 (s, 2H) ; 4.08 (d, 2H) ; 6.92 (m, 1H) ; 7.25 (t, 1H) ; 7.4 (s, 1H) ; 7.43 (m, 1H) ; 7.64 (s, 1H) ; 7.88 (s, 1H) ; 9.04 (s, 1H).

Example 224. Preparation of compound 401 in Table 15

An analogous reaction to that described in example 75 but starting with 3,5-difluoroaniline (54 mg, 0.42 mmol) yielded compound 100 in Table 3 (83 mg, 44 %).
MS ES$^+$: 555 $(M+H)^+$
^{1}HNMR ($DMSOd_6$, TFA): 1.66 (m, 2H) ; 2.02 (m, 2H) ; 2.16 (m, 1H) ; 2.76 (s, 3H) ; 3.03 (t, 2H) ; 3.45 (d, 2H) ; 3.97 (s, 3H) ; 4.03 (s, 2H) ; 4.08 (d, 2H) ; 6.90 (dd, 1H) ; 7.38 (m, 2H) ; 7.39 (s, 1H) ; 7.87 (s, 1H) ; 9.05 (s, 1H).

Example 225. Preparation of compound 402 in Table 15

An analogous reaction to that described in example 75 but starting with 3-fluoroaniline (47 mg, 0.42 mmol) yielded compound 101 in Table 3 (142 mg, 77 %).
MS ES$^+$: 537 $(M+H)^+$
^{1}HNMR ($DMSOd_6$, TFA) : 1.62 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 1H) ; 2.78 (s, 3H) ; 3.02 (t, 2H) ; 3.49 (d, 2H) ; 3.98 (s, 3H) ; 4.0 (s, 2H) ; 4.1 (d, 2H) ; 6.9 (s, 1H) ; 7.35 (s, 1H) ; 7.36 (m, 2H) ; 7.62 (m, 1H) ; 7.64 (s, 1H).; 7.9 (s, 1H) ; 9.08 (s, 1H).

Example 226. Preparation of compound 403 in Table 16

4-((2-amino-1,3-thiazol-5-yl)acetic acid)-6-methoxy-7-(3-N-methylpiperazinylpropoxy)quinazoline (142 mg, 0.3 mmol) in NMP (1.5 ml) was reacted with aniline (42 µl, 0.45 mmol) in presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N', tetramethyluronium hexafluorophosphate (173 mg, 0.45 mmol) and diisopropylethylamine (105 µl, 0.6 mmol) at 65°C under nitrogen over night. After cooling to room temperature, the reaction mixture was diluted with dichloromethane and purified by silicagel chromatography, eluant CH_2Cl_2, CH_2Cl_2 / MeOH, 9/1, CH_2Cl_2 / MeOH sat. NH_3, 9/1 to give title compound (24 mg, 15 %).

MS ES$^+$: 548.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.2 (m, 8H) ; 3.45 (t, 2H) ; 3.99 (s, 5H) ; 4.30 (t, 2H) ; 7.08 (t, 1H) ; 7.31 (s, 1H) ; 7.33 (, 2H) ; 7.62 (d, 2H) ; 7.64 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

2-nitro-4-(3-N-methylpiperazinylpropoxy)-5-methoxybenzonitrile

2-nitro-4-hydroxy-5-methoxybenzonitrile (45 g, 25 mmol) in CH_2Cl_2 (125 ml) was reacted with ditertiobutylazodicarboxylate (6.9 g, 30 mmol) triphenylphosphine (7.86 g, 30 mmol) at room temperature for 2 hours. A solution of ether (2.3N HCl, 55 ml) was added. The solid was recovered, washed with CH_2Cl_2, ether. The solid was dissolved in MeOH, treated with MeOH / NH_3, the solvent were evaporated, and the residue purified by silicagel chromatography eluant : CH_2Cl_2 / AcOEt 50/50, CH_2Cl_2 / MeOH 90/10, to give title compound (8.2 g, 98 %).

MS ES$^+$: 335.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.29 (t, 2H) ; 3.95 (s, 3H) ; 3.2-4 (m, 8H) ; 3.38 (t, 2H) ; 3.98 (s, 3H) ; 4.32 (t, 2H) ; 7.70 (s, 1H) ; 7.89 (s, 1H).

2-amino-4-(3-N-methylpiperazinylpropoxy)-5-methoxy-benzonitrile.

2-nitro-4-(3-N-methylpiperazinylpropoxy)-5-methoxybenzonitrile (1.67 g, 5 mmol), benzyltrimethylammonium chloride (0.46 g, 2.5 mmol) in methyle chloride (40 ml) was treated with sodium hydrosulfite (4.35 g, 5 mmol) in water (40 ml) at room temperature for 1 hour. HCl (6N, 28 ml) was added to the mixture which was heated at 60°C for 2.5 hours. The mixture was cooled, extracted with ethylacetate. The aqueous phase was treated with Na_2CO_3 (solid), extracted with ethylacetate. The organic phase was dried over $MgSO_4$, concentrated to give title compound (0.93 g, 61 %).

MS ES$^+$: 305.7 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.18 (t, 2H) ; 2.93 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.39 (t, 2H) ; 3.66 (s, 3H) ; 4.05 (t, 2H) ; 6.54 (s, 1H) ; 7.00 (s, 1H).

N'-(2-cyano-4-methoxy-5-(3-N-methylpiperazinylpropoxy)phenyl)-N,N-dimethylimidoformamide.

2-amino-4-(3-N-methylpiperazinylporpoxy)-5-methoxybenzonitrile (16.4 g, 54 mmol) was reacted with dimethylformamide dimethyl acetal (12 ml, 90 mmol) in toluene (400 ml) at reflux for 4 hours. The solvent was evaporated to give title compound (19.4 g, 100 %).

MS ES$^+$: 360.7 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.28 (t, 2H) ; 2.96 (s, 3H) ; 3.26 (s, 3H) ; 3.35 (s, 3H) ; 3.40 (t, 2H) ; 3.1-4 (m, 8H) ; 3.88 (s, 3H) ; 4.21 (t, 2H) ; 7.32 (s, 1H) ; 7.53 (s, 1H) ; 8.56 (s, 1H).

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6-methoxy-4-((3-N-methylpiperazinylpropoxy)quinazoline

N'-(2-cyano-4-methoxy-5-(3-N-piperazinylpropoxy)phenyl)-N,N-dimethylimidoformamide (9.7 g, 27 mmol) in acetic acid (100 ml) was reacted with methyl (2-amino-1,3-thiazole-5-yl)acetate (5.2 g, 30 mmol) at reflux for 4 hours. The solvent was evaporated and the residue purified by silicagel chromatography, Eluant : CH_2Cl_2 / MeOH 99/1 to 97/3 to give title compound (9.15 g, 70 %).

MS ES$^+$: 487.6$(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 2.97 (s, 3H) ; 3.2-4.2 (m, 8H) ; 3.48 (t, 2H) ; 3.97 (s, 2H) ; 4.00 (s, 3H) ; 4.33 (t, 2H) ; 7.36 (s, 1H) ; 7.61 (s, 1H) ; 7.93 (s, 1H) ; 9.10 (s, 1H).

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-(N-methylpiperazinylpropoxy) quinazoline

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6-methoxy-7-(3-(N-methylpiperazinylpropoxy) quinazoline (8.25 g, 17 mmol) in ethanol (80 ml) was treated with sodium hydroxyde (2N, 42.5 ml, 85 mmol) at room temperature for 1 hour. Hydrochloride acid (2N) was added to the solution (pH 3). The solution was evaporated, the residue dissolved in ethanol and N-ethyl diisopropyl amine (8.9 ml, 51 mmol). Ether was added to the solution, the solid was recovered, dried to give title compound (7.44 g, 93 %).

MS ES$^+$: 473.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.1 (m, 8H) ; 3.45 (t, 2H) ; 3.89 (s, 2H) ; 3.97 (s, 3H) ; 4.29 (t, 2H) ; 7.30 (s, 1H) ; 7.56 (s, 1H) ; 7.90 (s, 1H) ; 9.06 (s, 1H).

Example 227. Preparation of compound 404 in Table 16

An analogous reaction to that described in example 103 but starting with 3,4-difluoroaniline (77 mg, 0.6 mmol) yielded title compound (105 mg, 60 %).

MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 5H) ; 4.30 (t, 2H) ; 7.32 (s, 1H) ; 7.32 (m, 1H) ; 7.40 (q, 1H) ; 7.65 (s, 1H) ; 7.81 (m, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 228. Preparation of compound 405 in Table 16

An analogous reaction to that described in example 103 but starting with 2-aminopyridine (56 mg, 0.6 mmol) yielded title compound (53 mg, 36 %).

MS ES^+: 549.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.41 ('t, 2H) ; 3.99 (s, 3H) ; 4.02 (s, 2H) ; 4.32 (t, 2H) ; 7.21 (m, 1H) ; 7.34 (s, 1H) ; 7.64 (s, 1H) ; 7.91 (m, 2H) ; 8.03 (d, 1H) ; 8.37 (m, 1H) ; 9.98 (s, 1H).

Example 229. Preparation of compound 406 in Table 16

An analogous reaction to that described in example 103 but starting with 3-chloro-4-fluoroaniline (87 mg, 0.6 mmol) yielded title compound (134 mg, 74 %).

MS ES^+ : 600.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.43 (t, 2H) ; 3.1-4.1 (m, 8H) ; 3.99 (s, 5H) ; 4.32 (t, 2H) ; 7.33 (s, 1H) ; 7.38 (t, 1H) ; 7.50 (m, 1H) ; 7.64 (s, 1H) ; 7.90 (s, 1H) ; 7.96 (m, 1H) ; 9.09 (s, 1H).

Example 230. Preparation of compound 407 in Table 16

An analogous reaction to that described in example 103 but starting with 3-chloroaniline (77 mg, 0.6 mmol) yielded title compound (46 mg, 26 %).

MS ES^+: 582.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.2-4.1 (m, 8H) ; 3.45 (t, 2H) ; 3.99 (s, 3H) ; 4.07 (s, 2H) ; 4.30 (t, 2H) ; 7.22 (t, 1H) ; 7.31 (s, 1H) ; 7.35 (t, 1H) ; 7.53 (d, 1H) ; 7.65 (s, 1H) ; 7.74 (d, 1H) ; 7.92 (s, 1H) ; 9.08 (s, 1H).

Example 231. Preparation of compound 408 in Table 16

An analogous reaction to that described in example 103 but starting with 4-methylaniline (64 mg, 0.6 mmol) yielded title compound (105 mg, 62 %).

MS ES^+: 562.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.26 (s, 3H) ; 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.43 (t, 2H) ; 3.95 (s, 2H) ; 3.98 (s, 3H) ; 4.30 (t, 2H) ; 7.12 (d, 2H) ; 7.31 (s, 1H) ; 7.50 (d, 2H) ; 7.63 (s, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 232. Preparation of compound 409 in Table 16

An analogous reaction to that described in example 103 but starting with 2-methylaniline (64 mg, 0.6 mmol) yielded title compound (127 mg, 75 %).

MS ES+ : 562.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.24 (s, 3H) ; 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.2-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (s, 2H) ; 4.31 (t, 2H) ; 7.12 (t, 1H) ; 7.19 (t, 1H) ; 7.24 (d, 1H) ; 7.33 (s, 1H) ; 7.44 (d, 1H) ; 7.66 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 233. Preparation of compound 410 in Table 16

An analogous reaction to that described in example 103 but starting with 4-chloroaniline (77 mg, 0.6 mmol) yielded title compound (101 mg, 58 %).

MS ES^+: 582.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 4.00 (s, 5H) ; 4.31 (t, 2H) ; 7.33 (s, 1H) ; 7.40 (d, 2H) ; 7.65 (s, 1H) ; 7.66 (d, 2H) ; 7.92 (s, 1H) ; 9.10 (s, 1H).

Example 234. Preparation of compound 411 in Table 16

An analogous reaction to that described in example 103 but starting with 4-fluoroaniline (67 mg, 0.6 mmol) yielded title compound (97 mg, 57 %).

MS ES^+: 566.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.97 (s, 2H) ; 3.99 (s, 3H) ; 4.30 (t, 2H) ; 7.17 (t, 2H) ; 7.34 (s 1H) ; 7.64 (m, 3H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 235. Preparation of compound 412 in Table 16

An analogous reaction to that described in example 103 but starting with 2-amino-6-methylpyridine (65 mg, 0.6 mmol) yielded title compound (70 mg, 42 %).

MS ES^+ : 563.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.30 (t, 2H) ; 2.46 (s, 3H) ; 2.94 (s, 3H) ; 3.10-4.10 (m, 8H) ; 3.43 (t, 2H) ; 3.98 (s, 3H) ; 4.06 (s, 2H) ; 4.30 (t, 2H) ; 7.08 (d, 1H) ; 7.32 (s, 1H) ; 7.63 (s, 1H) ; 7.79 (t, 1H) ; 7.88 (d, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 236. Preparation of compound 413 in Table 16

An analogous reaction to that described in example 103 but starting with 2-methoxyaniline (74 mg, 0.6 mmol) yielded title compound (99 mg, 57 %).

MS ES$^+$: 578.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.43 (t, 2H) ; 3.74 (s, 3H) ; 3.97 (s, 2H) ; 3.99 (s, 3H) ; 4.30 (t, 2H) ; 6.67 (d, 1H) ; 7.15 (d, 1H) ; 7.24 (t, 1H) ; 7.33 (s, 2H) ; 7.64 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 237. Preparation of compound 414 in Table 16

An analogous reaction to that described in example 103 but starting with 2-amino-5-chloropyridine (77 mg, 0.6 mmol) yielded title compound (23 mg, 13 %).

MS ES$^+$: 583.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.10-4.10 (m, 8H) ; 3.45 (t, 2H) ; 3.98 (s, 3H) ; 4.06 (s, 2H) ; 4.30 (t, 2H) ; 7.31 (s, 1H) ; 7.63 (s, 1H) ; 7.90 (s, 1H) ; 7.91 (dd, 1H) ; 8.11 (d, 1H) ; 8.40 (d, 1H) ; 9.09 (s, 1H).

Example 238. Preparation of compound 415 in Table 16

An analogous reaction to that described in example 103 but starting with 3-chloroaniline (77 mg, 0.6 mmol) yielded title compound (96 mg, 55 %).

MS ES$^+$: 582.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.2 (m, 8H) ; 3.45 (t, 2H) ; 3.98 (s, 5H) ; 4.28 (t, 2H) ; 7.12 (d, 1H) ; 7.31 (s, 1H) ; 7.34 (t, 1H) ; 7.46 (d, 1H) ; 7.62 (s, 1H) ; 7.85 (s, 1H) ; 7.91 (s, 1H) ; 9.07 (s, 1H).

Example 239. Preparation of compound 416 in Table 16

An analogous reaction to that described in example 103 but starting with 2-fluoroaniline (67 mg, 0.6 mmol) yielded title compound (68 mg, 40 %).

MS ES$^+$: 596.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.28 (t, 2H) ; 2.91 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.40 (t, 2H) ; 3.95 (s, 3H) ; 4.03 (s, 2H) ; 4.26 (t, 2H) ; 7.13 (m, 2H) ; 7.25 (m, 2H) ; 7.28 (s, 1H) ; 7.60 (s, 1H) ; 7.87 (s, 1H) ; 9.05 (s, 1H).

Example 240. Preparation of compound 417 in Table 16

An analogous reaction to that described in example 103 but starting with 3-cyanoaniline (71 mg, 0.6 mmol) yielded title compound (101 mg, 63 %).

MS ES$^+$: 573.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.45 (t, 2H) ; 4.00 (s, 3H) ; 4.04 (s, 2H) ; 4.31 (t, 2H) ; 7.33 (s, 1H) ; 7.56 (s, 1H) ; 7.57 (m, 1H) ; 7.66 (s, 1H) ; 7.82 (m, 1H) ; 7.92 (s, 1H) ; 8.15 (s, 1H) ; 9.10 (s, 1H).

Example 241. Preparation of compound 418 in Table 16

An analogous reaction to that described in example 103 but starting with 2-fluoro-4-methylaniline (75 mg, 0.6 mmol) yielded title compound (109 mg, 63 %).

MS ES$^+$: 580.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.29 (m, 5H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.98 (s, 3H) ; 4.03 (s, 2H) ; 4.30 (t, 2H) ; 6.98 (d, 1H) ; 7.09 (d, 1H) ; 7.32 (s, 1H) ; 7.63 (s, 1H) ; 7.74 (t, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 242. Preparation of compound 419 in Table 16

An analogous reaction to that described in example 103 but starting with 3-fluoro-4-methoxyaniline (85 mg, 0.6 mmol) yielded title compound (121 mg, 68 %).

MS ES$^+$: 596.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.81 (s, 3H) ; 3.95 (s, 2H) ; 3.99 (s, 3H) ; 4.30 (t, 2H) ; 7.13 (t, 1H) ; 7.27 (m, 1H) ; 7.31 (s, 1H) ; 7.60 (m, 1H) ; 7.64 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 243. Preparation of compound 420 in Table 16

An analogous reaction to that described in example 103 but starting with 2-methyl-4-fluoroaniline (75 mg, 0.6 mmol) yielded title compound (130 mg, 75 %).

MS ES$^+$: 580.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.23 (s, 3H) ; 2.29 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.30 (t, 2H) ; 7.01 (m, 1H) ; 7.09 (dd, 1H) ; 7.32 (s, 1H) ; 7.40 (m, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 244. Preparation of compound 421 in Table 16

An analogous reaction to that described in example 103 but starting with 2-amino-4-methylpyridine (65 mg, 0.6 mmol) yielded title compound (87 mg, 52 %).

MS ES$^+$: 563.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.29 (t, 2H) ; 2.45 (s, 3H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.15 (s, 2H) ; 4.30 (t, 2H) ; 7.24 (d, 1H) ; 7.37 (s, 1H) ; 7.67 (s, 1H) ; 7.72 (s, 1H) ; 7.92 (s, 1H) ; 8.29 (d, 1H) ; 9.08 (s, 1H);

Example 245. Preparation of compound 422 in Table 16

An analogous reaction to that described in example 103 but starting with 2,5-difluoroaniline (77 mg, 0.6 mmol) yielded title compound (56 mg, 32 %).

MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.43 (t, 2H) ; 3.98 (s, 3H) ; 4.10 (s, 2H) ; 4.30 (t, 2H) ; 7.0 (m, 1H) ; 7.32 (s, 1H) ; 7.33 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (m, 2H) ; 9.09 (s, 1H).

Example 246. Preparation of compound 423 in Table 16

An analogous reaction to that described in example 103 but starting with 2-fluoro-4-chloroaniline (87 mg, 0.6 mmol) yielded title compound (69 mg, 38 %).

MS ES$^+$: 600.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.32 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.2 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.07 (s, 2H) ; 4.30 (t, 2H) ; 7.20 (dd, 1H) ; 7.33 (s, 1H) ; 7.51 (dd, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (t, 1H) ; 9.09 (s, 1H).

Example 247. Preparation of compound 424 in Table 16

An analogous reaction to that described in example 103 but starting with 2-fluoro-5-methylaniline (75 mg, 0.6 mmol) yielded title compound (81 mg, 46 %).

MS ES$^+$: 580.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.27 (s, 3H) ; 2.32 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.05 (s, 2H) ; 4.30 (t, 2H) ; 6.97 (m, 1H) ; 7.13 (dd, 1H) ; 7.34 (s, 1H) ; 7.63 (s, 1H) ; 7.74 (d, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 248. Preparation of compound 425 in Table 16

An analogous reaction to that described in example 103 but starting with 3-methylaniline (64 mg, 0.6 mmol) yielded title compound (116 mg, 69 %).

MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA): 2.28 (s, 3H) ; 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.45 (t, 2H) ; 3.96 (s, 2H) ; 3.98 (s, 3H) ; 4.30 (t, 2H) ; 6.88 (d, 1H) ; 7.19 (t, 1H) ; 7.30 (s, 1H) ; 7.39 (d, 1H) ; 7.47 (s, 1H) ; 7.62 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 249. Preparation of compound 426 in Table 16

An analogous reaction to that described in example 103 but starting with 2,4-difluoroaniline (77 mg, 0.6 mmol) yielded title compound (84 mg, 48 %).

MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA): 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.99 (s, 3H) ; 4.05 (s, 2H) ; 4.30 (t, 2H) ; 7.07 (t, 1H) ; 7.32 (m, 2H) ; 7.64 (s, 1H) ; 7.86 (m, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 250. Preparation of compound 427 in Table 16

An analogous reaction to that described in example 103 but starting with 2-methyl-5-fluoroaniline (75 mg, 0.6 mmol) yielded title compound (98 mg, 57 %).

MS ES$^+$: 580.6$(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA): 2.23 (s, 3H) ; 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.43 (t, 2H) ; 3.98 (s, 3H) ; 4.05 (s, 2H) ; 4.30 (t, 2H) ; 6.91 (m, 1H) ; 7.25 (t, 1H) ; 7.32 (s, 1H) ; 7.44 (dd, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 251. Preparation of compound 428 in Table 16

An analogous reaction to that described in example 103 but starting with 3,5-difluoroaniline (77 mg, 0.6 mmol) yielded title compound (54 mg, 31 %).

MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA): 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.45 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (s, 2H) ; 4.31 (t, 2H) ; 6.92 (m, 1H) ; 7.33 (s, 1H) ; 7.35 (m, 2H) ; 7.66 (s, 1H) ; 7.92 (s, 1H) ; 9.10 (s, 1H).

Example 252. Preparation of compound 429 in Table 16

An analogous reaction to that described in example 103 but starting with 3-fluoroaniline (67 mg, 0.6 mmol) yielded title compound (120 mg, 70 %).

MS ES^+: 566.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.2 (m, 8H) ; 3.44 (t, 2H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.30 (t, 2H) ; 6.90 (s, 1H) ; 7.34 (s, 1H) ; 7.36 (m, 2H) ; 7.61 (m, 1H) ; 7.64 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 253. Preparation of compound 430 in Table 17

N-(3-chlorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide (141 mg, 0.22 mmol) in acetonitrile (2 ml) was reacted with pyrrolidine (3.3 mmol) in presence of potassium iodide (100 mg, 0.6 mmol) at 80°C for 15 h / 30 hours. When the reaction was completed (tlc) DMF (2 ml), silicagel (2 g) was added, the mixture evaporated, and the residue was purified by silica gel chromatography, eluant : CH_2Cl_2 / MeOH 95/5, CH_2Cl_2 / MeOH sat. NH_3 90/10 to give title compound (81 mg, 29 %).

MS ES^+: 553.4, 554.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.90 (m, 2H) ; 2.06 (m, 2H) ; 2.26 (t, 2H) ; 3.09 (m, 2H) ; 3.36 (t, 2H) ; 3.67 (m, 2H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.29 (t, 2H) ; 7.14 (d, 1H) ; 7.30 (s, 1H) ; 7.37 (t, 1H) ; 7.47 (d, 1H) ; 7.65 (s, 1H) ; 7.85 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

3-methoxy-4-benzyloxybenzonitrile

3-methoxy-4-benzyloxybenzoldehyde (4.87 g, 20 mmol) in acetic acid (25 ml) was treated with hydroxylamine HCl (2.8 g, 40 mmol), sodium acetate (3.3 g, 40 mmol) at reflux for 6 hours. The mixture was cooled, extracted with water and methylenechloride, dried over $MgSO_4$, evaporated, to give title compound (4.8 g, 100 %).

^{1}HNMR ($DMSOd_6$, TFA): 3.72 (s, 3H) ; 5.15 (s, 2H) ; 7.18 (d, 1H) ; 7.39 (m, 7H).

2-nitro-4-benzyloxy-5-methoxybenzonitrile.

3-methoxy-4-benzyloxybenzonitrile (4.78 g, 20 mmol) in acetic acid (10 ml) was slowly added to nitric acid (d = 1.42, 25 ml) at 20-30° with cooling in an ice bath. The mixture was then stirred at room temperature for 6 hours. The reaction mixture was treated with potassium hydroxyde (10N) at 0°C. The basic mixture (pH 10) was extracted with CH_2Cl_2, the organic phase was dried over $MgSO_4$, concentrated to give title compound (3.62 g, 64 %).

MS ES^+: 285 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 3.97 (s, 3H) ; 5.33 (s, 2H) ; 7.42 (m, 5H) ; 7.70 (s, 1H) ; 8.03 (s, 1H).

2-amino-4-benzyloxy-5-methoxybenzonitrile.

2-nitro-4-benzyloxy-5-methoxybenzonitrile (40 g, 125 mmol) tetrabutylammonium chloride (21 g, 75 mmol) in methylenechloride (500 ml) was treated with $Na_2S_2O_4$ (180 g, 87.9 mmol) in H_2O (700 ml), sodium hydrosulfite was added over 45 minutes, and the mixture was stirred for 2 hours at room temperature. Sodium hydroxyde was added (pH 8.2) the mixture was extracted with methylene chloride. The organic phase was made acidic with HCl-ether (2.3N, 250 ml), the solid was recovered, suspended in methanol (250 ml) and treated with a saturated solution of sodium bicarbonate (pH 8.1). The solid was recovered, washed with water, ether to give title compound (30.7 g, 97 %).

^{1}HNMR (DMSOd_6) : 3.65 (s, 3H) ; 5.04 (s, 2H) ; 5.61 (s, 2H) ; 6.51 (s, 1H) ; 6.91 (s, 1H) ; 7.40 (m, 5H).

N'-(2-cyano-4-methoxy-5-benzyloxyphenyl)-N,N-dimethylimidoformamide.

2-amino-4-benzyloxy-5-methoxy benzonitrile (102 g, 400 mmol) in toluene (1.5 l) was reacted with DMF-DMA (110 ml, 780 mmol) at reflux for 5 hours. The solvent was evaporated, the residue triturated with ether to give title compound as yellow solid.

^{1}HNMR (DMSOd_6) : 2.96 (s, 3H) ; 3.06 (s, 3H) ; 3.73 (s, 3H) ; 5.15 (s, 2H) ; 6.87 (s, 1H) ; 7.11 (s, 1H) ; 7.40 (m, 5H) ; 7.89 (s, 1H).

N'-(2-cyano-4-methoxy-5-hydroxyphenyl)-N,N-dimethylimidoformamide.

N'-(2-cyano-4-methoxy-5-benzyloxyphenyl)-N,N-dimethylimidoformamide (15.45 g, 50 mmol) in TFA (200 ml) was irradiated in a microwave oven at 75°C for 45 minutes. The solvent was evaporated, the residue dissolved in dichloromethane washed with sodium bicarbonate, dried over magnesiumsulfate, evaporated to give a pale yellow solid (10.26 g, 94 %).

^{1}HNMR (DMSOd_6, TFA) : 3.24 (s, 3H) ; 3.34 (s, 3H) ; 3.87 (s, 3H) ; 7.02 (s, 1H) ; 7.49 (s, 1H) ; 8.56 (s, 1H).

N'-(2-cyano-4-methoxy-5-(3-chloropropoxyphenyl)-N,N-dimethylimidoformamide.

N'-(2-cyano-4-methoxy-5-hydroxyphenyl)-N,N-dimethylimidoformamide (439 mg, 2 mmol) in acetonitrile (5 ml) was reacted with 1-bromo-3-chloropropane (0.22 ml, 2.2 mmol) and cesium carbonate (1.95 g, 5.98 mmol) at 85°C for 0.5 hour. The reaction mixture was evaporated, taken up in methylene chloride water, extracted with CH_2Cl_2, dried over $MgSO_4$, evaporated to give title compound as a pale yellow solid (450 mg, 76 %).

MS ES$^+$: 296.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.26 (t, 2H) ; 3.26 (s, 3H) ; 3.37 (s, 3H) ; 3.81 (t, 2H) ; 3.87 (s, 3H) ; 4.23 (t, 2H) ; 7.34 (s, 1H) ; 7.53 (s, 1H) ; 8.56 (s, 1H).

g) N-(3-chlorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-ylamino)1,3-thiazol-5-yl)acetamide.

N'-(2-cyano-4-methoxy-5-(3-chloropropoxyphenyl)-N,N-dimethylimidoformamide (296 mg, 1 mmol) and 2-(2-amino-1,3-thiazol-5-yl)-N-(3-chlorophenyl)acetamide (268 mg, 1 mmol) in AcOH (1.5 ml, was irradiated in a microwave oven at 120°C for 40 minutes. The mixture was cooled, the solid was filtered to give title compound (445 mg, 72 %).

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.84 (t, 2H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.32 (t, 2H) ; 7.13 (d, 1H) ; 7.29 (s, 1H) ; 7.36 (t, 1H) ; 7.46 (d, 1H) ; 7.63 (s, 1H) ; 7.85 (s, 1H) ; 7.88 (s, 1H) ; 9.07 (s, 1H).

Example 254. Preparation of compound 431 in Table 17

An analogous reaction to that described in example 130 but starting with N-(3,4-difluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide (52 mg, 0.1 mmol) and pyrrolidine (150 µl, 1.8 mmol) yielded title compound (26 mg, 47 %).

^{1}HNMR (DMSOd_6, TFA): 1.91 (m, 2H) ; 2.07 (m, 2H) ; 2.28 (t, 2H) ; 3.10 (m, 2H) ; 3.37 (t, 2H) ; 3.67 (m, 2H) ; 3.99 (s, 5H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.33 (m, 1H) ; 7.40 (q, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Starting material N-(3,4-difluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxy quinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide was obtained by an analogous reaction to that described in example 130 but starting with 2-(2-amino-1,3-thiazol-5-yl)-N-(3,4-difluorophenyl)acetamide (540 mg, 2 mmol) to give title compound (980 mg, 78 %).

MS ES$^+$: 520.4, 522.4$(M+H)^+$

1HNMR (DMSOd6) : 1.26 (t, 2H) ; 3.82 (t, 2H) ; 3.88 (s, 2H) ; 3.97 (s, 3H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.32 (m, 1H) ; 7.36 (s, 1H) ; 7.39 (t, 1H) ; 7.80 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 255. Preparation of compound 432 in Table 17

An analogous reaction to that described in example 130 but starting with N-(3,5-difluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide (138 mg, 0.22 mmol) and dimethylamine (3.6 M in CH_2Cl_2, 3 ml, 3.6 mmol) yielded title compound (47 mg, 40 %).

MS ES^+: 529.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.25 (t, 2H) ; 3.28 (t, 2H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.28 (t, 2H) ; 6.93 (m, 1H) ; 7.30 (s, 1H) ; 7.34 (m, 2H) ; 7.65 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Starting material N-(3,5-difluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide was obtained by an analogous reaction to that described in example 130 but starting with 2-(2-amino-1,3-thiazole-5-yl)-N-(3,5-difluorophenyl)acetamide (810 mg, 3 mmol) to give title compound (630 mg, 40 %).

MS ES^+: 520.4, 522.4 $(M+H)^+$

1HNMR (DMSOd6) : 2.26 (t, 2H) ; 3.84 (t, 2H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.30 (t, 2H) ; 6.94 (m, 1H) ; 7.30 (s, 1H) ; 7.35 (m, 2H) ; 7.40 (s, 1H) ; 8.14 (s, 1H) ; 8.69 (s, 1H) ; 10.64 (s, 1H).

Example 256. Preparation of compound 433 in Table 17

An analogous reaction to that described in example 130 but starting with N-(3-chloro-4-fluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide (123 mg, 0.22 mmol) and 2-amino-2-methyl-1-propanol (89.1 mg, 3.3 mmol) yielded title compound (6 mg, 5 %).

MS ES^+: 589.4 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.24 (s, 6H) ; 2.22 (t, 2H) ; 3.10 (t, 2H) ; 3.45 (s, 2H) ; 3.98 (s, 3H) ; 4.31 (t, 2H) ; 7.29 (s, 1H) ; 7.38 (t, 1H) ; 7.50 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (s, 1H) ; 9.09 (s, 1H).

Starting material N-(3-chloro-4-fluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide was obtained by an analogous reaction to that described in example 130 but starting with 2-(2-amino-1,3-thiazole-5-yl)-N-(3-chloro-4-fluorophenyl)acetamide (2.29 g, 8.0 mmol) to give title compound (3.62 g, 84 %).

MS ES^+ : 536.3, 538.3 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 2.26 (t, 2H) ; 3.82 (t, 2H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.29 (t, 2H) ; 7.28 (s, 1H) ; 7.38 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (m, 1H) ; 7.93 (m, 1H) ; 8.12 (s, 1H) ; 8.67 (s, 1H) ; 10.47 (s, 1H).

Example 257. Preparation of compound 434 in Table 17

An analogous reaction to that described in example 130, but starting with N-(3-fluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide (116 mg, 0.22 mmol) and 2-amino-2-methyl-1-propanol (89 mg, 3.3 mmol) yielded title compound (40 mg, 33 %).

MS ES$^+$: 555.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.22 (t, 2H) ; 3.09 (t, 2H) ; 3.16 (s, 2H) ; 3.97 (s, 3H) ; 4.30 (t, 2H) ; 6.86 (t, 1H) ; 7.28 (s, 1H) ; 7.33 (m, 2H) ; 7.58 (m, 1H) ; 7.62 (s, 1H) ; 7.91 (s, 1H) ; 9.07 (s, 1H).

Starting material N-(3-fluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide was obtained by an analogous reaction to that described in example 130 but starting with 2-(2-amino-1,3-thiazole-5-yl)-N-(3-fluorophenyl)acetamide (2.01 g, 8 mmol) to give title compound (3.08 g, 77 %).

MS ES$^+$: 502.4, 504.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.28 (t, 2H) ; 3.84 (t, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.31 (t, 2H) ; 6.91 (t, 1H) ; 7.30 (s, 1H) ; 7.35 (m, 2H) ; 7.39 (s, 1H) ; 7.63 (d, 1H) ; 8.14 (s, 1H) ; 8.69 (s, 1H) ; 10.48 (s, 1H).

Example 258. Preparation of compound 435 in Table 17

An analogous reaction to that described in example 131 but starting with 4-hydroxyperidine (405 mg, 4.0 mmol) yielded compound 135 in Table 17 (82 mg, 70 %).

MS ES$^+$: 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.43 (m, 2H) ; 1.73 (m, 2H) ; 1.95 (m, 2H) ; 2.03 (t, 2H) ; 2.44 (t, 2H) ; 2.74 (m, 2H) ; 3.38 (m, 1H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.53 (d, 1H) ; 7.26 (s, 1H) ; 7.31 (m, 1H) ; 7.39 (s, 1H) ; 7.42 (ddd, 1H) ; 7.83 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.50 (s, 1H).

Example 259. Preparation of compound 436 in Table 17

An analogous reaction to that described in example 131 but starting with N,N-dimethylenediamine (0.44 ml, 4.0 mmol) yielded compound 136 in Table 17 (40 mg, 35 %).

MS ES$^+$: 572.5 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.95 (m, 2H) ; 2.14 (s, 6H) ; 2.33 (t, 2H) ; 2.63 (t, 2H) ; 2.73 (t, 2H) ; 3.89 (s, 2H) ; 3.97 (s, 3H) ; 4.22 (t, 2H) ; 7.26 (s, 1H) ; 7.34 (m, 1H) ; 7.38 (s, 1H) ; 7.41 (ddd, 1H) ; 7.82 (m, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.50 (s, 1H).

Example 260. Preparation of compound 437 in Table 17

An analogous reaction to that described in example 131 but starting with piperidine (0.4 ml, 3.0 mmol) yielded compound 137 in Table 17 (67 mg, 59 %).

MS ES$^+$: 569.5 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.40 (m, 2H) ; 1.52 (m, 4H) ; 1.95 (m, 2H) ; 2.42 (m, 4H) ; 2.48 (t, 2H) ; 3.89 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 7.25 (s, 1H) ; 7.33 (m, 1H) ; 7.39 (s, 1H) ; 7.41 (ddd, 1H) ; 7.82 (m, 1H) ; 8.11 (s, 1H) ; 8.68 (s, 1H) ; 10.51 (s, 1H).

Example 261. Preparation of compound 438 in Table 17

An analogous reaction to that described in example 131 but starting with 2-methylaminoethanol (248 mg, 3.3 mmol) yielded compound 138 in Table 17 (23 mg, 19 %).

MS ES$^+$: 559 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.95 (m, 2H) ; 2.23 (s, 3H) ; 2.47 (m, 2H) ; 3.32 (m, 2H) ; 3.49 (m, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.21 (t, 2H) ; 4.37 (m, 1H) ; 7.27 (s, 1H) ; 7.34 (m, 1H) ; 7.38 (s, 1H) ; 7.40 (dd, 1H) ; 7.82 (ddd, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.50 (s, 1H).

Example 262. Preparation of compound 439 in Table 17

An analogous reaction to that described in example 131 but starting with 1,2-diamino-2-methylpropane (291 mg, 3.3 mmol) yielded compound 139 in Table 17 (16 mg, 13 %).

MS ES$^+$: 572 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.10 (s, 6H) ; 1.96 (m, 2H) ; 2.48 (s, 2H) ; 2.75 (t, 2H) ; 3.89 (s, 2H) ; 3.97 (s, 3H) ; 4.26 (t, 2H) ; 7.27 (s, 1H) ; 7.34 (m, 1H) ; 7.37 (s, 1H) ; 7.42 (dd, 1H) ; 7.83 (ddd, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H) ; 10.50 (s, 1H).

Example 263. Preparation of compound 440 in Table 17

An analogous reaction to that described in example 131 but starting with cyclohexylamine (327 mg, 3.3 mmol) yielded compound 140 in Table 17 (70 mg, 55 %).

MS ES^+: 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.12 (m, 1H) ; 1.27 (m, 4H) ; 1.63 (brd, 1H) ; 1.78 (m, 2H) ; 2.04 (m, 2H) ; 2.16 (m, 2H) ; 3.03 (m, 1H) ; 3.16 (t, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.29 (t, 2H) ; 7.31 (s, 1H) ; 7.34 (m, 1H) ; 7.40 (s, 1H) ; 7.42 (dd, 1H) ; 7.82 (ddd, 1H) ; 8.16 (brs, 1H) ; 8.70 (s, 1H) ; 10.51 (s, 1H).

Example 264. Preparation of compound 441 in Table 17

An analogous reaction to that described in example 131 but starting with N,N,N'-trimethylethylenediamine (337 mg, 3.3 mmol) yielded compound 141 in Table 17 (63 mg, 49 %).

MS ES^+: 587 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.33 (m, 2H) ; 2.88 (s, 6H) ; 2.93 (s, 3H) ; 3.38 (m, 2H) ; 3.56 (m, 4H) ; 3.98 (s, 5H) ; 4.30 (t, 2H) ; 7.29 (m, 1H) ; 7.33 (s, 1H) ; 7.35 (dd, 1H) ; 7.63 (s, 1H) ; 7.80 (ddd, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 265. Preparation of compound 442 in Table 17

An analogous reaction to that described in example 131 but starting with (R)-(-)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 142 in Table 17 (90 mg, 70 %).

MS ES^+: 585 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.79 (m, 1H) ; 1.91 (m, 1H) ; 2.03 (m, 1H) ; 2.11 (m, 1H) ; 2.29 (m, 2H) ; 3.21 (m, 2H) ; 3.62 (m, 4H) ; 3.77 (m, 1H) ; 3.98 (s, 5H) ; 4.29 (t, 2H) ; 7.30 (s, 1H) ; 7.32 (m, 1H) ; 7.39 (dd, 1H) ; 7.64 (s, 1H) ; 7.80 (ddd, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 266. Preparation of compound 443 in Table 17

An analogous reaction to that described in example 131 but starting with (S)-(+)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 143 in Table 17 (82 mg, 63 %).

MS ES^+: 585 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.76 (m, 1H) ; 1.88 (m, 1H) ; 2.01 (m, 1H) ; 2.10 (m, 1H) ; 2.26 (m, 2H) ; 3.21 (m, 2H) ; 3.59 (m, 4H) ; 3.74 (dd, 1H) ; 3.95 (s, 5H) ; 4.27 (t, 2H) ; 7.27 (s, 1H) ; 7.28 (m, 1H) ; 7.34 (dd, 1H) ; 7.60 (s, 1H) ; 7.77 (ddd, 1H) ; 7.88 (s, 1H) ; 9.05 (s, 1H).

Example 267. Preparation of compound 444 in Table 17

An analogous reaction to that described in example 131 but starting with 3-pyrrolidinol (288 mg, 3.3 mmol) yielded compound 144 in Table 17 (15 mg, 12 %).

MS ES$^+$: 571 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.85-2.04 (m, 2H) ; 2.28 (m, 2H) ; 3.03-3.54 (m, 4H) ; 3.75 (m, 2H) ; 3.99 (s, 5H) ; 4.28 (m, 2H) ; 4.40-4.52 (m, 1H) ; 7.29 (s, 1H) ; 7.33 (m, 1H) ; 7.39 (dd, 1H) ; 7.64 (s, 1H) ; 7.81 (ddd, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 268. Preparation of compound 445 in Table 17

An analogous reaction to that described in example 131 but starting with 1-(2-aminoethyl)pyrrolidine (377 mg, 3.3 mmol) yielded compound 145 in Table 17 (20 mg, 15 %).

MS ES$^+$: 598 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.92 (m, 2H) ; 2.06 (m, 2H) ; 2.24 (m, 2H) ; 3.11 (m, 2H) ; 3.23 (t, 2H) ; 3.42 (m, 2H) ; 3.49 (m, 2H) ; 3.52 (m, 2H) ; 4.00 (s, 5H) ; 4.32 (t, 2H) ; 7.32 (s, 1H) ; 7.33 (m, 1H) ; 7.39 (dd, 1H) ; 7.65 (s, 1H) ; 7.81 (ddd, 1H) ; 7.92 (s, 1H) ; 9.10 (s, 1H).

Example 269. Preparation of compound 446 in Table 17

An analogous reaction to that described in example 131 but starting with 1-acetylpiperazine (423 mg, 3.3 mmol) yielded compound 146 in Table 17 (100 mg, 74 %).

MS ES$^+$: 612 $(M+H)^+$

^{1}HNMR (DMSOd_6): 2.00 (s, 5H) ; 2.35 (m, 2H) ; 2.42 (m, 2H) ; 3.92-3.06 (m, 1H) ; 3.45 (m, 4H) ; 3.56 (t, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.23 (t, 2H) ; 7.28 (s, 1H) ; 7.34 (m, 1H) ; 7.40 (s, 1H) ; 7.42 (dd, 1H) ; 7.83 (ddd, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H).

Example 270. Preparation of compound 447 in Table 17

An analogous reaction to that described in example 131 but starting with 1-(2-morpholinoethyl)-piperazine (658 mg, 3.3 mmol) yielded compound 147 in Table 17 (44 mg, 29 %).

MS ES^+: 683 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.98 (m, 2H) ; 2.30-2.70 (m, 18H) ; 3.58 (m, 4H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.21 (t, 2H) ; 7.26 (s, 1H) ; 7.33 (m, 1H) ; 7.40 (s, 1H) ; 7.41 (dd, 1H) ; 7.82 (ddd, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.54 (s, 1H).

Example 271. Preparation of compound 448 in Table 17

An analogous reaction to that described in example 131 but starting with 2-piperidineethanol (426 mg, 3.3 mmol) yielded compound 148 in Table 17 (19 mg, 14 %).

MS ES^+: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.45-1.92 (m, 7H) ; 2.00-2.15 (m, 1H) ; 2.20-2.40 (m, 2H) ; 3.10-3.70 (m, 7H) ; 3.99 (s, 5H) ; 4.30 (m, 2H) ; 7.30 (s, 1H) ; 7.34 (m, 1H) ; 7.40 (dd, 1H) ; 7.64 (s, 1H) ; 7.81 (ddd, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 272. Preparation of compound 449 in Table 17

An analogous reaction to that described in example 131 but starting with 1-(2-hydroxyethyl)piperazine (430 mg, 3.3 mmol) yielded compound 149 in Table 17 (90 mg, 66 %).

MS ES^+: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H) ; 2.35-2.47 (m, 12H) ; 3.49 (q, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 1H) ; 4.37 (t, 1H) ; 7.25 (s, 1H) ; 7.33 (m, 1H) ; 7.39 (s, 1H) ; 7.41 (dd, 1H) ; 7.81 (ddd, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.50 (s, 1H) ; 12.03 (brs, 1H).

Example 273. Preparation of compound 450 in Table 17

An analogous reaction to that described in example 131 but starting with cyclopentylamine (281 mg, 3.3 mmol) yielded compound 150 in Table 17 (43 mg, 34 %).

MS ES^+: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.53 (m, 4H) ; 1.69 (m, 2H) ; 1.93 (m, 2H) ; 2.10 (m, 2H) ; 3.00 (m, 2H) ; 3.38 (m, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.28 (t, 2H) ; 7.30 (s, 1H) ; 7.32 (m, 1H) ; 7.42 (dd, 1H) ; 7.81 (ddd, 1H) ; 8.15 (brs, 1H) ; 8.70 (s, 1H) ; 10.51 (s, 1H).

Example 274. Preparation of compound 451 in Table 17

An analogous reaction to that described in example 131 but starting with 4-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 151 IN Table 17 (53 mg, 39 %).

MS ES$^+$: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H) ; 1.36 (m, 3H) ; 1.63 (brd, 2H) ; 1.87 (m, 2H) ; 1.95 (m, 2H) ; 2.45 (m, 1H) ; 2.86 (m, 2H) ; 3.44 (m, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.32 (t, 1H) ; 7.26 (s, 1H) ; 7.31 (m, 1H) ; 7.40 (s, 1H) ; 7.42 (dd, 1H) ; 7.82 (ddd, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.50 (s, 1H) ; 12.02 (brs, 1H).

Example 275. Preparation of compound 452 in Table 17

An analogous reaction to that described in example 131 but starting with L-alanine-T-butylester hydrochloride (599 mg, 3.3 mmol) and treating the crude reaction mixture with a 1:1 solution of CH_2Cl_2-TFA (4 ml) yielded compound 152 in Table 17 (75 mg, 60 %).

MS ES$^+$: (573 $(M+H)^+$.

^{1}HNMR ($DMSOd_6$, TFA): 1.48 (d, 3H) ; 2.24 (m, 2H) ; 3.22 (m, 2H) ; 3.97 (s, 5H) ; 4.15 (q, 1H) ; 4.30 (m, 2H) ; 7.30 (s, 1H) ; 7.34 (m, 1H) ; 7.40 (dd, 1H) ; 7.64 (s, 1H) ; 7.81 (ddd, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H) ; 10.60 (s, 1H).

Example 276. Preparation of compound 453 in Table 17

An analogous reaction to that described in example 131 but starting with 3-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 153 in Table 17 (84 mg, 65 %).

MS ES$^+$: 585 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.07 (m, 1H) ; 1.41 (m, 1H) ; 1.62 (m, 1H) ; 1.76 (m, 2H) ; 1.87 (m, 1H) ; 1.95 (m, 2H) ; 2.47 (m, 2H) ; 2.68 (m, 1H) ; 2.85 (m, 1H) ; 3.48 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.20 (t, 2H) ; 4.59 (d, 1H) ; 7.26 (s, 1H) ; 7.31 (m, 1H) ; 7.39 (s, 1H) ; 7.42 (dd, 1H) ; 7.81 (ddd, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.50 (s, 1H) ; 12.02 (brs, 1H).

Example 277. Preparation of compound 454 in Table 17

An analogous reaction to that described in example 131 but starting with 4-hydroxymethylpiperidine (380 mg, 3.3 mmol) yielded compound 154 in Table 17 (42 mg, 32 %).

MS ES$^+$: 599 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.13 (m, 2H) ; 1.33 (m, 1H) ; 1.62 (brd, 2H) ; 1.90 (m, 2H) ; 1.95 (m, 2H) ; 2.44 (m, 2H) ; 2.88 (m, 2H) ; 3.22 (t, 2H) ; 3.86 (s, 2H) ; 3.93 (s, 3H) ; 4.17 (t, 2H) ; 4.38 (t, 1H) ; 7.22 (s, 1H) ; 7.31 (m, 1H) ; 7.36 (s, 1H) ; 7.38 (dd, 1H) ; 7.80 (ddd, 1H) ; 8. 09 (brs, 1H) ; 8.65 (s, 1H) ; 10.46 (s, 1H) ; 12.00 (brs, 1H).

Example 278. Preparation of compound 455 in Table 17

An analogous reaction to that described in example 130 but starting with 1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 155 in Table 17 (52 mg, 42 %).

MS ES$^+$: 573 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H) ; 1.95 (m, 2H) ; 2.48 (m, 2H) ; 2.72 (t, 2H) ; 3.68 (m, 1H) ; 3.89 (s, 2H) ; 3.97 (s, 3H) ; 4.23 (t, 2H) ; 4.46 (m, 1H) ; 7.26 (s, 1H) ; 7.32 (m, 1H) ; 7.38 (s, 1H) ; 7.41 (dd, 1H) ; 7.81 (ddd, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.49 (s, 1H).

Example 279. Preparation of compound 456 in Table 17

An analogous reaction to that described in example 130 but starting with L-alanine-t-butylester hydrochloride (599 mg, 3.3 mmol) and treating the crude reaction mixture with CH_2Cl_2-TFA (1/1, 4 ml) yielded compound 156 in Table 17 (106 mg, 84 %).

MS ES$^+$: 571 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.40 (d, 3H) ; 2.25 (m, 2H) ; 3.20 (m, 2H) ; 3.98 (s, 3H) ; 4.00 (s, 2H) ; 4.14 (m, 1H) ; 4.31 (t, 2H) ; 7.13 (dd, 1H) ; 7.32 (s, 1H) ; 7.35 (t, 1H) ; 7.47 (dd, 1H) ; 7.63 (s, 1H) ; 7.86 (t, 1H) ; 7.90 (s, 1H) ; 8.30 (m, 1H) ; 9.08 (s, 1H) ; 10.60 (s, 1H).

Example 280. Preparation of compound 457 in Table 17

An analogous reaction to that described in example 130 but starting with2-methylaminoethanol (248 mg, 3.3 mmol) yielded compound 157 in Table 17 (86 mg, 70 %).

MS ES$^+$: 557 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.93 (m, 2H) ; 2.20 (s, 3H) ; 2.43 (t, 2H) ; 2.48 (m, 1H) ; 2.55 (m, 1H) ; 3.47 (dd, 2H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.19 (t, 2H) ; 4.34 (t, 1H) ; 7.13 (brd, 1H) ; 7.25 (s, 1H) ; 7.35 (t, 1H) ; 7.38 (s, 1H) ; 7.47 (s, 1H) ; 7.84 (s, 1H) ; 8.11 (dd, 1H) ; 8.66 (s, 1H) ; 10.44 (s, 1H) ; 12.00 (dd, 1H).

Example 281. Preparation of compound 458 in Table 17

An analogous reaction to that described in example 130 but starting with 1,2-diamino-2-methylpropane (291 mg, 3.3 mmol) yielded compound 158 in Table 17 (21 mg, 17 %).

MS ES$^+$: 570 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.39 (s, 1H) ; 2.28 (m, 2H) ; 3.23 (m, 4H) ; 3.98 (s, 3H) ; 4.00 (s, 2H) ; 4.32 (m, 2H) ; 7.14 (ddd, 1H) ; 7.31 (s, 1H) ; 7.36 (t, 1H) ; 7.47 (ddd, 1H) ; 7.64 (s, 1H) ; 7.86 (t, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 282. Preparation of compound 459 in Table 17

An analogous reaction to that described in example 130 but starting with cyclohexylamine (327 mg, 3.3 mmol) yielded compound 159 in Table 17 -85 mg, 66 %).

MS ES$^+$: 581 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.13 (m, 1H) ; 1.26 (m, 4H) ; 1.62 (brd, 1H) ; 1.77 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 2H) ; 3.07 (m, 1H) ; 3.14 (t, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.29 (t, 2H) ; 7.13 (brd, 1H) ; 7.29 (s, 1H) ; 7.36 (t, 1H) ; 7.39 (s, 1H) ; 7.46 (dd, 1H) ; 8.16 (dd, 1H) ; 8.26 (brs, 1H) ; 8.69 (s, 1H) ; 10.45 (s, 1H).

Example 283. Preparation of compound 460 in Table 17

An analogous reaction to that described in example 130 but starting with N,N-dimethylethylenediamine (291 mg, 3.3 mmol) yielded compound 160 in Table 17 (41 mg, 32 %).

MS ES$^+$: 570 $(M+H)^+$

^{1}HNMR (DMSOd_6): 2.00 (m, 1H) ; 2.17 (s, 6H) ; 2.38 (t, 2H) ; 2.72 (t, 2H) ; 2.81 (t, 2H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.24 (t, 2H) ; 7.14 (dd, 1H) ; 7.27 (s, 1H) ; 7.37 (t, 1H) ; 7.40 (s, 1H) ; 7.49 (dd, 1H) ; 7.86 (t, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H) ; 10.50 (s, 1H).

Example 284. Preparation of compound 461 in Table 17

An analogous reaction to that described in example 130 but starting with N,N,N'-trimethylethylenediamine (337 mg, 3.3 mmol) yielded compound 161 in Table 17 (11 mg, 8 %).

MS ES$^+$: 584 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.91 (m, 2H) ; 2.12 (s, 6H) ; 2.20 (s, 3H) ; 2.33 (m, 3H) ; 2.42 (m, 3H) ; 3.76 (s, 2H) ; 3.91 (s, 3H) ; 4.12 (t, 2H) ; 6.98 (s, 1H) ; 7.11 (dd, 1H) ; 7.16 (s, 4H) ; 7.35 (t, 1H) ; 7.52 (dd, 1H) ; 7.83 (s, 1H) ; 7.88 (t, 1H) ; 8.37 (s, 1H) ; 10.56 (s, 1H).

Example 285. Preparation of compound 462 in Table 17

An analogous reaction to that described in example 130 but starting with (R)-(-)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 162 in Table 17 (76 mg, 59 %).

MS ES$^+$: 583 $((M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.77 (m, 1H) ; 1.89 (m, 1H) ; 2.02 (m, 1H) ; 2.4 (m, 1H) ; 2.29 (m, 2H) ; 3.21 (m, 2H) ; 3.62 (m, 4H) ; 3.76 (m, 1H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.29 (t, 2H) ; 7.13 (dd, 1H) ; 7.29 (s, 1H) ; 7.35 (t, 1H) ; 7.46 (dd, 1H) ; 7.63 (s, 1H) ; 7.85 (t, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 286. Preparation of compound 463 in Table 17

An analogous reaction to that described in example 130 but starting with (S)-(+)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 163 in Table 17 (72 mg, 56 %).

MS ES$^+$: 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.78 (m, 1H) ; 1.90 (m, 1H) ; 2.03 (m, 1H) ; 2.13 (m, 1H) ; 2.30 (m, 2H) ; 3.23 (m, 2H) ; 3.62 (m, 4H) ; 3.77 (m, 1H) ; 3.98 (s, 3H) ; 4.00 (s, 2H) ; 4.30 (t, 2H) ; 7.14 (dd, 1H) ; 7.30 (s, 1H) ; 7.36 (t, 1H) ; 7.46 (dd, 1H) ; 7.64 (s, 1H) ; 7.85 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 287. Preparation of compound 464 in Table 17

An analogous reaction to that described in example 130 but starting with 4-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 164 in Table 17 (63 mg, 49 %).

MS ES$^+$: 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.41 (m, 2H) ; 1.73 (m, 2H) ; 1.96 (m, 2H) ; 2.04 (m, 2H) ; 2.74 (m, 2H) ; 2.50 (m, 2H) ; 3.43 (s, 1H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.54 (d, 1H) ; 7.14 (d,

1H) ; 7.26 (s, 1H) ; 7.37 (t, 1H) ; 7.40 (s, 1H) ; 7.49 (d, 1H) ; 7.86 (t, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.46 (s, 1H).

Example 288. Preparation of compound 465 in Table 17

An analogous reaction to that described in example 130 but starting with 3-pyrrolidinol (288 mg, 3.3 mmol) yielded compound 165 in Table 17 (57 mg, 45 %).

MS ES$^+$: 569 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.56 (m, 1H) ; 1.99 (m, 4H) ; 2.36 (m, 1H) ; 2.56 (m, 4H) ; 2.74 (m, 1H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.21 (t, 2H) ; 4.70 (d, 1H) ; 7.14 (dd, 1H) ; 7.26 (s, 1H) ; 7.37 (t, 1H) ; 7.40 (s, 1H) ; 7.49 (dd, 1H) ; 7.86 (t, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.47 (s, 1H) ; 12.03 (brs, 1H).

Example 289. Preparation of compound 466 in Table 17

An analogous reaction to that described in example 130 but starting with 1-(2-aminoethyl)pyrrolidine (377 mg, 3.3 mmol) yielded compound 166 in Table 17 (39 mg, 29 %).

MS ES$^+$: 596 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.91 (m, 2H) ; 2.06 (m, 2H) ; 2.24 (m, 2H) ; 3.11 (m, 2H) ; 3.23 (t, 2H) ; 3.42 (m, 2H) ; 3.48 (m, 2H) ; 3.67 (m, 2H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ;4.31 (t, 2H) ; 7.14 (d, 1H) ; 7.31 (s, 1H) ; 7.35 (t, 1H) ; 7.47 (d, 1H) ; 7.64 (s, 1H) ; 7.85 (t, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 290. Preparation of compound 467 in Table 17

An analogous reaction to that described in example 130 but starting with 4-hydroxymethylpiperidine (380 mg, 3.3 mmol) yielded compound 167 in Table 17 (64 mg, 49 %).

MS ES$^+$: 597 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H) ; 1.35 (m, 1H) ; 1.65 (brd, 2H) ; 1.88 (m, 2H) ; 1.97 (m, 2H) ; 2.47 (m, 2H) ; 2.90 (brd, 2H) ; 3.25 (t, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.41 (t, 1H) ; 7.14 (d, 1H) ; 7.25 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (s, 1H) ; 7.86 (s, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.46 (s, 1H) ; 12.03 (s, 1H).

Example 291. Preparation of compound 468 in Table 17

An analogous reaction to that described in example 130 but starting with 1-(2-hydroxyethyl)piperazine (430 mg, 3.3 mmol) yielded compound 168 in Table 17 (63 mg, 47 %).

MS ES$^+$: 612 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H) ; 2.41 (m, 12H) ; 3.50 (q, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.37 (t, 1H) ; 7.14 (dd, 1H) ; 7.25 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (d, 1H) ; 7.86 (t, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.46 (s, 1H) ; 12.04 (s, 1H).

Example 292. Preparation of compound 469 in Table 17

An analogous reaction to that described in example 130 but starting with cyclopentylamine 281 mg, 3.3 mmol) yielded compound 169 in Table 17 (77 mg, 61 %).

MS ES$^+$: 567 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.58 (m, 4H) ;1.73 (m, 2H) ; 2.00 (m, 2H) ; 2.17 (m, 2H) ; 3.12 (t, 2H) ; 3.56 (m, 1H) ; 3.92 (s, 3H) ; 3.99 (s, 3H) ; 4.31 (t, 2H) ; 7.15 (d, 1H) ; 7.31 (s, 1H) ; 7.37 (t, 1H) ; 7.41 (s, 1H) ; 7.48 (d, 1H) ; 7.86 (s, 1H) ; 8.16 (brs, 1H) ; 8.71 's, 1H) ; 10.47 (s, 1H) ; 12.03 (brs, 1H).

Example 293. Preparation of compound 470 in Table 17

An analogous reaction to that described in example 130 but starting with 4-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 170 in Table 17 (78 mg, 58 %).

MS ES$^+$: 611 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.16 (m, 2H) ; 1.36 (m, 3H) ; 1.63 (d, 2H) ; 1.88 (t, 2H) ; 1.96 (m, 2H) ; 2.44 (t, 2H) ; 2.87 (d, 2H) ; 3.44 (m, 2H) ; 3.9 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.33 (t, 1H) ; 7.14 (d, 1H) ; 7.25 (s, 1H) ; 7.37 (t, 1H) ; 7.40 (s, 1H) ; 7.49 (d, 1H) ; 7.86 (t, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.46 (s, 1H) ; 12.04 (s, 1H).

Example 294. Preparation of compound 471 in Table 17

An analogous reaction to that described in example 130 but starting with 3-hydroxypiperidine (339 mg, 3.3 mmol) yielded compound 171 in Table 17 (117 mg, 91 %).

MS ES$^+$: 583 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.07 (m, 1H) ; 1.41 (m, 1H) ; 1.62 (m, 1H) ; 1.70-1.90 (m, 3H) ; 1.95 (m, 2H) ; 2.46 (m, 2H) ; 2.67 (m, 1H) ; 2.83 (brd, 1H) ; 3.47 (m, 1H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.20 (t, 2H) ; 4.57 (d, 1H) ; 7.13 (ddd, 1H) ; 7.24 (s, 1H) ; 7.36 (t, 1H) ; 7.38 (s, 1H) ; 7.47 (d, 1H) ; 7.84 (t, 1H) ; 8.11 (brs, 1H) ; 8.67 (s, 1H) ; 10.46 (s, 1H) ; 12.00 (brs, 1H).

Example 295. Preparation of compound 472 in Table 17

An analogous reaction to that described in example 130 but starting with (S)-1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 172 in Table 17 (55 mg, 45 %).

MS ES$^+$: 557 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.06 (d, 3H) ; 1.96 (m, 2H) ; 2.48 (m, 2H) ; 2.73 (t, 2H) ; 3.70 (m, 1H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.24 (t, 2H) ; 4.48 (brs, 1H) ; 7.14 (d, 1H) ; 7.27 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.49 (d, 1H) ; 7.86 (t, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.46 (s, 1H).

Example 296. Preparation of compound 473 in Table 17

An analogous reaction to that described in example 130 but starting with (R)-1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 172 in Table 17 (84 mg, 68 %).

MS ES$^+$: 557 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.04 (d, 3H) ; 1.93 (m, 2H) ; 2.45 (m, 2H) ; 2.70 (t, 2H) ; 3.67 (m, 1H) ; 3.88 (s, 2H) ; 3.95 (s, 3H) ; 4.21 (t, 2H) ; 4.46 (brs, 1H) ; 7.12 (d, 1H) ; 7.24 (s, 1H) ; 7.35 (t, 1H) ; 7.37 (s, 1H) ; 7.47 (d, 1H) ; 7.84 (t, 1H) ; 8.09 (s, 1H) ; 8.65 (s, 1H) ; 10.45 (s, 1H).

Example 297. Preparation of compound 474 in Table 17

An analogous reaction to that described in example 130 but starting with tert-butyl-1-piperazinecarboxylate (615 mg, 3.3 mmol) and treating the crude reaction mixture with hydrochloric acid in 1,4 dioxane (4.0 M , 2 ml) yielded compound 174 (3 HCl) in Table 17 (89 mg, 61 %.

MS ES$^+$: 568 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.34 (m, 2H) ; 3.25-3.68 (m, 10H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.33 (t, 2H) ; 7.14 (dd, 1H) ; 7.35 (s, 1H) ; 7.37 (t, 1H) ; 7.49 (d, 1H) ; 7.65 (s, 1H) ; 7.86 (t, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H) ; 10.66 (s, 1H).

Example 298. Preparation of compound 475 in Table 17

An analogous reaction to that described in example 130 but starting with 2-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 175 in Table 17 (29 mg, 22 %).

MS ES$^+$: 611 $(M+H)^+$

^{1}HNMR (DMSOd$_6$): 1.30 (m, 2H) ; 1.48 (m, 4H) ; 1.60 (m ,2H) ; 1.76 (m, 1H) ; 1.93 (m, 2H) ; 2.26 (m, 1H) ; 2.48 (m, 1H) ; 2.79 (m, 2H) ; 3.46 (m, 2H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.18 (t, 2H) ; 4.40 (brs, 1H) ; 7.13 (d, 1H) ; 7.24 (s, 1H) ; 7.35 (t, 1H) ; 7.38 (s, 1H) ; 7.47 (d, 1H) ; 7.84 (s, 1H) ; 8.11 (brs, 1H) ; 8.67 (s, 1H) ; 10.44 (s, 1H).

Example 299. Preparation of compound 476 in Table 17

An analogous reaction to that described in example 130 but starting with 2-amino-2-methyl-1-propanol (294 mg, 3.3 mmol) yielded compound 176 in Table 17 (49 mg, 39 %).

MS ES$^+$: 571 $(M+H)^+$

1HNMR (DMSOd6, TFA) : 1.25 (s, 6H) ; 2.22 (m, 2H) ; 3.10 (m, 2H) ; 3.46 (s, 2H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.32 (t, 2H) ; 7.15 (d, 1H) ; 7.30 (s, 1H) ; 7.37 (t, 1H) ; 7.47 (d, 1H) ; 7.65 (s, 1H) ; 7.86 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 4H) ; 10.56 (s, 1H).

Example 300. Preparation of compound 477 in Table 17

An analogous reaction to that described in example 130 but starting with 1-(2-dimethylaminoethyl)piperazine (519 mg, 3.3 mmol) yielded compound 177 in Table 17 (19 mg, 15 %).

MS ES$^+$: 639 $(M+H)^+$

^{1}HNMR (DMSOd$_6$): 1.96 (m, 2H) ; 2.13 (s, 6H) ; 2.30-2.52 (m, 14H) ; 3.89 (s, 2H) ; 3.95 (s, 3H) ; 4.18 (t, 2H) ; 7.13 (d, 1H) ; 7.23 (s, 1H) ; 7.35 (t, 1H) ; 7.38 (s, 1H) ; 7.84 (t, 1H) ; 8.10 (s, 1H) ; 8.67 (s, 1H) ; 10.45 (s, 1H).

Example 301. Preparation of compound 478 in Table 17

An analogous reaction to that described in example 130 but starting with a solution of dimethylamine in chloroform (3,6M, 3 ml, 3.6 mmol) yielded compound 178 in Table 17 (44 mg, 34 %).

MS ES$^+$: 527 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.95 (m, 2H) ; 2.17 (s, 6H) ; 2.41 (t, 2H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.18 (t, 2H) ; 7.12 (d, 1H) ; 7.23 (s, 1H) ; 7.35 (t, 1H) ; 7.38 (s, 1H) ; 7.47 (d, 1H) ; 7.84 (t, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.45 (s, 1H).

Example 302. Preparation of compound 479 in Table 17

An analogous reaction to that described in example 130 but starting with aminomethylcyclopropane (234 mg, 3.3 mmol) yielded compound 179 in Table 17 (88 mg, 65 %).

MS ES$^+$: 553 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 0.18 (m, 2H) ; 0.46 (m, 2H) ; 0.94 (m, 1H) ; 2.01 (m, 2H) ; 2.51 (d, 2H) ; 2.79 (t, 2H) ; 3.94 (s, 2H) ; 4.01 (s, 3H) ; 4.28 (t, 2H) ; 7.18 (d, 1H) ; 7.31 (s, 1H) ; 7.41 (t, 1H) ; 7.43 (s, 1H) ; 7.53 (d, 1H) ; 7.90 (s, 1H) ; 8.16 (s, 1H) ; 8.72 (s, 1H) ; 10.53 (s, 1H).

Example 303. Preparation of compound 480 in Table 17

An analogous reaction to that described in example 130 but starting with piperidine (344 mg, 4.0 mmol) yielded compound 180 in Table 17 (52 mg, 40 %).

MS ES- : 565 $(M-H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.43 (m, 1H) ; 1.69 (m, 3H) ; 1.87 (d, 2H) ; 2.30 (m, 2H) ; 2.96 (t, 2H) ; 3.27 (t, 2H) ; 3.55 (d, 2H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.31 (t, 2H) ; 7.15 (d, 1H) ; 7.31 (s, 1H) ; 7.37 (t, 1H) ; 7.47 (d, 1H) ; 7.65 (s, 1H) ; 7.86 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H) ; 10.56 (s, 1H).

Example 304. Preparation of compound 481 in Table 17

An analogous reaction to that described in example 132 but starting with 1-(2-dimethylaminomethyl)piperazine (281 mg, 3.3 mmol) yielded compound 181 in Table 17 (81 mg, 64 %).

MS ES$^+$: 641 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.33 (m, 2H) ; 2.80-3.70 (m, 14H) ; 2.84 (s, 6H) ; 3.98 (s, 3H) ; 4.01 (s, 2H) ; 4.30 (brt, 1H) ; 6.90 (m, 1H) ; 7.32 (s, 2H) ; 7.35 (dd, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 305. Preparation of compound 482 in Table 17

An analogous reaction to that described in example 132 but starting with (S)-(+)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 182 in Table 17 (58 mg, 45 %).
MS ES$^+$: 585 $(M+H)^+$
^{1}HNMR ($DMSOd_6$, TFA) : 1.79 (m, 1H) ; 1.90 (m, 1H) ; 2.02 (m, 1H) ; 2.13 (m, 1H) ; 2.30 (m, 2H) ; 3.33 (m, 2H) ; 3.62 (m, 4H) ; 3.77 (dd, 1H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.30 (brt, 2H) ; 6.91 (t, 1H) ; 7.30 (s, 1H) ; 7.35 (dd, 2H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 306. Preparation of compound 483 in Table 17

An analogous reaction to that described in example 132 but starting with 4-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 183 in Table 17 (28 mg, 22 %).
MS ES$^+$: 585 $(M+H)^+$
^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H) ; 1.73 (m, 2H) ; 1.96 (m, 2H) ; 2.03 (m, 2H) ; 2.45 (m, 2H) ; 2.74 (m, 2H) ; 3.45 (m, 1H) ; 3.92 (s, 2H) ; 3.97 (s, 3H) ; 3.97 (t, 2H) ; 4.54 (d, 1H) ; 6.95 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.14 (brs, 1H) ;8.68 (s, 1H) ; 10.65 (s, 1H) ; 12.04 (brs, 1H).

Example 307. Preparation of compound 484 in Table 17

An analogous reaction to that described in example 132 but starting with 3-pyrrolidinol (288 mg, 3.3 mmol) yielded compound 184 in Table 17 (30 mg, 23 %).
MS ES$^+$: 571 $(M+H)^+$
^{1}HNMR ($DMSOd_6$) : 1.57 (m, 1H) ; 1.97 'm, 4H) ; 2.37 (m, 1H) ; 2.58 (m, 4H) ; 2.74 (m, 1H) ; 3.92 (s, 2H) ; 3.98 (s 3H) ; 4.22 (brt, 2H) ; 4.72 (brs, 1H) ; 6.95 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.65 (s, 1H) ; 12.04 (brs, 1H).

Example 308. Preparation of compound 485 in Table 17

An analogous reaction to that described in example 132 but starting with 1-(2-aminoethyl)pyrrolidine (377 mg, 3.3 mmol) yielded compound 185 in Table 17 (25 mg, 19 %).
MS ES$^+$: 598 $(M+H)^+$
^{1}HNMR ($DMSOd_6$, TFA) : 1.91 (m, 2H) ; 2.06 (m, 2H) ; 2.24 (m, 2H) ; 3.11 (m, 2H) ; 3.23 (t, 2H) ; 3.41 (lm, 2H) ; 3.49 (m, 2H) ; 3.67 (m, 2H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.31 (t, 2H) ; 6.89 (t, 1H) ; 7.32 (s, 1H) ; 7.34 (d, 2H) ; 7.64 (s, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 309. Preparation of compound 486 in Table 17

An analogous reaction to that described in example 132 but starting with 4-hydroxymethylpyperidine (380 mg, 3.3 mmol) yielded compound 186 in Table 17 (62 mg, 47 %).

MS ES$^+$: 599 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H) ; 1.34 (m, 1H) ; 1.65 (d, 2H) ; 1.88 (t, 2H) ; 1.96 (m, 2H) ; 2.45 (t, 2H) ; 2.90 (d, 2H) ; 3.25 (t, 2H) ; 3.92 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.41 (t, 1H) ; 6.94 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.64 (s, 1H) ; 12.07 (brs, 1H).

Example 310. Preparation of compound 487 in Table 17

An analogous reaction to that described in example 132 but starting with 2-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 187 in Table 17 (61 mg, 45 %).

MS ES$^+$: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.47-1.90 (m, 7H) ; 2.09 (m, 1H) ; 2.27 (m, 2H) ; 3.08-3.70 (m, 7H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.30 (m, 2H) ; 6.84 (m, 1H) ; 7.29 (d, 1H) ; 7.34 (dd, 1H) ; 7.62 (s, 1H) ; 7.92 (s, 1H) ; 9.08 (s, 1H).

Example 311. Preparation of compound 488 in Table 17

An analogous reaction to that described in example 132 but starting with 1-(2-hydroxyethyl)piperazine (430 mg, 3.3 mmol) yielded compound 188 in Table 17 (124 mg, 92 %).

MS ES$^+$: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.96 (m, 2H) ; 2.40 (m, 12H) ; 2.70 (m, 1H) ; 3.48 (m, 2H) ; 3.90 (s, 2H) ; 3.95 (s, 3H) ; 4.18 (t, 2H) ; 4.35 (brt, 1H) ; 6.43 (m, 1H) ; 7.23 (s, 1H) ; 7.34 (dd, 2H) ; 7.38 (s, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H) ; 10.63 (s, 1H).

Example 312. Preparation of compound 489 in Table 17

An analogous reaction to that described in example 132 but starting with 4-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 189 in Table 17 (54 mg, 40 %).

MS ES^+: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H) ; 1.36 (m, 3H) ; 1.63 (brd, 2H) ; 1.88 (m, 2H) ; 1.96 (m, 2H) ; 2.44 (m, 2H) ; 2.87 (brd, 2H) ; 3.44 (m, 2H) ; 3.92 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.33 (t, 1H) ; 6.95 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.64 (s, 1H) ; 12.04 (brs, 1H).

Example 313. Preparation of compound 490 in Table 17

An analogous reaction to that described in example 132 but starting with 3-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound in Table 17 (53 mg, 41 %).

MS ES^+: 559 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.09 (m, 1H) ; 1.43 (m, 1H) ; 1.64 (m, 1H) ; 1.79 (m, 2H) ; 1.87 (m, 1H) ; 1.96 (m, 2H) ; 2.47 (m, 2H) ; 2.69 (m, 2H) ; 2.85 (m, 2H) ; 3.49 (m, 1H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.21 (t, 2H) ; 4.60 (d, 1H) ; 6.95 (t, 1H) ; 7.26 (s, 1H) ; 7.36 (d, 2H) ; 7.40 (s, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.65 (s, 1H) ; 12.04 (brs, 1H).

Example 314. Preparation of compound 491 in Table 17

An analogous reaction to that described in example 132 but starting with N,N,N'-trimethylethylenediamine (337 mg, 3.3 mmol) yielded compound 191 in Table 17 (54 mg, 42 %).

MS ES^+: 586 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.32 (m, 1H) ; 2.34 (m, 1H) ; 2.88 (s, 6H) ; 2.93 (s, 3H) ; 3.39 (m, 2H) ; 3.56 (m, 4H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.30 (t, 2H) ; 6.91 (m, 1H) ; 7.33 (s, 1H) ; 7.35 (dd, 2H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 315. Preparation of compound 492 in Table 17

An analogous reaction to that described in example 132 but starting with piperidine (281 mg, 3.3 mmol) yielded compound 192 in Table 17 (81 mg, 64 %).

MS ES^+: 569 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 1.38 (m, 2H) ; 1.50 (m, 4H) ; 2.34 (brs, 4H) ; 2.41 (t, 2H) ; 3.90 (s, 2H) ; 3.96 (s, 3H) ; 4.19 (t, 2H) ; 6.93 (t, 1H) ; 7.24 (s, 1H) ; 7.34 (d, 2H) ; 7.38 (s, 1H) ; 8.11 (brs, 1H) ; 8.67 (s, 1H) ; 10.63 (s, 1H) ; 11.98 (brs, 1H).

Example 316. Preparation of compound 493 in Table 17

An analogous reaction to that described in example 132 but starting with pyrrolidine (235 mg, 3.3 mmol) yielded compound 193 in Table 17 (66 mg, 54 %).

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.90 (m, 2H) ; 2.06 (m, 2H) ; 2.28 (m, 2H) ; 3.09 (m, 2H) ; 3.36 (m, 2H) ; 3.68 (m, 2H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.29 (t, 2H) ; 6.93 (m, 1H) ; 7.30 (s, 1H) ; 7.34 (dd, 2H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 317. Preparation of compound 494 in Table 17

An analogous reaction to that described in example 132 but starting with 2-amino-2-methyl-1-propanol (294 mg, 3.3 mmol) yielded compound 194 in Table 17 (28 mg, 22 %).

MS ES$^+$: 573 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.24 (s, 6H) ; 2.23 (m, 2H) ; 3.10 (t, 2H) ; 3.45 (s, 2H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.31 (t, 2H) ; 6.91 (m, 1H) ; 7.30 (s, 1H) ; 7.34 (dd, 2H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 318. Preparation of compound 495 in Table 17

An analogous reaction to that described in example 132 but starting with 2-methylaminoethanol (248 mg, 3.3 mmol) yielded compound 195 in Table 17 (33 mg, 27 %).

MS ES$^+$: 559 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 1.95 (m, 2H) ; 2.24 (s, 3H) ; 2.48 (m, 2H) ; 2.45 (m, 2H) ; 3.49 (m, 2H) ; 3.93 (s, 2H) ; 3.98 (s, 3H) ; 4.21 (t, 2H) ; 4.38 (m, 1H) ; 6.95 (m, 1H) ; 7.27 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.65 (s, 1H) ; 12.04 (brs, 1H).

Example 319. Preparation of compound 496 in Table 17

An analogous reaction to that described in example 132 but starting with N,N-dimethylethylenediamine (291 mg, 3.3 mmol) yielded compound 196 in Table 17 (22 mg, 17 %).

MS ES$^+$: 572 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.23 (m, 2H) ; 2.89 (s, 6H) ; 3.22 (m, 2H) ; 3.41 (s, 4H) ; 3.96 (s, 3H) ; 4.01 (s, 2H) ; 4.31 (t, 2H) ; 6.92 (m, 1H) ; 7.31 (s, 1H) ; 7.35 (dd, 2H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 320. Preparation of compound 497 in Table 17

An analogous reaction to that described in example 132 but starting with (S(-(+)-1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 197 in Table 17 (32 Mg, 26 %).

MS ES$^+$: 559 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.15 (d, 3H) ; 2.24 (m, 2H) ; 2.83 (dd, 1H) ; 3.06 (dd, 1H) ; 3.15 (t, 2H) ; 3.95 (m, 1H) ; 3.99 (s, 3H) ; 4.01 (s, 3H) ; 4.29 (t, 1H) ; 6.92 (m, 1H) ; 7.28 (s, 1H) ; 7.34 (dd, 2H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 321. Preparation of compound 498 in Table 17

An analogous reaction to that described in example 132 but starting with (R)-(-)-1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 198 in Table 17 (40 mg, 32 %).

MS ES$^+$: 559 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.15 (d, 3H) ; 2.24 (m, 2H) ; 2.83 (dd, 1H) ; 3.06 (dd, 1H) ; 3.15 (t, 2H) ; 3.95 (m, 1H) ; 3.99 (s, 3H) ; 4.01 (s, 3H) ; 4.29 (t, 1H) ; 6.90 (m, 1H) ; 7.28 (s, 1H) ; 7.34 (dd, 2H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 322. Preparation of compound 499 in Table 17

An analogous reaction to that described in example 132 but starting with tert-butyl-1-piperazine carboxylate (615 mg, 3.3 mmol) and treating the crude reaction mixture with hydrochloric acid in 1,4-dioxane (4M, 2 ml) yielded compound 199 in Table 17 (66 mg, 45 %, 3 HCl).

MS ES$^+$: 570 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.35 (m, 2H) ; 3.20-3.94 (m, 10H) ; 3.99 (s, 3H) ; 4.03 (s, 2H) ; 4.33 (t, 2H) ; 6.93 (m, 1H) ; 7.36 (s, 1H) ; 7.37 (dd, 2H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 323. Preparation of compound 500 in Table 17

An analogous reaction to that described in example 132 but starting with N-allylpiperazine (416 mg, 3.3 mmol) yielded compound 200 in Table 17 (33 mg, 25 %).

MS ES$^+$: 610 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 1.96 (m, 2H) ; 2.30-2.50 (m, 10H) ; 2.93 (d, 2H) ; 3.92 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 5.12 (d, 1H) ; 5.18 (d, 1H) ; 5.82 (m, 1H) ; 6.95 (m, 1H) ; 7.25 (s, 1H) ; 7.35 (dd, 2H) ; 7.40 (s, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.64 (s, 1H) ; 11.99 (brs, 1H).

Example 324. Preparation of compound 501 in Table 17

An analogous reaction to that described in example 132 but starting with (R)-(-)-2-pyrrolidinemethanol (334 mg, 3.3 mol) yielded compound 201 in Table 17 (51 mg, 40 %).

MS ES$^+$: 585 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.57 (m, 1H) ; 1.67 (m, 2H) ; 1.82 (m, 1H) ; 1.96 (m, 2H) ; 2.18 (q, 1H) ; 2.45 (m, 3H) ; 2.98 (m, 1H) ; 3.10 (m, 1H) ; 3.20 (m, 1H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.22 (t, 2H) ; 4.35 (brs, 1H) ; 6.95 (m, 1H) ; 7.27 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H) ; 10.66 (s, 1H) ; 12.00 (brs, 1H).

Example 325. Preparation of compound 502 in Table 17

An analogous reaction to that described in example 132 but starting with cyclopentylamine (281 mg, 3.3 mmol) yielded compound 202 in Table 17 (28 mg, 22 %).

MS ES$^+$: 569 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.31 (m, 2H) ; 1.47 (m, 2H) ; 1.62 (m, 2H) ; 1.73 (m, 2H) ; 1.93 (m, 2H) ; 2.70 (t, 2H) ; 3.03 (m, 1H) ; 3.92 (s, 2H) ; 3.97 (s, 3H) ; 4.23 (t, 2H) ; 6.94 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (dd, 2H) ; 7.39 (s, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.66 (s, 1H).

Example 326. Preparation of compound 503 in Table 17

An analogous reaction to that described in example 133 but starting with 2-methylaminoethanol (248 mg, 3.3 mmol) yielded compound 203 in Table 17 (31 mg, 24 %).

MS ES$^+$: 575 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (m, 2H) ; 2.88 (s, 3H) ; 3.16-3.45 (m, 4H) ; 3.77 (t, 2H) ; 3.99 (s, 5H) ; 4.29 (t, 2H) ; 7.30 (s, 1H) ; 7.38 (t, 1H) ; 7.50 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (dd, 1H) ; 9.09 (s, 1H).

Example 327. Preparation of compound 504 in Table 17

An analogous reaction to that described in example 133 but starting with N,N,N'-trimethylethylenediamine (337 mg, 3.3 mmol) yielded compound 204 in Table 17 (28 mg, 21 %).

MS ES$^+$: 602 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (m, 2H) ; 2.89 (s, 6H) ; 2.93 (s, 3H) ; 3.38 (m, 2H) ; 3.56 (brs, 4H) ; 3.99 (s, 5H) ; 4.30 (t, 2H) ; 7.35 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (dd, 1H) ; 9.09 (s, 1H).

Example 328. Preparation of compound 505 in Table 17

An analogous reaction to that described in example 133 but starting with N-allylpyperazine (416 mg, 3.3 mmol) yielded compound 205 in Table 17 (42 mg, 30 %).

MS ES$^+$: 626 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.33 (m, 2H) ; 3.20-3.80 (m, 10H) ; 3.91 (d, 2H) ; 3.99 (s, 5H) ; 4.32 (t, 2H) ; 5.60 (m, 2H) ; 5.94 (m, 1H) ; 7.33 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (dd, 1H) ; 9.09 (s, 1H).

Example 329. Preparation of compound 506 in Table 17

An analogous reaction to that described in example 133 but starting with 4-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 206 in Table 17 (32 mg, 25 %).

MS ES$^+$: 601 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 1.41 (m, 2H) ; 1.73 (m, 2H) ; 1.96 (m, 2H) ; 2.03 (m, 2H) ; 2.45 (m, 2H) ; 2.74 (m, 2H) ; 3.46 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.21 (t, 2H) ; 4.55 (brs, 1H) ; 7.26 (s, 1H) ; 7.40 (s, 1H) ; 7.41 (t, 1H) ; 7.51 (m, 1H) ; 7.97 (dd, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.49 (s, 1H) ; 12.03 (brs, 1H).

Example 330. Preparation of compound 507 in Table 17

An analogous reaction to that described in example 133 but starting with 3-pyrrolidinol (288 mg, 3.3 mmol) yielded compound 207 in Table 17 (24 mg, 19 %).

MS ES$^+$: 587 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.57 (m, 1H) ; 1.98 (m, 3H) ; 2.30-2.81 (m, 6H) ; 3.38 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.22 (t, 2H) ; 4.74 (brs, 1H) ; 7.27 (s, 1H) ; 7.39 (s, 1H) ; 7.40 (t, 1H) ; 7.50 (m, 1H) ; 7.96 (dd, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.49 (s, 1H) ; 12.05 (brs, 1H).

Example 331. Preparation of compound 508 in Table 17

An analogous reaction to that described in example 133 but starting with 1-(2-aminoethyl)pyrrolidine (377 mg, 3.3 mmol) yielded compound 208 in Table 17 (18 mg, 13 %).

MS ES$^+$: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.91 (m, 2H) ; 2.06 (m, 2H) ; 2.23 (m, 2H) ; 3.11 (m, 2H) ; 3.22 (t, 2H) ; 3.41 (m, 2H) ; 3.47 (m, 2H) ; 3.67 (m, 2H) ; 3.98 (s, 5H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.36 (t, 1H) ; 7.49 (m, 1H) ; 7.63 (s, 1H) ; 7.91 (s, 1H). 7.95 (dd, 1H) ; 9.09 (s, 1H).

Example 332. Preparation of compound 509 in Table 17

An analogous reaction to that described in example 133 but starting with N-acetylpiperazine (423 mg, 3.3 mmol) yielded compound 209 in Table 17 (113 mg, 82 %).

MS ES$^+$: 628 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.98 (m, 2H) ; 2.00 (s, 3H) ; 2.36 (t, 2H) ; 2.42 (t, 2H) ; 2.92 (t, 0.5H) ; 2.99 (t, 0.5H) ; 3.45 (m, 4H) ; 3.55 (t, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.23 (t, 2H) ; 7.27 (s, 1H) ; 7.40 (s, 1H) ; 7.41 (t, 1H) ; 7.52 (m, 1H) ; 7.97 (dd, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H) ; 10.51 (s, 1H).

Example 333. Preparation of compound 510 in Table 17

An analogous reaction to that described in example 133 but starting with 2-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 210 in Table 17 (34 mg, 24 %).

MS ES$^+$: 629 $(M+H)^+$

Example 344. Preparation of compound 521 in Table 17

An analogous reaction to that described in example 134 but starting with 1,2-diamino-2-methylpropane (291 mg, 3.3 mmol) yielded compound 221in Table 17 (10 mg, 8 %).

MS ES^+: 554 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.39 (s, 6H) ; 2.27 (m, 2H) ; 3.22 (m, 4H) ; 3.97 (s, 3H) ; 3.98 (s, 2H) ; 4.32 (t, 2H) ; 6.89 (m, 1H) ; 7.29-7.39 (m, 3H) ; 7.62 (d, 1H) ; 7.63 (s, 1H) ; 7.92 (s, 1H) ; 9.08 (s, 1H).

Example 345. Preparation of compound 522 in Table 17

An analogous reaction to that described in example 134 but starting with N,N-dimethylethylenediamine (291 mg, 3.3 mmol) yielded compound 222 in Table 17 (26 mg, 22 %).

MS ES^+: 554 $(M+H)^+$

^{1}HNMR ($DMSOd_6$)) : 1.95 (m, 2H) ; 2.15 (s, 6H) ; 2.33 (t, 2H) ; 2.63 (t, 2H) ; 2.73 (t, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.23 (t, 2H) ; 6.91 (m, 1H) ; 7.26 (s, 1H) ; 7.31-7.42 (m, 2H) ; 7.39 (s, 1H) ; 7.64 (d, 1H) ; 8.11 (s, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H).

Example 346. Preparation of compound 523 in Table 17

An analogous reaction to that described in example 134 but starting with N,N,N'-trimethylethylenediamine (337 mg, 3.3 mmol) yielded compound 223 in Table 17 (37 mg, 30 %).

MS ES^+: 568 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.34 (m, 2H) ; 2.88 (s, 6H) ; 2.93 (s, 3H) ; 3.38 (m, 2H) ; 3.55 (m, 4H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.29 (t, 2H) ; 6.89 (m, 1H) ; 7.29-7.41 (m, 2H) ; 7.33 (s, 1H) ; 7.63 (d, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 347. Preparation of compound 524 in Table 17

An analogous reaction to that described in example 134 but starting with N-allylpiperazine (416 mg, 3.3 mmol) yielded compound 224 in Table 17 (77 mg, 59 %).

MS ES^+: 592 $(M+H)^+$

MS ES$^+$: 586 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (m, 2H) ; 3.00-3.95 (m, 10 H) ; 3.99 (s, 5H) ; 4.31 (t, 2H) ; 7.32 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (dd, 1H) ; 9.10 (s, 1H).

Example 341. Preparation of compound 518 in Table 17

An analogous reaction to that described in example 133 but starting with 1-(2-morpholinoethyl)piperazine (519 mg, 3.3 mmol) yielded compound 218 in Table 17 (69 mg, 48 %).

MS ES$^+$: 699 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (m, 2H) ; 2.98 (m, 2H) ; 3.10-37.5 (m, 16H) ; 3.86 (m, 4H) ; 3.99 (s, 5H) ; 4.31 (t, 2H) ; 7.33 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.65 (s, 1H) ; 7.92 (s, 1H) ; 7.97 (dd, 1H) ; 9.10 (s, 1H).

Example 342. Preparation of compound 519 in Table 17

An analogous reaction to that described in example 131 but starting with pyrrolidine (235 mg, 3.3 mmol) yielded compound 219 in Table 17 (55 mg, 44 %).

MS ES$^+$: 571 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.90 (m, 2H) ; 2.06 (m, 2H) ; 2.27 (m, 2H) ; 3.09 (m, 2H) ; 3.36 (t, 2H) ; 3.66 (m, 2H) ; 3.98 's, 5H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.64 (s, 1H) ; 7.90 (s,1H) ; 7.96 (dd, 1H) ; 9.09 (s, 1H).

Example 343. Preparation of compound 520 in Table 17

An analogous reaction to that described in example 134 but starting with 2-methylaminoethanol (248 mg, 3.3 mmol) yielded compound 220 in Table 17 (34 mg, 29 %).

MS ES$^+$: 541 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.30 (m, 2H) ; 3.57 (s, 3H) ; 3.16-3.45 (m, 4H) ; 3.75 (t, 2H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.29 (t, 2H) ; 6.89 (t, 1H) ; 7.29 (s, 1H) ; 7.30-7.40 (m, 2H) ; 7.62 (d, 1H) ; 7.63 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 337. Preparation of compound 514 in Table 17

An analogous reaction to that described in example 133 but starting with 3-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 214 in Table 17 (96 mg, 73 %).

MS ES^+:601 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 1.09 (m, 1H) ; 1.43 (m, 1H) ; 1.63 (m, 1H) ; 1.78 (m, 2H) ; 1.87 (m, 1H) ; 1.96 (m, 2H) ; 2.47 (m, 2H) ; 2.68 (m, 1H) ; 2.84 (brd, 1H) ; 3.50 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.20 (t, 2H) ; 4.59 (d, 1H) ; 7.26 (s, 1H) ; 7.40 (s, 1H) ; 7.41 (t, 1H) ; 7.51 (m, 1H) ; 7.97 (dd, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.03 (brs, 1H).

Example 338. Preparation of compound 515 in Table 17

An analogous reaction to that described in example 133 but starting with 4-hydroxymethylpyperidine (380 mg, 3.3 mmol) yielded compound 214 in Table 17 (18 mg, 13 %).

MS ES^+: 615 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H) ; 1.35 (m, 1H) ; 1.65 (d, 2H) ; 1.88 (m, 2H) ; 1.97 (m, 2H) ; 2.46 (m, 2H) ; 2.91 (m, 2H) ; 3.25 (t, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.21 (t, 2H) ; 4.41 (t, 1H) ; 7.26 (s, 1H) ; 7.40 (s, 1H) ; 7.41 (t, 1H) ; 7.50 (m, 1H) ; 7.97 (dd, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.49 (s, 1H) ; 12.03 (brs, 1H).

Example 339. Preparation of compound 516 in Table 17

An analogous reaction to that described in example 133 but starting with 1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 216 in Table 17 (14 mg, 11 %).

MS ES^+: 575 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H) ; 1.96 (m, 2H) ; 2.49 (m, 2H) ; 2.74 (t, 2H) ; 3.71 (m, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.24 (t, 2H) ; 4.50 (brs, 1H) ; 7.27 (s, 1H) ; 7.39 (s, 1H) ; 7.41 (t, 1H) ; 7.51 (m, 1H) ; 7.97 (dd, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.49 (s, 1H).

Example 340. Preparation of compound 517 in Table 17

An analogous reaction to that described in example 133 but starting with tert-butyl-1-piperazinecarboxylate (615 mg, 3.3 mmol) and treating the crude reaction mixture with hydrochloric acid in 1,4-dioxane (4.M, 2 ml) yielded compound 217 in Table 17 (61 mg, 47 %).

^{1}HNMR (DMSOd_6, TFA): 1.48-1.90 (m, 7H) ; 2.08 (m, 1H) ; 2.27 (m, 2H) ; 3.09-3.69 (m, 7H) ; 3.99 (s, 5H) ; 4.30 (m, 2H) ; 7.30 (d, 1H) ; 7.38 (t, 1H) ; 7.50 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (dd, 1H) ; 9.09 (s, 1H).

Example 334. Preparation of compound 511 in Table 17

An analogous reaction to that described in example 133 but starting with 2-(2-hydroxyethyl)piperazine (430 mg, 3.3 mmol) yielded compound 211 in Table 17 (80 mg, 58 %).

MS ES$^+$: 630 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.96 (m, 2H) ; 2.42 (m, 12H) ; 3.49 (dd, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.37 (t, 1H) ; 7.25 (s, 1H) ; 7.39 (s, 1H) ; 7.40 (t, 1H) ; 7.51 (m, 1H) ; 7.97 (dd, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.42 (s, 1H) ; 12.02 (brs, 1H).

Example 335. Preparation of compound 512 in Table 17

An analogous reaction to that described in example 133 but starting with cyclopentylamine (281 mg, 3.3 mmol) yielded compound 212 in Table 17 (12 mg, 9 %).

MS ES$^+$: 585 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.59 (m, 4H) ; 1.73 (m, 2H) ; 2.00 (m, 2H) ; 2.21 (m, 2H) ; 3.13 (t, 2H) ; 3.56 (m, 1H) ; 3.99 (s, 5H) ; 4.31 (t, 2H) ; 7.29 (s, 1H) ; 7.37 (t, 1H) ; 7.49 (m, 1H) ; 7.64 (s, 1H) ; 7.92 (s, 1H) ; 7.96 (dd, 1H) ; 9.09 (s, 1H).

Example 336. Preparation of compound 513 in Table 17

An analogous reaction to that described in example 133 but starting with 4-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 213 in Table 17 (54 mg, 39 %).

MS ES$^+$: 629 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 1.15 (m, 2H) ; 1.36 (m, 3H) ; 1.63 (d, 2H) ; 1.88 (t, 2H) ; 1.96 (m, 2H) ; 2.44 (t, 2H) ; 2.87 (d, 2H) ; 3.44 (m, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2HJ) ; 4.33 (t, 1H) ; 7.25 (s, 1H) ; 7.40 (s, 1H) ; 7.41 (t, 1H) ; 7.51 (m, 1H) ; 7.97 (dd, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.03 (brs, 1H).

^{1}HNMR (DMSOd_6, TFA): 2.34 (m, 2H) ; 3.00-3.08 (m, 8H) ; 2.86 (d, 2H) ; 3.92 (m, 2H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.31 (t, 2H) ; 5.53-5.66 (m, 2H) ; 5.60-5.87 (m, 1H) ; 6.89 (m, 1H) ; 7.31-7.40 (m, 3H) ; 7.62 (d, 1H) ; 7.63 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 348. Preparation of compound 525 in Table 17

An analogous reaction to that described in example 134 but starting with 4-hydroxypyperidine (334 mg, 3.3 mmol) yielded compound 225 in Table 17 (21 mg, 17 %).

MS ES$^+$: 567 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.59 (m, 1H) ; 1.85 (m, 2H) ; 2.01 (d, 1H) ; 2.28 (m, 2H) ; 3.03 (t, 1H) ; 3.21 (m, 1H) ; 3.28 (m, 2H) ; 3.40 (m, 1H) ; 3.57 (d, 1H) ; 3.68 (m, 1H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.28 (t, 2H) , 6.90 (t, 1H) ; 7.29 (s, 1H) ; 7.30-7.40 (m, 2H) ; 7.63 (d, 1H) ; 7.64 (s,1H) , 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 349. Preparation of compound 526 in Table 17

An analogous reaction to that described in example 134 but starting with 3-pyrrolidinol (288 mg, 3.3 mmol) yielded compound 226 in Table 17 (18 mg, 15 %).

MS ES$^+$: 553 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.84-2.03 (m, 2H) ; 2.27 (m, 2H) ; 3.02-3.79 (m, 6H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.29 (m, 2H) ; 4.41-4.51 (m, 1H) ; 6.91 (m, 1H) ; 7.28 (d, 1H) ; 7.31-7.41 (m, 2H) ; 7.63 (d, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 350. Preparation of compound 527 in Table 17

An analogous reaction to that described in example 134 but starting with 1-(aminoethyl)pyrrolidine (377 mg, 3.3 mmol) yielded compound 227 in Table 17 (34 mg, 27 %).

MS ES$^+$: 580$(M+H)^+$

^{1}HNMR (DMSOd_6): 1.68 (m, 4H) ; 1.97 (m, 2H) ; 2.47 (m, 6H) ; 2.70 (t, 2H) ; 2.77 (t, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.24 (t, 2H) ; 6.91 (m, 1H) ; 7.27 (s, 1H) ; 7.30-7.42 (m, 2H) ; 7.39 (s, 1H) ; 7.64 (d,1H) , 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.49 (s, 1H).

Example 351. Preparation of compound 528 in Table 17

An analogous reaction to that described in example 134 but starting with N-acetylpiperazine (423 mg, 3.3 mmol) yielded compound 228 in Table 17 (93 mg, 71 %).

MS ES$^+$: 594 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.99 (m, 2H) ; 2.00 (s, 3H) ; 2.35 (t, 2H) ; 2.41 (t, 2H) ; 2.49 (m, 2H) ; 3.45 (m, 4H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.23 (t, 2H) ; 6.92 (m, 1H) ; 7.27 (s, 1H) ; 7.32-7.42 (m, 2H) ; 7.40 (s, 1H) ; 7.63 (d, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.48 (s, 1H).

Example 352. Preparation of compound 529 in Table 17

An analogous reaction to that described in example 134 but starting with 1-(2-hydroxyethyl)piperazine (430 mg, 3.3 mmol) yielded compound 229 in Table 17 (91 mg, 69 %).

MS ES$^+$: 596 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H) ; 2.41 (m, 12H) ; 3.50 (q, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.37 (t, 1H) ; 6.91 (t, 1H) ; 7.25 (s, 1H) ; 7.32-7.42 (m, 2H) ; 7.39 (s, 1H) ; 7.65 (d, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.04 (brs, 1H).

Example 353. Preparation of compound 530 in Table 17

An analogous reaction to that described in example 134 but starting cyclopentylamine (281 mg, 3.3 mmol) yielded compound 230 in Table 17 (47 mg, 39 %).

MS ES$^+$: 551 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.39 (m, 2H) ; 1.50 (m, 2H) ; 1.65 (m, 2H) ; 1.80 (m, 2H) ; 2.00 (m, 2H) ; 2.80 (t, 2H) ; 3.16 (m, 1H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.25 (t, 2H) ; 6.98 (t, 1H) ; 7.28 (s, 1H) ; 7.31-7.42 (m, 2H) ; 7.40 (s, 1H) ; 7.64 (d, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H) ; 10.49 (s, 1H).

Example 354. Preparation of compound 531 in Table 17

An analogous reaction to that described in example 134 but starting with 4-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 231 in Table 17 (65 mg, 50 %).

MS ES$^+$: 595 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H) ; 1.36 (m, 3H) ; 1.63 (d, 2H) ; 1.88 (m, 2H) ; 1.96 (m, 2H) ; 2.44 (m, 2H) ; 2.87 (d, 2H) ; 3.44 (m, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.33 (t, 1H) ; 6.91 (t, 1H) ; 7.25 (s, 1H) ; 7.32-7.42 (m, 2H) ; 7.40 (s, 1H) ; 7.63 (d, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.03 (s, 1H).

Example 355. Preparation of compound 532 in Table 17

An analogous reaction to that described in example 134 but starting with 3-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 232 in Table 17 (72 mg, 58 %).

MS ES^+: 567 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.09 (m, 1H) ; 1.43 (m, 1H) ; 1.63 (m, 1H) ; 1.78 (m, 2H) ; 1.87 (m, 1H) ; 1.96 (t, 2H) ; 2.47 (m, 2H) ; 2.69 (m, 1H) ; 2.85 (brd, 1H) ; 3.49 (m, 1H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.20 (t, 2H) ; 4.60 (d, 1H) , 6.91 (t, 1H) ; 7.26 (s, 1H) ; 7.31-7.42 (m, 2H) ; 7.40 (s, 1H) ; 7.64 (d, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.02 (brs, 1H).

Example 356. Preparation of compound 533 in Table 17

An analogous reaction to that described in example 134 but starting with 4-hydroxymethylpyperidine (380 mg, 3.3 mmol) yielded compound 233 in Table 17 (56 mg, 44 %).

MS ES^+: 581 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H) ; 1.34 (m, 1H) ; 1.65 (d, 2H) ; 1.88 (t, 2H) ; 1.97 (m, 2H) ; 2.45 (t, 2H) ; 2.90 (d, 2H) ; 3.25 (t, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.41 (t, 1H) ; 6.93 (t, 1H) ; 7.25 (s, 1H) ; 7.32-7.42 (m, 2H) ; 7.40 (s, 1H) ; 7.63 (d, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.03 (brs, 1H).

Example 357. Preparation of compound 534 in Table 17

An analogous reaction to that described in example 134 but starting with 1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 234 in Table 17 (36 mg, 30 %).

MS ES^+: 541 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H) ; 1.95 (m, 2H) ; 2.48 (m, 2H) ; 2.72 (t, 2H) ; 3.69 (m, 1H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.23 (t, 2H) ; 4.47 (brs, 1H) ; 6.91 (t, 1H) ; 7.26 (s, 1H) ; 7.32-7.41 (m, 2H) ; 7.39 (s, 1H) ; 7.63 (d, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.48 (s, 1H).

Example 358. Preparation of compound 535 in Table 17

An analogous reaction to that described in example 134 but starting with (R)-(-)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 235 in Table 17 (66 mg, 53 %).

MS ES$^+$: 567 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.57 (m, 1H) ; 1.67 (m, 2H) ; 2.82 (m, 1H) ; 1.96 (m, 2H) ; 2.18 (m, 1H) ; 2.45 (m, 2H) ; 2.98 (m, 1H) ; 3.10 (m, 1H) ; 3.20 (m, 1H) ; 3.41 (m, 1H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.22 (t, 2H) ; 4.35 (brs, 1H) ; 6.91 (t, 1H) ; 7.26 (s, 1H) ; 7.31-7.42 (m, 2H) ; 7.39 (s, 1H) ; 7.64 (d, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.01 (brs, 1H).

Example 359. Preparation of compound 536 in Table 17

An analogous reaction to that described in example 134 but starting with (S)-(+)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 236 in Table 17 (59 mg, 48 %).

MS ES$^+$: 567 $(M+H)^+$

1HNMR (DMSOd6, TFA) : 1.78 (m, 1H) ; 1.90 (m, 1H) ; 2.03 (m, 1H) ; 2.13 (m, 1H) ; 2.31 (m, 2H) ; 3.23 (m, 2H) ; 3.61 (m, 4H) ; 3.77 (q, 1H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.29 (t, 2H) ; 6.89 (t, 1H) ; 7.29 (s, 1H) ; 7.30-7.40 (m, 2H) ; 7.63 (d, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 360. Preparation of compound 537 in Table 17

An analogous reaction to that described in example 134 but starting with t-butyl-1-pyperazinecarboxylate (615 mg, 3.3 mmol) and treating the crude reaction mixture with hydrochloric acid in 1,4-dioxane (4M, 2 ml) yielded compound 237 in Table 17 (35 mg, 27 %).

MS ES$^+$: 552 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H) ; 2.33 (brs, 4H) ; 2.42 (t, 2H) ; 2.73 (t, 4H) ; 3.89 (s, 2H) ; 3.95 (s, 3H) ; 4.19 (t, 2H) ; 6.89 (t, 1H) ; 7.24 (s, 1H) ; 7.32-7.42 (m, 2H) ; 7.37 (s, 1H) ; 7.62 (d, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H) ; 10.47 (s, 1H).

Example 361. Preparation of compound 538 in Table 17

An analogous reaction to that described in example 134 but starting with 1-(2-morpholinoethyl)piperazine (519 mg, 3.3 mmol) yielded compound 238 in Table 17 (50 mg, 37 %).

MS ES$^+$: 665 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.33 (m, 2H) ; 2.99 (t, 2H) ; 3.05-3.75 (m, 16H) ; 3.86 (brs, 4H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.29 (t, 2H) ; 6.90 (t, 1H) ; 7.32 (s, 1H) ; 7.41-7.31 (m, 2H) ; 7.62 (d, 1H) ; 7.64 (s, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 362. Preparation of compound 539 in Table 17

An analogous reaction to that described in example 134 but starting with 2-amino-2-methyl-1-propanol (294 mg, 3.3 mmol) yielded compound 239 in Table 17 (40 mg, 33 %).

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 0.96 (s, 6H) ; 1.91 (m, 2H) ; 2.67 (t, 2H) ; 3.19 (s, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.24 (t, 2H) ; 4.53 (brs, 1H) ; 6.91 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (m, 2H) ; 7.38 (s, 1H) ; 7.63 (d, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.48 (s, 1H).

Example 363. Preparation of compound 540 in Table 18

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (125 mg, 0.27 mmol) in DMF (2.5 ml) was reacted with N-ethylaniline (84.3 µl, 0.707 mmol) in presence of O-(7-azabenzotriazol-1-yl) -N,N,N',N'- tetramethyluronium hexafluorophosphate (136 mg, 0.37 mmol) and DIEA (95 µl, 0.54 mmol) at 50°C for 13 hours. The reaction mixture was cooled, sodium bicarbonate (sat., 1 ml) 3 g alumina were added, the mixture was evaporated to dryness, and the residue purified by chromatography over alumina, Eluant CH_2Cl_2, CH_2Cl_2/MeOH 99/1 to 95/5 to give title compound (68 mg, 44 %).

MS ES$^+$: 563.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA) : 1.05 (t, 3H) ; 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.65 (m, 6H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.31 (s, 1H) ; 7.38 (s, 1H) ; 7.40 (m, 2H) ; 7.46 (m, 1H) ; 7.53 (m, 2H) ; 7.87 (s, 1H) ; 9.06 (s, 1H).

Example 364. Preparation of compound 541 in Table 18

An analogous reaction to that described in example 240 but starting with 3-chloro-4-fluoro-N-methylaniline (97 mg, 0.35 mmol) yielded title compound (98 mg, 60 %).

MS ES$^+$: 601.5, 603.5 $(M+H)^+$

^{1}H NMR (DMSOd$_6$, TFA) : 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.21 (s, 3H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.7 (m, 4H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.31 (s, 1H) ; 7.41 (s, 1H) ; 7.50 (m, 2H) ; 7.80 (m, 1H) ; 7.87 (s, 1H) ; 9.06 (s, 1H).

N-(tert-butyloxycarbonyl)-3-chloro-4-fluoroaniline

3-chloro-4-fluoroaniline (2 g, 13.7 mmol) in THF (12.5 ml) under argon, was treated with NaHMDS (1 M, 27.5 ml, 27.5 mmol) at room temperature for 15 minutes. Di-tert-butyl dicarbonate in THF (10 ml) was slowly added to the reaction mixture, and the mixture stirred at room temperature for 45 minutes. The solvent was evaporated, diluted HCl (0.1 N) was added, and the mixture extracted with ethylacetate, dried, purified by silica gel chromatography, ether/petroleum ether 10-20 / 90-80 to give title compound (2.77 g, 82 %).

^{1}H NMR ($CDCl_3$) : 1.49 (s, 9H) ; 6.42 (s, 1H) ; 7.01 (t, 1H) ; 7.01 (m, 1H) ; 7.54 (m, 1H).

3-chloro-4-fluoro-N-methylaniline

To a solution of N-(tert-butyloxycarbonyl)-3-chloro-4-fluoroaniline (250 mg, 1.02 mmol) in THF (4 ml) at 0°C was added sodium hydride (60 %, 45 mg, 1.12 mmol), and the mixture was stirred for 20 minutes. Methyl iodide (70 µl, 1.12 mmol) was added to the mixture which was stirred at room temperature for 4 hours. The solvent was evaporated, a saturated solution of sodium chloride was added, and the mixture was extracted with CH_2Cl_2, dried, and purified by silica gel chromatography, ether / petroleum ether, 8/2 to give compound (235 mg). This compound was dissolved in CH_2Cl_2(2 ml) and TFA (2 ml), H_2O (200 µl) was added, the mixture was stirred for 1 hour at room temperature, the solvent was evaporated, to give title compound (256 mg, 89 %).

^{1}HNMR ($CDCl_3$) : 2.98 (s, 3H) ; 7.3 (m, 3H).

Example 365. Preparation of compound 542 in Table 18

An analogous reaction to that described in example 240 but starting with ethyl-2-(3-chloro-4-fluoroaniline)acetate (151 mg, 0.65 mmol) yielded title compound (10 mg, 4.5 %).

MS ES$^+$: 673.6 $(M+H)^+$

^{1}H NMR (DMSOd$_6$, TFA): 1.18 (t, 3H) ; 2.30 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.83 (s, 1H) ; 3.97 (s, 3H) ; 4.03 (m, 4H) ; 4.13 (s, 2H) ; 4.29 (t, 2H) ; 4.41 (s, 1H) ; 7.30 (s, 1H) ; 7.44 (s, 1H) ; 7.55 (m, 2H) ; 7.78 (m, 1H) ; 7.87 (s, 1H) ; 9.06 (s, 1H).

Example 366. Preparation of compound 543 in Table 18

An analogous reaction to that described in example 240 but starting with 2-anilinoacetonitrile (371 mg, 2.72 mmol) yielded title compound (110 mg, 18 %).

MS ES$^+$: 574.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.77 (s, 1H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 4.81 (s, 2H) ; 7.31 (s, 1H) ; 7.43 (s, 1H) ; 7.57 (m, 5H) ; 7.88 (s, 1H) ; 9.09 (s, 1H).

Example 367. Preparation of compound 544 in Table 18

An analogous reaction to that described in example 240 but starting with 3-anilinoacetonitrile (335 mg, 2.18 mmol) yielded title compound (100 mg, 18 %).

MS ES$^+$: 588.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.29 (t, 2H) ; 2.75 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (m, 4H) ; 3.95 (t, 2H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.42 (s, 1H) ; 7.48 (m, 3H) ; 7.55 (m, 2H) ; 7.87 (s, 1H) ; 9.08 (s, 1H).

Example 368. Preparation of compound 545 in Table 18

An analogous reaction to that described in example 240 but starting with N-(2-tert-butylethyl)-3-chloro-4-fluoroaniline (346 mg, 1.42 mmol) yielded title compound (147 mg, 30 %).

MS ES$^+$: 687.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 1.08 (s, 9H) ; 2.31 (t, 2H) ; 3.14 (t, 2H) ; 4.3-4.5 (m, 4H) ; 3.55 (d, 2H) ; 3.68 (m, 6H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.30 (s, 1H) ; 7.41 (s, 1H) ; 7.51 (m, 2H) ; 7.78 (m, 1H) ; 7.87 (s, 1H) ; 9.06 (s, 1H).

N-(2-hydroxyethyl)-3-chloro-4-fluoroaniline.

ethyl-2-(3-chloro-4-fluoroanilino)acetate (J. Med. Chem. 1965, 405-407) (2 g, 8.6 mmol) in THF (15 ml) ether (10 ml) was treated with Li Al H4 (460 mg, 12.1 mmol) at 40°C for 4 hours. The mixture was then poured onto ice, treated with NaOH (2N, 10 ml), extracted with ethyl acetate, dried, evaporated to give title compound (1.48 g, 90 %).

^{1}H NMR ($CDCl_3$) : 1.67 (s, 1H) ; 3.24 (t, 2H) ; 3.84 (t, 2H) ; 3.92 (s, 1H) ; 6.47 (m, 1H) ; 6.64 (m, 1H) ; 6.95 (t, 1H).

N-(2-tert-butoxyethyl)-3-chloro-4-fluoroaniline

N-2-hydroxyethyl-3-chloro-4-fluoroaniline (1.48 g, 7.81 mmol) in CH_2Cl_2 (20 ml) was reacted with N,N-diisopropyl O-tert-butyl-isourea (6.25 g, 31.2 mmol) at room temperature over night. The product was purified by silicagel chromatography, Eluant, ether / petroleum ether 5/95, 10/90 to give title compound (1.15 g, 60 %).

^{1}H NMR ($CDCl_3$) : 1.20 (s, 9H) ; 3.18 (t, 2H) ; 3.55 (t, 2H) ; 4.00 (s, 1H) ; 6.44 (m, 1H) ; 6.62 (m, 1H) ; 6.93 (t, 1H).

Example 369. Preparation of compound 546 in Table 18

An analogous reaction to that described in example 240 but starting with N-allylaniline (0.3 ml, 2.18 mmol) yielded title compound (252 mg, 50 %).

MS ES$^+$: 575.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (m, 4H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.28 (m, 4H) ; 5.12 (m, 2H) ; 5.82 (m, 1H) ; 7.30 (s, 1H) ; 7.38 (m, 3H) ; 7.40 (s, 1H) ; 7.51 (m, 2H) ; 7.87 (s, 1H) ; 9.07 (s, 1H).

Example 370. Preparation of compound 547 in Table 18

An analogous reaction to that described in example 240 but starting with N-ethyl-3,4-(methylenedioxy)aniline (320 µl, 2.18 mmol) yielded title compound (351 mg, 66 %).

MS ES$^+$: 607.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 1.04 (t, 3H) ; 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (m, 6H) ; 3.97 (s, 3H) ; 4.09 (d, 2H) ; 4.29 (t, 2H) ; 6.12 (s, 2H) ; 6.83 (d, 1H) ; 7.02 (m, 2H) ; 7.30 (s, 1H) ; 7.42 (s, 1H) ; 7.86 (s, 1H) ; 9.06 (s, 1H).

Example 371. Preparation of compound 548 in Table 18

An analogous reaction to that described in example 240 but starting with ethyl-4-(N-butylamino)benzoate (482 mg, 2.18 mmol) yielded title compound (58 mg, 10 %).

MS ES$^+$: 663.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 0.85 (t, 3H) ; 1.32 (m, 7H) ; 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.70 (m, 6H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 4.35 (s, 2H) ; 7.30 (s, 1H) ; 7.41 (s, 1H) ; 7.54 (d, 2H) ; 7.87 (s, 1H) ; 8.07 (d, 2H) ; 9.07 (s, 1H).

Example 372. Preparation of compound 549 in Table 18

An analogous reaction to that described in example 240 but starting with N-ethyl-m-toluidine (294 mg, 2.18 mmol) yielded title compound (294 mg, 58 %).

MS ES$^+$: 577.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 1.05 (t, 9H) ; 2.31 (t, 2H) ; 2.38 (s, 3H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.67 (m, 6H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.18 (m, 2H) ; 7.28 (d, 1H) ; 7.30 (s, 1H) ; 7.39 (s, 1H) ; 7.42 (d, 1H) ; 7.86 (s, 1H) ; 9.07 (s, 1H).

Example 373. Preparation of compound 550 in Table 18

Compound 245 (120 mg) in CH_2Cl_2 (2 ml) was treated with TFA (3 ml) and H_2O (200 µl) at room temperature for 3 hours. The solvent was evaporated to give title compound (45 mg, 41 %).

MS ES$^+$: 631.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA) : 2.29 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.51 (t, 2H) ; 3.54 (d, 2H) ; 3.70 (m, 6H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.42 (s, 1H) ; 7.54 (m, 2H) ; 7.78 (d, 1H) ; 7.87 (s, 1H) ; 9.06 (s, 1H).

Example 374. Preparation of compound 551 in Table 19

4-((2-amino-4-methyl-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (118 mg, 0.25 mmol) in DMF (1.5 ml) was reacted with aniline (32 mg, 0.35 mmol) in presence of O-(7-azabenzotriazol-1-yl) -N,N,N',N'-tetramethyluronium hexafluorophosphate (142 mg, 0.375 mmol) and DIEA (65 mg, 0.5 mmol) at 65° over night. The mixture was cooled, sodium bicarbonate was added, and the resulting mixture was evaporated. The residue was dissolved in CH_2Cl_2 / MeOH 92/8 and purified by chromatography over alumina, Eluant CH_2Cl_2, CH_2Cl_2 /MeOH 98/2 to 95/5 a second purification over silicagel was performed, Eluant CH_2Cl_2 /MeOH 95/5 to 90/10 to give title compound (86 mg, 62 %).

MS ES$^+$: 549.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.34 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.72 (t, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ;(4.03) ; (d, 2H) ; 4.30 (t, 2H) ; 7.08 (t, 2H) ; 7.29 (s, 1H) ; 7.31 (t, 2H) ; 7.62 (d, 2H) ; 7.85 (s, 1H) ; 9.05 (s, 1H).

4-(ethyl(2-amino-4-methyl-1,3-thiazole-5-yl)acetate)-6-methoxy-7-(3-morpholinopropoxy)quinazoline

N'-(2-cyano-4-methoxy-5-(3-morpholinopropoxy)phenyl)-N,N-dimethylimidoformamide (1.38 g, 4 mmol) in acetic acid was reacted with ethyl-2-amino-4-methyl-1,3-thiazole-5-yl)acetate at reflux for 3.5 hours. The mixture was cooled, evaporated, HCl (1N) was added and the mixture extracted with ethylacetate. Sodium bicarbonate was cautiously added to the aqueous phase, which was extracted with ethylacetate. The organic fractions were dried, evaporated, the residue was purified by chromatography over alumina, Eluant CH_2Cl_2, CH_2Cl_2 /AcOEt 1/1, CH_2Cl_2 /AcOEt/MeOH 50/45/5 to give starting material as a yellow solid. (1.12 g, 52 %).

MS ES$^+$: 502.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 1.24 (t, 3H) ; 2.28 (m, 5H) ; 3.15 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3:92 (s, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.15 (q, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.86 (s, 1H) ; 9.05 (s, 1H).

4-((2-amino-4-methyl-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline

4-(ethyl(2-amino-4-methyl-1,3-thiazole-5-yl)acetate)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (1.1 g, 2.2 mmol) in ethanol (11 ml) was treated with NaOH (2N, 5.5 ml, 11 mmol) at room temperature for 1 hour. The mixture was then acidified with HCl (2N) to pH 3. The solution was evaporated, the solid suspended in CH_2Cl_2 (8 ml) MeOH (6 ml), and DIEA was added (852 mg, 6.6 mmol). The mixture was stirred for 10 minutes, filtered. The filtrate was concentrated, ethanol was added and the solid recovered to give title compound (980 mg, 94 %).

MS ES$^+$: 474.5 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.28 (m, 5H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.70 (t, 2H) ; 3.83 (s, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.86 (s, 1H) ; 9.05 (s, 1H).

Example 375. Preparation of compound 552 in Table 19

An analogous reaction to that described in example 251 but starting with 3-chloro-4-fluoroaniline (51 mg, 0.35 mmol) yielded the title compound (60 mg, 40 %).

MS ES$^+$: 601.5 $(M+H)^+$

^{1}H NMR (DMSOd$_6$, TFA): 2.30 (t, 2H) ; 2.33 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; (3.55) (d, 2H) ; 3.69 (t, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.28 (s, 1H) ; 7.39 (t, 1H) ; 7.49 (m, 1H) ; 7.86 (s, 1H) ; 7.96 (m, 1H) ; 9.05 (s, 1H).

Example 376. Preparation of compound 553 in Table 19

An analogous reaction to that described in example 251 but starting with 2-aminopyridine (33 mg, 0.35 mmol) yielded the title compound (45 mg, 32 %).

MS ES$^+$: 550.6 $(M+H)^+$

^{1}H NMR (DMSOd$_6$, TFA): 2.31 (t, 2H) ; 2.35 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.98 (s, 3H) ; 4.04 (m, 4H) ; 4.30 (t, 2H) ; 7.30 (m, 2H) ; 7.87 (s, 1H) ; 7.95 (d, 1H) ; 8.05 (m, 1H) ; 8.40 (d, 1H) ; 9.04 (s, 1H).

Example 377. Preparation of compound 554 in Table 19

An analogous reaction to that described in example 251 but starting with 3,4 difluoroaniline (50 mg, 0.39 mmol) yielded the title compound (120 mg, 74 %).

MS ES$^+$: 585.6 $(M+H)^+$

^{1}H NMR (DMSOd$_6$, TFA) : 2.30 (t, 2H) ; 2.33 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.67 (t, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.05 (d, 2H) ; 4.31 (t, 2H) ; 7.28 (s, 1H) ; 7.32 (m, 1H) ; 7.40 (q, 1H) ; 7.80 (m, 1H) ; 7.86 (s, 1H) ; 9.05 (s, 1H).

Compound 378. Preparation of compound 555 in Table 20

N'-(2-cyano-5-((2S)-2-hydroxy-3-piperidinylpropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide (381 mg, 0.96 mmol) in acetic acid (6 ml) was irradiated in a microwave oven in presence of N-(4-fluoro-3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (275 mg, 0.96 mmol) at reflux for 0.5 hour. The solvent was evaporated, and the residue purified by silica gel chromatography, eluant CH_2Cl_2 / MeOH sat. NH_3 95/5 to 93/7 to give title compound (230 mg, 40 %).

MS ES$^+$: 601.5 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA) : 1.42 (m, 1H) ; 1.6-1.9 (m, 5H) ; 3.02 (m, 2H) ; 3.28 (m, 2H) ; 3.52 (m, 2H) ; 3.99 (s, 5H) ; 4.19 (d, 2H) ; 4.43 (m, 1H) ; 7.35 (s, 1H) ; 7.40 (t, 1H) ; 7.48 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.95 (m, 1H) ; 9.08 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-piperidinylpropoxy)-4-methoxyphenyl)-N,N,-dimethylimidoformamide.

N'-(2-cyano-5-(2S)-oxiranylmethoxy-4-methoxyphenyl)-N,N-dimethylimidoformamide (850 mg, 3.09 mmol) in chloroform (6 ml) and ethanol (12 ml) was irradiated with piperidine (0.46 ml, 4.6 mmol) in a microwave oven at reflux for 10 minutes. The solvent was evaporated and the residue was purified by silica gel chromatography, eluant CH_2Cl_2 / MeOH 90/10 to give title compound (954 mg, 86 %).

MS ES^+: 361.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.43 (m, 6H) ; 2.4 (m, 6H) ; 2.97 (s, 3H) ; 3.06 (s, 3H) ; 3.75 (s, 3H) ; 3.95 (d, 2H) ; 4.03 (m, 1H) ; 4.83 (s, 1H) ; 6.75 (s, 1H) ; 7.10 (s, 1H) ; 7.90 (s, 1H).

N'-(2-cyano-5-(2S)-oxiranylmethoxy-4-methoxyphenyl)-N,N-dimethylimidoformamide.

N'-(2-cyano-4-methoxy-5-hydroxyphenyl)-N,N-dimethyl-imidoformamide (1 g, 4.57 mmol) in DMF (25 ml) was reacted with (2S) glycidyl toxylate (1.15 g, 5.02 mmol) in presence of cesium carbonate (5.95 g, 18.3 mmol) at 60°C under argon for 2 hours. The solvent was evaporated, water was added, and the mixture was extracted with ethylacetate, dried, concentrated and purified by silica gel chromatography, eluant CH_2Cl_2 / AcOEt 80/20 to 70/30 to give title compound (1.18 g, 94 %).

MS ES^+: 276.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.70 (m, 1H) ; 2.86 (m, 1H) ; 2.95 (s, 3H) ; 3.01 (s, 3H) ; 3.35 (m, 1H) ; 3.75 (s, 3H) ; 3.90 (m, 1H) ; 4.37 (m, 1H) ; 6.75 (s, 1H) ; 7.11 (s, 1H) ; 7.89 (s, 1H).

methyl-(2-tritylamino-1,3-thiazole-5-yl)acetate

Methyl-(2-amino-1,3-thiazole-5-yl)acetate (1 g, 5.8 mmol) in CH_2Cl_2 (15 ml) was reacted with triphenylmethyl chloride (1.73 g, 6.2 mmol) and triethylamine (0.89 ml, 6.4 mmol) at 0°C for 1.5 hour. Water was added to the mixture which was extracted with ethyl acetate, dried, purified by silica gel chromatography to give title compound (2.21 g, 91 %).

^{1}HNMR ($DMSOd_6$): 3.58 (s, 3H) ; 3.59 (s, 2H) ; 6.57 (s, 1H) ; 7.23 (m, 15H) ; 8.40 (s, 1H).

(2-tritylamino-1,3-thiazol-5-yl)acetic acid

Methyl(2-tritylamino-1,3-thiazole-5-yl)acetate (2 g, 4.8 mmol) in THF (10 ml) and ethanol (10 ml) was reacted with sodium hydroxyde (1N, 7.2 ml, 7.2 mmol) at room temperature for 1.5 hour. The solvent was evaporated, HCl (6N) was added, the solid recovered by filtration to give title compound (1.96 g).

^{1}HNMR ($DMSOd_6$): 3.63 (s, 2H) ; 5.70 (s, 1H) ; 7.32 (m, 15H).

N-(4-fluoro-3-chlorophenyl)-2-tritylamino-1,3-thiazole-5-yl)acetamide

(2-tritylamino-1,3-thiazol-5-yl)acetic acid (1.96 g, 4.9 mmol) in DMF (25 ml) was reacted with 3-chloro-4-fluoroaniline (1.07 g, 7.3 mmol) in presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (2.42 g, 6.37 mmol) and DIEA (1.7 ml, 9.8 mmol) at 50°C for 18 hours. DMF was evaporated, the residue taken up in CH_2Cl_2 / EtOAc, washed with a saturated solution of sodium bicarbonate. The solid precipitating in the organic phase was recovered, the organic phase was evaporated, MeOH was added to the residue to give a solid, a second crop of title compound was thus recovered to give together (1.38 g, 53 %).

^{1}HNMR ($DMSOd_6$): 3.56 (s, 2H) ; 6.61 (s, 1H) ; 7.28 (m, 17H) ; 7.88 (m, 1H) ; 8.41 (s, 1H).

N-(4-fluoro-3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide

N-(4-fluoro-3-chlorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide (12.28 g, 23 mmol) was dissolved in TFA (100 ml) and water (10 ml). The mixture was stirred at room temperature for 45 minutes. Water (300 ml) was added to the reaction mixture, a solid was recovered by filtration, washed with water and ether. The solid was dissolved in MeOH, and the solution treated with ammonia (pH 8), MeOH was then partially evaporated, water (300 ml) was added and a precipitate of title compound recovered, dried (5.37 g, 81 %).

^{1}HNMR ($DMSOd_6$): 3.64 (s, 2H) ; 6.76 (m, 3H) ; 7.38 (t, 1H) ; 7.48 (m, 1H) ; 7.92 (m, 1H).

Example 379. Preparation of compound 556 in Table 20

An analogous reaction to that described in example 255 but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-pyrrolidinylpropoxy)-4-methoxyphenyl)-N,N,-dimethylimido-formamide (267 mg, 0.77 mmol) yielded title compound (213 mg, 52 %).

MS ES$^+$: 587.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.68 (m, 4H) ; 2.5 (m, 5H) ; 2.66 (m, 1H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.00 (m, 1H) ; 4.07 (m, 1H) ; 4.20 (m, 1H) ; 4.95 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (s, 1H) ; 7.37 (m, 1H) ; 7.47 (m, 1H) ; 7.95 (m, 1H) ; 8.11 (s, 1H) ; 8.66 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-pyrrolinylpropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide.

An analogous reaction to that described in example 255, but starting with pyrrolidine (1.4 ml, 16 mmol) yielded title compound (2.8 g, 74 %).

MS ES$^+$: 347.6 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 1.67 (m, 4H) ; 1.45 (m, 4H) ; 1.63 (m, 2H) ; 2.95 (s, 3H) ; 3.05 (s, 3H) ; 3.73 (s, 3H) ; 3.95 (m, 2H) ; 4.04 (m, 1H) ; 4.93 (m, 1H) ; 6.73 (s, 1H) ; 7.08 (s, 1H) ; 7.89 (s, 1H).

Example 380. Preparation of compound 557 in Table 20

An analogous reaction to that described in example 255 but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-(4-hydroxypiperidinyl)propoxy)-4-methoxy-phenyl)-N,N-dimethylimidoformamide (195 mg, 0.52 mmol) yielded title compound (88 mg, 30 %).

MS ES$^+$: 617.5, 619.5 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.40 (m, 2H) ; 1.70 (m, 2H) ; 2.13 (m, 2H) ; 2.43 (m, 2H) ; 2.77 (m, 2H) ; 3.43 (m, 1H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.03 (m, 2H) ; 4.19 (m, 1H) ; 4.52 (d, 1H) ; 4.87 (m, 1H) ; 7.27 (s, 1H) ; 7.39 (m, 2H) ; 7.49 (m, 1H) ; 7.99 (m, 1H) ; 8.67 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-(4-hydroxypiperidinyl)propoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide

An analogous reaction to that described in example 255, but starting with 4-hydroxypiperidine (131 mg, 1.27 mmol) yielded title compound (200 mg, 58 %).

MS ES$^+$: 377.6 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.39 (m, 2H) ; 1.68 (m, 2H) ; 2.10 (m, 2H) ; 2.40 (m, 2H) ; 2.75 (m, 2H) ; 2.95 (s, 3H) ; 3.05 (s, 3H) ; 3.21 (s, 3H) ; 3.31 (m, 1H) ; 3.95 (m, 2H) ; 4.00 (m, 1H) ; 4.52 (m, 1H) ; 4.82 (m, 1H) ; 6.73 (s, 1H) ; 7.08 (s, 1H) ; 7.88 (s, 1H).

Example 381. Preparation of compound 558 in Table 20

An analogous reaction to that described in example 255a, but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-(4-tert-butyloxycarbonylpiperazinyl)propoxy)-4-methoxtphenyl)-N,N-dimethylimidoformamide (355 mg, 0.77 mmol) yielded title compound (70 mg, 17 %).

MS ES$^+$: 602.4 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 2.42 (m, 6H) ; 2.73 (d, 4H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.04 (m, 2H) ; 4.19 (m, 1H) ; 4.90 (m, 1H) ; 7.28 (s, 1H) ; 7.37 (m, 2H) ; 7.47 (m, 1H) ; 7.94 (m, 1H) ; 8.11 (s, 1H) ; 8.66 (s, 1H) .

N'-(2-cyano-5-((2S)-2-hydroxy-3-(4-tert-butyloxycarbonylpiperazinyl)propoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide.

An analogous reaction to that described in example 255, but starting with tert-butyloxycarbonylpiperazine (284 mg, 1.53 mmol) yielded title compound (444 mg, 88 %).

MS ES$^+$: 462.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.39 (s, 9H) ; 2.40 (m, 6H) ; 2.95 (s, 3H) ; 3.04 (s, 3H) ; 3.30 (m, 4H) ; 3.72 (s, 3H) ; 3.95 (m, 2H) ; 4.02 (m, 1H) ; 4.91 (d, 1H) ; 6.74 (s, 1H) ; 7.09 (s, 1H) ; 7.88 (s, 1H).

Example 382. Preparation of compound 559 in Table 20

An analogous reaction to that described in example 255 , but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-cyclopentylaminopropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide (290 mg, 0.77 mmol) yielded title compound (226 mg, 54 %).

MS ES$^+$: 601.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.32 (m, 2H) , 1.48 (m, 2H) ; 1.62 (m, 2H) ; 1.73 (m, 2H) ; 2.63 (m, 1H) ; 2.71 (m, 1H) ; 3.05 (m, 1H) ; 3.89 (s, 2H) ; 3.98 (m, 4H) ; 4.09 (m, 1H) ; 4.17 (m, 1H) ; 5.03 (m, 1H) ; 7.27 (s, 1H) ; 7.40 (m, 2H) ; 7.51 (m, 1H) ; 7.97 (m, 1H) ; 8.12 (s, 1H) ; 8.67 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-cyclopentylaminopropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide.

An analogous reaction to that described in example 255, but starting with cyclopentylamine (2.7 ml, 27 mmol) yielded title compound (1.6 g, 82 %).

MS ES$^+$: 361.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.30 (m, 2H) ; 1.48 (m, 2H) ; 1.60 (m, 2H) ; 1.72 (m, 2H) ; 2.56 (m, 1H) ; 2.67 (m, 1H) ; 2.97 (s, 3H) ; 3.01 (m, 1H) ; 3.07 (s, 3H) ; 3.75 (s, 3H) ; 3.89 (m, 1H) ; 4.00 (m, 2H) ; 5.01 (m, 1H) ; 6.75 (s, 1H) ; 7.10 (s, 1H) ; 7.91 (s, 1H).

Example 383. Preparation of compound 560 in Table 20

An analogous reaction to that described in example 255, but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-((2-hydroxy-1,1-dimethylethyl)amino)propoxy-4-methoxyphenyl)-N,N-dimethylimidoformamide (350 mg, 0.77 mmol) yielded title compound (147 mg, 34 %).

MS ES$^+$: 305.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 0.97 (s, 3H) ; 0.98 (s, 3H) ; 2.63 (m, 2H) ; 3.19 (dd, 2H) ; 3.89 (m, 3H) ; 3.98 (s, 3H) ; 4.10 (m, 1H) ; 4.18 (m, 1H) ; 4.56 (m, 1H) ; 7.29 (s, 1H) ; 7.39 (m, 2H) ; 7.50 (m, 1H) ; 7.97 (m, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-((2-hydroxy-1,1-dimethylethyl)amino)propoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide.

An analogous reaction to that described in example 255, but starting with 2-amino-2-methyl-1-propanol (1.8 ml, 18.2 mmol) yielded title compound (1.25 g, 93 %).

^{1}HNMR (DMSOd_6): 0.93 (s, 3H) ; 0.94 (s, 3H) ; 2.58 (m, 2H) ; 3.19 (m, 2H) ; 3.73 (s, 3H) ; 3.80 (m, 1H) ; 3.97 (m, 1H) ; 4.03 (m, 1H) ; 4.50 (m, 1H) ; 4.95 (m, 1H) ; 6.75 (s, 1H) ; 7.10 (s, 1H) ; 7.91 (s, 1H).

Example 384. Preparation of compound 561 in Table 20

An analogous reaction to that described in example 255, but starting with N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) and acetic acid (3 ml) yielded title compound (263 mg, 60 %).

MS ES$^+$: 585.5 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.37 (m, 2H) ; 1.50 (m, 4H) ; 2.41 (m, 6H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.03 (m, 2H) ; 4.18 (d, 1H) ; 4.88 (m, 1H) ; 7.28 (s, 1H) ; 7.40 (s, 1H) ; 7.40 (m, 2H) ; 7.80 (m, 1H) ; 8.11 (s, 1H) ; 8.66 (s, 1H).

N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 255, but starting with N-(3,4-difluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide (1,75 g, 3.42 mmol) yielded title compound (642 mg, 70 %).

^{1}HNMR (DMSOd_6): 3.62 (s, 2H) ; 6.73 (s, 1H) ; 6.74 (s, 2H) ; 7.28 (m, 1H) ; 7.37 (q, 1H) ; 7.77 (m, 1H).

N-(3,4-difluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 255, but starting with 3,4-difluoroaniline (0.97 ml, 9.75 mmol) yielded title compound (1.75 g, 46 %).

MS ES$^+$: 512.5 $(M+H)^+$

^{1}HNMR (DMSOd_6): 3.54 (s, 2H) ; 6.58 (s, 1H) ; 7.25 (m, 17H) ; 7.71 (m, 1H) ; 8.39 (s, 1H).

Example 385. Preparation of compound 562 in Table 20

An analogous reaction to that described in example 256 but starting with N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (226 mg, 53 %).

MS ES$^+$: 571.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.70 (m, 4H) ; 2.52 (m, 5H) ; 2.68 (m, 1H) ; 3.89 (s, 2H) ; 3.98 (s, 3H) ; 4.06 (m, 2H) ; 4.21 (m, 1H) ; 4.95 (m, 1H) ; 7.28 (s, 1H) ; 7.33 (m, 1H) ; 7.39 (s, 1H) ; 7.40 (m, 1H) ; 7.81 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 386. Preparation of compound 563 in Table 20

An analogous reaction to that described in example 257, but starting with N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (220 mg, 49 %).

MS ES$^+$: 601.5$(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H) ; 1.70 (m, 2H) ; 2.12 (m, 2H) ; 2.40 (m, 2H) ; 2.78 (m, 2H) ; 3.43 (m, 1H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.03 (m, 2H) ; 4.18 (m, 1H) ; 4.51 (d, 1H) ; 4.87 (m, 1H) ; 7.27 (s, 1H) ; 7.32 (m, 1H) ; 7.38 (s, 1H) ; 7.40 (m, 1H) ; 7.80 (m, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H).

Example 387. Preparation of compound 565 in Table 20

An analogous reaction to that described in example 259, but starting with N-(3,4-difluorophenyl)-2-(2(amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (233 mg, 53 %).

MS ES$^+$: 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.32 (m, 2H) ; 1.47 (m, 2H) ; 1.61 (m, 2H) ; 1.72 (m, 2H) ; 2.63 (m, 1H) ; 2.72 (m, 1H) ; 3.05 (m, 1H) ; 3.89 (s, 2H) ; 3.97 (m, 4H) ; 4.09 (m, 1H) ; 4.16 (m, 1H) ; 5.05 (m, 1H) ; 7.27 (s, 1H) ; 7.34 (m, 1H) ; 7.38 (s, 1H) ; 7.42 (m, 1H) ; 7.82 (m, 1H) ; 8.12 (s, 1H) ; 8.67 (s, 1H).

Example 388. Preparation of compound 566 in Table 20

An analogous reaction to that described in example 256 but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (238 mg, 56 %).

MS ES$^+$: 569.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.70 (s, 1H) ; 2.52 (m, 5H) ; 2.68 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.06 (m, 2H) ; 4.21 (m, 1H) ; 4.97 (m, 1H) ; 7.14 (d, 1H) ; 7.27 (s, 1H) ; 7.37 (m, 2H) ; 7.48 (d, 1H) ; 7.85 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 255, but starting with N-(3-chlorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide (3.62 g, 7.1 mmol) yielded title compound (1.6 g, 84 %).

^{1}HNMR ($DMSOd_6$): 3.63 (s, 2H) ; 6.74 (m, 3H) ; 7.11 (m, 1H) ; 7.33 (t, 1H) ; 7.42 (d, 1H) ; 7.79 (m, 1H).

N-(3-chlrophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 255, but starting with 3-chloroaniline (1.4 ml, 13 mmol) yielded title compound (3.62 g, 71 %).

^{1}HNMR ($DMSOd_6$): 3.55 (s, 2H) ; 6.59 (s, 1H) ; 7.21 (m, 18H) ; 7.76 (m, 1H) ; 8.39 (s, 1H).

Example 389. Preparation of compound 567 in Table 20

An analogous reaction to that described in example 257, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.75 mmol) yielded title compound (156 mg, 35 %).

MS ES$^+$: 599.4, 601.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H) ; 1.70 (m, 2H) ; 2.12 (m, 2H) ; 2.42 (m, 2H) ; 2.77 (m, 2H) ; 3.42 (m, 1H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.02 (m, 2H) ; 4.18 (m, 1H) ; 4.52 (d, 1H) ; 4.89 (m, 1H) ; 7.12 (d, 1H) ; 7.26 (s, 1H) ; 7.35 (t, 1H) ; 7.38 (s, 1H) ; 7.46 (d, 1H) ; 7.84 (m, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H).

Example 390. Preparation of compound 568 in Table 20

An analogous reaction to that described in example 259, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.75 mmol) yielded title compound (255 mg, 58 %).

MS ES$^+$: 583.5, 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.32 (m, 2H) ; 1.48 (m, 2H) ; 1.62 (m, 2H) ; 1.73 (m, 2H) ; 2.63 (m, 1H) ; 2.72 (m, 1H) ; 3.04 (m, 1H) ; 3.90 (s, 2H) ; 3.97 (m, 4H) ; 4.09 (m, 1H) ; 4.16 (m, 1H) ; 5.05 (m, 1H) ; 7.12 (d, 1H) ; 7.27 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 391. Preparation of compound 569 in Table 20

An analogous reaction to that described in example 260, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (130 mg, 30 %).

MS ES$^+$: 587.5, 589.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 0.97 (s, 6H) ; 2.63 (m, 2H) ; 3.19 (m, 2H) ; 3.90 (m, 3H) ; 3.98 (s, 3H) ; 4.10 (m, 1H) ; 4.18 (m, 1H) ; 4.55 (m, 1H) ; 5.03 (m, 1H) ; 7.13 (d, 1H) ; 7.29 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (d, 1H) ; 7.86 (m, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H).

Example 392. Preparation of compound 570 in Table 20

An analogous reaction to that described in example 258, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.75 mmol) yielded title compound (211 mg, 48 %).

MS ES$^+$: 584.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.37 (m, 6H) ; 2.70 (m, 4H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.05 (m, 2H) ; 4.19 (m, 1H) ; 4.90 (m, 1H) ; 7.12 (d, 1H) ; 7.27 (s, 1H) ; 7.35 (t, 1H) ; 7.37 (s, 1H) ; 7.47 (d, 1H) ; 7.84 (m, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H).

Example 393. Preparation of compound 571 in Table 20

An analogous reaction to that described in example 266, but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-methoxy)propoxy-4-methoxyphenyl)-N,N-dimethyl imidoformamide (252 mg, 0.82 mmol) yielded title compound (200 mg, 50 %).

MS ES$^+$: 530.4, 532.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 3.22 (s, 3H) ; 3.42 (m, 2H) ; 3.91 (s, 2H) ; 3.98 (s, 2H) ; 4.10 (m, 3H) ; 5.21 (d, 1H) ; 7.13 (d, 1H) ; 7.26 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (d, 1H) ; 7.85 (m, 1H) ; 8.13 (m, 1H) ; 8.69 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-methoxy)propoxy-4-methoxy-phenyl)-N,N-dimethylimidoformamide.

N'-(2-cyano-5-(2S)-oxiranylmethoxy-4-methoxyphenyl)-N,N-dimethylimidoformamide (1 g, 3.6 mmol) in methanol (80 ml) was treated with sodium methoxide (10 g, 218 mmol) at reflux in a microwave oven for 0.5 hour. The solvent was evaporated and the mixture purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH 95/5 to give title compound (896 mg, 80 %).

^{1}HNMR ($DMSOd_6$): 2.97 (s, 1H) ; 3.07 (s, 1H) ; 3.29 (s, 1H) ; 3.38 (m, 2H) ; 3.75 (s, 3H) ; 3.98 (m, 3H) ; 5.16 (d, 1H) ; 6.75 (s, 1H) ; 7.10 (s, 1H) ; 7.93 (s, 1H).

Example 394. Preparation of compound 572 in Table 20

An analogous reaction to that described in example 255, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.75 mmol) yielded title compound (268 mg, 61 %).

MS ES$^+$: 583.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.38 (m, 2H) ; 1.50 (m, 4H) ; 2.43 (m, 6H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.05 (m, 2H) ; 4.21 (m, 1H) ; 4.88 (m, 1H) ; 7.14 (d, 1H) ; 7.29 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (d, 1H) ; 7.85 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 395. Preparation of compound 573 in Table 20

An analogous reaction to that described in example 255, but starting with N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (157 mg, 36 %).

MS ES$^+$: 585.5 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.37 (m, 2H) ; 1.50 (m, 4H) ; 2.40 (m, 6H) ; 3.90 (s, 2H) ; 3.96 (s, 3H) ; 4.05 (m, 2H) ; 4.19 (m, 1H) ; 4.88 (m, 1H) ; 6.92 (m, 1H) ; 7.28 (s, 1H) ; 7.34 (m, 2H) ; 7.38 (s, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H).

N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl) acetamide

An analogous reaction to that described in example 255, but starting with N-(3,5-difluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide (11.4 g, 28.5 mmol) yielded title compound (4.75 g, 62 %).

^{1}HNMR (DMSOd_6: 3.64 (s, 2H) ; 6.74 (s, 1H) ; 6.76 (s, 2H) ; 6.89 (m, 1H) ; 7.29 (m, 2H).

N-(3,5-difluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 255, but starting with 3,5-difluoroaniline (1.68 g, 13 mmol) yielded title compound (3.53 g, 69 %).

^{1}HNMR (DMSOd_6: 3.56 (s, 2H) ; 6.59 (s, 1H) ; 6.90 (m, 1H) ; 7.28 (m, 17H) ; 8.40 (s, 1H).

Example 396. Preparation of compound 574 in Table 20

An analogous reaction to that described in example 256 but starting with N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (200 mg, 47 %).

MS ES$^+$: 571.5 $(M+H)^+$

^{1}HNMR (DMSOd_6: 1.65 (m, 4H) ; 2.50 (m, 5H) ; 2.65 (m, 1H) ; 3.91 (s, 1H) ; 3.96 (s, 3H) ; 4.04 (m, 2H) ; 4.20 (m, 1H) ; 4.95 (m, 1H) ; 6.92 (m, 1H) ; 7.26 (s, 1H) ; 7.34 (m, 2H) ; 7.38 (s, 1H) ; 8.11 (s, 1H) ; 8.66 (s, 1H).

Example 397. Preparation of compound 575 in Table 20

An analogous reaction to that described in example 260 but starting with N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (177 mg, 40 %).

MS ES$^+$: 589.4 $(M+H)^+$

^{1}HNMR (DMSOd_6: 0.96 (s, 3H) ; 0.97 (s, 3H) ; 2.64 (m, 2H) ; 3.19 (dd, 2H) ; 3.92 (m, 3H) ; 3.98 (s, 3H) ; 4.09 (m, 1H) ; 4.20 (m, 1H) ; 4.56 (m, 1H) ; 5.05 (m, 1H) ; 6.94 (m, 1H) ; 7.29 (s, 1H) ; 7.35 (m, 2H) ; 7.39 (s, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 398. Preparation of compound 576 in Table 20

An analogous reaction to that described in example 258 but starting with N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (40 mg, 9 %).

MS ES^+: 628.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$: 2.05 (s, 3H) ; 2.40 (m, 4H) ; 2.57 (m, 2H) ; 2.69 (m, 4H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.35 (m, 2H) ; 5.31 (m, 1H) ; 6.93 (m, 1H) ; 7.33 (s, 1H) ; 7.35 (m, 2H) ; 7.39 (s, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H).

Example 399. Preparation of compound 577 in Table 20

An analogous reaction to that described in example 258 but starting with N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (192 mg, 44 %).

MS ES^+: 586.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$: 2.42 (m, 6H) ; 2.74 (m, 4H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.09 (m, 2H) ; 4.20 (m, 1H) ; 4.92 (m, 1H) ; 6.93 (m, 1H) ; 7.29 (s, 1H) ; 7.35 (m, 2H) ; 7.39 (s, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 400. Preparation of compound 578 in Table 20

An analogous reaction to that described in example 256 but starting with N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.8 mmol) yielded title compound (156 mg, 35 %).

MS ES^+: 553.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$: 1.70 (m, 4H) ; 2.5 (m, 5H) ; 2.67 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.06 (m, 2H) ; 4.20 (m, 1H) ; 4.97 (m, 1H) ; 6.92 (m, 1H) ; 7.28 (m, 1H) ; 7.35 (m, 2H) ; 7.39 (s, 1H) ; 7.63 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide

An analogous reaction to that described in example 255 but starting with N-(3-fluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide (14.6 g, 38.4 mmol) yielded title compound (6.21 g, 65 %).

^{1}HNMR ($DMSOd_6$: 3.65 (s, 2H) ; 6.76 (m, 3H) ; 6.89 (t, 1H) ; 7.35 (m, 2H) ; 7.59 (d, 1H).

N-(3-fluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 255 but starting with 3-fluoroaniline yielded title compound (14.6 g, 79 %).

^{1}HNMR (DMSOd_6: 3.56 (s, 2H) ; 6.61 (s, 1H) ; 6.89 (t, 1H) ; 7,25 (m, 17H) ; 7.56 (d, 1H) ; 8.41 (s, 1H).

Example 401. Preparation of compound 579 in Table 20

An analogous reaction to that described in example 255 but starting with N-(3-fluororphenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.8 mmol) yielded title compound (214 mg, 47 %).

MS ES$^+$: 567.6 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.38 (m, 2H) ; 1.52 (m, 4H) ; 2.42 (m, 6H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.04 (m, 2H) ; 4.20 (m, 1H) ; 4.89 (m, 1H) ; 6.91 (m, 1H) ; 7.29 (s, 1H) ; 7.37 (m, 2H) ; 7.39 (s, 1H) ; 7.63 (m, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H).

Example 402. Preparation of compound 580 in Table 20

An analogous reaction to that described in example 258 but starting with N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.8 mmol) yielded title compound (210 mg, 46 %).

MS ES$^+$: 568.5 $(M+H)^+$

^{1}HNMR (DMSOd_6: 2.38 (m, 6H) ; 2.70 (m, 4H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.02 (m, 2H) ; 4.19 (m, 1H) ; 4.98 (m, 1H) ; 6.89 (m, 1H) ; 7.27 (s, 1H) ; 7.32 (m, 2H) ; 7.37 (s, 1H) ; 7.61 (m, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H).

Example 403. Preparation of compound 581 in Table 20

An analogous reaction to that described in example 258 but starting with N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.8 mmol) yielded title compound (35 mg, 7 %).

MS ES$^+$: 610.5 $(M+H)^+$

^{1}HNMR (DMSOd_6: 2.03 (s, 3H) ; 2.38 (m, 4H) ; 2.57 (m, 2H) ; 2.69 (m, 4H) ; 3.88 (s, 2H) ; 3.95 (s, 3H) ; 4.34 (m, 2H) ; 5.30 (m, 1H) ; 6.89 (m, 1H) ; 7.31 (s, 1H) ; 7.34 (m, 2H) ; 7.37 (s, 1H) ; 7.62 (m, 1H) ; 8.11 (s, 1H) ; 8.66 (s, 1H).

Example 404. Preparation of compound 582 in Table 20

An analogous reaction to that described in example 259 but starting with N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.8 mmol) yielded title compound (196 mg, 43 %).

MS ES$^+$: 567.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 1.30 (m, 2H) ; 1.47 (m, 2H) ; 1.61 (m, 2H) ; 1.73 (m, 3H) ; 2.62 (m, 1H) ; 2.71 (m,1H) ; 3.0 (m, 1H) ; 3.89 (m, 1H) ; 3.97 (s, 3H) ; 4.07 (m, 1H) ; 4.13 (m, 1H) ; 5.03 (m, 1H) ; 6.90 (m, 1H) ; 7.25 (s, 1H) ; 7.35 (m, 2H) ; 7.37 (s, 1H) ; 7.62 (m, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H).

Example 405. Preparation of compound 583 in Table 21

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6,7-dimethoxyquinazoline (173 mg, 0.5 mmol) in NMP (2 ml) was reacted with 3,5-difluoroaniline (98 mg, 0.75 mmol) in the presence of 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (285 mg, 0.75 mmol) and DIEA (130 µl, 0.75 mmol) at 50°C for 20 hours. The mixture was cooled, dimethylamine (2M MeOH, 2 ml) was added, and the resulting solution was stirred at room temperature for 15 hours, MeOH was evaporated, and water (20 ml) added to the mixture, the precipitate was recovered, washed with water, and purified by silicagel chromatography, eluant CH_2Cl_2 / MeOH 50/40/10 to give title compound (22 mg, 10 %).

^{1}HNMR ($DMSOd_6$) : 3.90 (s, 2H) ; 3.95 (s, 6H) ; 6.93 (t, 1H) ; 7.26 (s, 1H) ; 7.34 (d, 2H) ; 7.39 (s, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6,7-dimethoxyquinazoline

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6,7-dimethoxyquinazoline (3.92 g, 10.9 mmol) in ethanol 50 ml was treated with sodium hydroxyde (2N, 27 ml, 54.5 mmol) for 45 minutes. The solvent was evaporated, the residue dissolved in CH_2Cl_2 / MeOH triethylamine (3 eq.) was added the solid removed by filtration, the filtrate was evaporated and triturated with ethanol to give title compound as a solid (1.88 g, 50 %).

^{1}HNMR ($DMSOd_6$) : 3.83 (s, 2H) ; 3.96 (s, 6H) ; 7.27 (s, 1H) ; 7.35 (s, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H).

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6,7-dimethoxyquinazoline

N'-(2-cyano-4,5-dimethoxyphenyl)-N,N-dimethylimidoformamide (3.5 g, 15 mmol) in acetic acid (35 ml) was reacted with methyl (2-amino-1,3-thiazole-5-yl)acetate (3.22 g, 18.7 mmol)

at reflux for 4 hours. The solvent was evaporated and the residue purified by silicagel chromatography, Eluant CH_2Cl_2 / MeOH 95/5 to give title compound (3.92 g, 73 %).
^{1}HNMR ($DMSOd_6$) : 3.69 (s, 3H) ; 3.95 (s, 2H) ; 3.96 (s, 6H) ; 7.27 (s, 1H) ; 7.38 (s, 1H) ; 8.12 (s, 1H) ; 8.69 (s, 1H).

Example 406. Preparation of compound 584 in Table 21

An analogous reaction to that described in example 283 but starting with 3-chloroaniline (80 µl, 0.75 mmol) yielded title compound (81 mg, 26 %).
MS ES$^+$: 456.4, 458.4 $(M+H)^+$
^{1}HNMR ($DMSOd_6$) : 3.91 (s, 2H) ; 3.96 (s, 6H) ; 7.14 (d, 1H) ; 7.28 (s, 1H) ; 7.37 (t, 1H) ; 7.48 (d, 1H) ; 7.85 (m, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H).

Example 407. Preparation of compound 585 in Table 21

An analogous reaction to that described in example 283 but starting 3-chloro-4-fluoroaniline (110 mg, 0.75 mmol) yielded title compound (93.7 mg, 40 %).
MS ES$^+$: 474.4, 476.4 $(M+H)^+$
^{1}HNMR : 3.90 (s, 2H) ; 3.97 (s, 3H) ; 7.28 (s, 1H) ; 7.40 (m, 1H) ; 7.40 (s, 1H) ; 7.50 (m, 1H) ; 7.96 (m, 1H) ; 8.14 (s, 1H) ; 8.70 (s, 1H).

Example 408. Preparation of compound 586 in Table 21

An analogous reaction to that described in example 283 but starting 3,4-difluoroaniline (75 mg, 0.75 mmol) yielded title compound (130 mg, 60 %).
MS ES$^+$: 458.5 $(M+H)^+$
^{1}HNMR : 3.89 (s, 2H) ; 3.97 (s, 6H) ; 7.28 (s, 1H) ; 7.33 (m, 1H) ; 7.40 (s, 1H) ; 7.41 (m, 1H) ; 7.82 (m, 1H) ; 8.14 (s, 1H) ; 8.69 (s, 1H).

Example 409. Preparation of compound 587 in Table 22

4-((2-amino-1,3-thiazole-5-yl)(hydroxy)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (143 mg, 0.3 mmol) in DMF (4 ml) was reacted with aniline (36 mg, 0.39 mmol) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (63 mg, 0.33 mmol), 2-hydroxypyridine N-oxyde (33 mg, 0.3 mmol) and DIEA (36 mg, 0.3 mmol) at 90°C for 1 hour. The mixture was cooled, diluted with CH_2Cl_2 (8 ml) and purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH 90/10 to 85/15. The combined fractions

containing product were evaporated, the residue was dissolved in MeOH, water was added and the precipitate recovered, dissolved in MeOH / CH_2Cl_2, dried, concentrated to give title compound (145 mg, 88 %).

MS ES$^+$: 551.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.71 (t, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.31 (t, 2H) ; 5.47 (s, 1H) ; 7.11 (t, 1H) ; 7.31 (s, 1H) ; 7.33 (t, 2H) ; 7.70 (s, 1H) ; 7.73 (d, 2H) ; 7.92 (s, 1H) ; 9.12 (s, 1H).

4-(2-amino-1,3-thiazole-5-yl)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.

N'-(2-cyano-4-methoxy-5-(3-morpholinopropoxy)phenyl)-N,N-dimethylimidoformamide (692 mg, 2 mmol) was reacted with amino-1,3-thiazole (240 mg, 2.4 mmol) in acetic acid (6.9 ml) at reflux for 4 hours. The mixture was concentrated, the residue dissolved in AcOEt, washed with aqueous sodium bicarbonate, the organic phase was dried, concentrated, the residual oil triturated in ether to give a solid (560 mg, 70 %).

MS ES$^+$: 402.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.29 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.31 (t, 2H) ; 7.32 (s, 1H) ; 7.47 (d, 1H) ; 7.75((d, 1H) ; 7.95 (s, 1H) ; 9.11 (s, 1H).

4-((2-amino-1,3-thiazole-5-yl)(hydroxy)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.

4-(2-amino-1,3-thiazole-5-yl)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (1.6 g, 4 mmol) in water (16 ml), MeOH (16 ml), was reacted with glyoxylic acid (740 mg, 8 mmol) at pH 11.5 (NaOH 6N) and 45-50°C for 6 hours. Methanol was evaporated, and the pH of the aqueous phase adjusted to 3 (HCl 6N), and the solution poured on a strong cation exchanger (isolute®) column, washed with water (120 ml), methanol (120 ml) and eluted with CH_2Cl_2/ MeOH, NH_3 (3N) 1/1 200 ml to give title compound (1.58 g, 83 %).

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.15 (t,2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.30 (t, 2H) ; 5.38 (s, 1H) ; 7.32 (s, 1H) ; 7.68 (s, 1H) ; 7.91 (s, 1H) ; 9.12 (s, 1H).

Example 410. Preparation of compound 588 in Table 22

An analogous reaction to that described in example 287 but starting with 3,4(difluoroaniline (34 mg, 0.26 mmol) yielded title compound (30 mg, 26 %).

MS ES$^+$: 587.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.69 (t, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 5.48 (s, 1H) ; 7.32 (s, 1H) ; 7.40 (q, 1H) ; 7.57 (m, 1H) ; 7.70 (s, 1H) ; 7.92 (m, 2H) ; 9.12 (s, 1H).

Example 411. Preparation of compound 589 in Table 22

N'-(2-cyano-4-methoxy-5-(3-N-methylpiperazinylpropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide (144 mg, 0.4 mmol) was reacted with N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)-2-hydroxyacetamide (137 mg, 0.4 mmol) in acetic acid (350 µl) at reflux for 40 minutes. The solvent was removed, and the residue purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH / Et3N, 90.10.1 to give title compound (180 mg, 37 %).

MS ES$^+$: 600.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.30 (t, 2H) ; 5.48 (s, 1H) ; 7.32 (s, 1H) ; 7.40 (q, 1H) ; 7.57 (m, 1H) ; 7.70 (s, 1H) ; 7.92 (m, 2H) ; 9.12 (s, 1H).

Methyl(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)acetate

Methyl(2-amino-1,3-thiazol-5-yl)acetate (4.3 g, 25 mmol) was reacted with di-tert-butyl dicarbonate (10.9 g, 50 mmol) neat, at 100°C for 2 hours. The cold mixture was triturated in ether to give title compound as a solid (4.3 g, 63 %).

^{1}HNMR (DMSOd_6): 1.48 (s, 9H) ; 3.66 (s, 3H) ; 3.86 (s, 2H) ; 7.17 (s, 1H).

Methyl(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)(oxo)acetate.

Methyl(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)acetate (4.08 g, 15 mmol) in dioxane (60 ml) was reacted with selenium dioxide (4 g, 36 mmol) at reflux for 45 minutes. The mixture was cooled, CH_2Cl_2 / MeOH 8/2 (150 ml) was added, the insoluble material was filtered, the organic phase was washed with a saturated solution of sodium bicarbonate, and extracted with CH_2Cl_2, dried, purified by chromatography over alumina, eluant CH_2Cl_2 / MeOH 9/1 to give title compound (1 g, 23 %).

^{1}HNMR (DMSOd_6): 1.57 (s, 9H) ; 3.94 (s, 3H) ; 8.48 (s, 1H).

(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)(oxo)acetic acid.

Methyl(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)(oxo)acetate (1.14 g, 4 mmol) in ethanol (10 ml) was treated with sodium hydroxyde (2N, 4 ml, 8 mmol) for 3M minutes at room temperature. Ethanol was removed, the aqueous solution was acidified (pH 3). The solid was recovered, dried to give title product (900 mg, 82 %).

^{1}HNMR (DMSOd_6): 1.53 (s, 9H) ; 8.41 (s, 1H).

N-(3,4-difluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)(oxo)acetamide

2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)(oxo)acetic acid (136 mg, 0.5 mmol) in DMF (2 ml) was reacted with 3,4-difluoroaniline (77 mg, 0.6 mmol) in presence of 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (203 mg, 0.55 mmol) and DIEA (77 mg, 0.6 mmol) for 15 minutes. The mixture was diluted with water, the solid was filtered, washed with water, dried, to give title compound (162 mg, 84 %).

^{1}HNMR (DMSOd_6): 1.53 (s, 9H) ; 7.48 (q, 1H) ; 7.68 (m, 1H) ; 7.98 (m, 1H) ; 8.61 (s, 1H).

N-(3,4-difluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide.

N-(3,4-difluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl) (oxo) acetamide (938 mg, 2.4 mmol) in THF (50 ml) and MeOH (10 ml) was treated with sodium borohydride (93 mg, 2.4 mmol) for 30 minutes. The mixture was evaporated, the residue dissolved in ethanol (3 ml) water (25 ml) was added, and the pH adjusted to 6, more water was added, a solid was recovered, dried, recristalized in ether / petroleum ether to give title compound (850 mg, 90 %).

^{1}HNMR (DMSOd_6): 1.48 (s, 9H) ; 5.34 (d, 1H) ; 6.78.(d, 1H) ; 7.33 (s, 1H) ; 7.40 (s, 1H) ; 7.56 (m, 1H) ; 7.90 (m, 1H).

N-(3,4-difluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide (847 mg, 2.2 mmol) in CH_2Cl_2 (12 ml) and TFA (4 ml) was stirred at room temperature for 3 hours. The solvent was evaporated, the residue dissolved in MeOH / H_2O, the pH adjusted to 7 and the mixture was extracted with ethyl acetate. The organic layer was dried, evaporated, the residue was triturated in ether, the solid filtered to give title compound (515 mg, 82 %).

^{1}HNMR (DMSOd_6): 5.17.(d, 1H) ; 6.51 (d, 1H) ; 6.91 (m, 3H) ; 7.39 (s, 1H) ; 7.52 (m, 1H) ; 7.87 (m, 1H).

Example 412. Preparation of compound 590 in Table 22

N'-(2-cyano-4-methoxy-5-(3-piperidinylpropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide (100 mg, 0.29 mmol) was reacted with N-(3-fluorophenyl)-2-(2-

amino-1,3-thiazole-5-yl)-2-hydroxyacetamide (82 mg, 0.3 mmol) in acetic acid (260 mg) at 105°C for 40 minutes. The mixture was evaporated and purified by silica gel chromatography, eluant CH_2Cl_2 / MeOH (NH_3 3N) 9/1 to give title compound (42 mg, 26 %).

MS ES^+: 567.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.4 (m, 2H) ; 1.51 (m, 4H) ; 1.95 (t, 2H) ; 2.40 (m, 6H) ; 3.95 (s, 3H) ; 4.19 (t, 2H) ; 5.41 (d, 1H) ; 6.78 (d, 1H) ; 6.91 'm, 1H) ; 7.25 (s, 1H) ; 7.35 (q, 1H) ; 7.50 (s, 1H) ; 7.55 (d, 1H) ; 7.71 (m, 1H) ; 8.10 (s, 1H) ; 8.68 (s, 1H).

N'-(2-cyano-4-methoxy-5-(3-piperidinylpropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide.

N'-(2-cyano-4-methoxy-5-(3-chloropropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide (3 g, 10 mmol) in acetonitrile (50 ml) was reacted with piperidine (10 ml, 100 mmol) in presence of KI (300 mg, 1.8 mmol) and K_2CO_3 (2.1 g, 0.015 mmol) at 75°C under argon for 3 hours. The solvent was evaporated, and the residue purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH, NH_3 3N 95/5 to give title compound (3.48 g, 100 %).

MS ES^+: 345.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.4 (m, 2H) ; 1.50 (m, 4H) ; 1.88 (m, 2H) ; 2.35 (m, 6H) ; 2.95 (s, 3H) ; 3.05 (s, 3H) ; 3.72 (s, 3H) ; 4.05 (t, 2H) ; 6.72 (s, 1H) ; 7.07 (s, 1H) ; 7.89 (s, 1H).

N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)-2-hydroxyacetomide.

An analogous reaction to that described in example 289, but starting with N-(3-fluorobenzyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide (2.55 g, 0.69 mmol) yielded title compound (1.37 g, 75 %).

MS ES^+: 268.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 5.16 (d, 1H) ; 6.45 (d, 1H) ; 6.90 (m, 4H) ; 7.34 (q, 1H) ; 7.49 (d, 1H) ; 7.70 (m, 1H).

N-(3-fluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide.

An analogous reaction to that described in example 289, but starting with N-(3-fluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl) (oxo) acetamide (2.92 g, 8 mmol) yielded title compound (2.59 g, 88 %).

^{1}HNMR ($DMSOd_6$): 1.48 (s, 9H) ; 5.34 (d, 1H) ; 6.74 (d, 1H) ; 6.90 (m, 1H) ; 7.33 (m, 2H) ; 7.54 (d, 1H) ; 7.70 (m, 1H).

N-(3-fluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl) (oxo) acetamide.

An analogous reaction to that described in example 289, but starting with 3-fluoroaniline (1.6 g, 14.4 mmol) yielded title compound (4.06 g, 93 %).

^{1}HNMR (DMSOd$_6$): 1.54 (s, 9H) ; 7.01 (m, 1H) ; 7.42 (m, 1H) ; 7.69 (m, 1H) ; 7.80 (m, 1H) ; 8.6 (s, 1H).

Example 413. Preparation of compound 591 in Table 22

An analogous reaction to that described in example 290, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)-2-hydroxyacetamide (99 mg, 0.35 mmol) yielded title compound (47 mg, 23 %).

MS ES$^+$: 583.4 $(M+H)^+$

^{1}HNMR (DMSOd$_6$) : 1.38 (m, 2H) ; 1.51 (m, 4H) ; 1.95 (m, 2H) ; 2.38 (m, 6H) ; 3.95 (s, 3H) ; 4.19 (t, 2H) ; 5.40 (d, 1H) ; 6.79 (d, 1H) ; 7.14 (d, 1H) ; 7.24 (s, 1H) ; 7.35 (t, 1H) ; 7.50 (s, 1H) ; 7.67 (d, 1H) ; 7.95 (s, 1H) ; 8.10 (s, 1H) ; 8.68 (s, 1H).

N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)-2-hydroxyacetamide.

An analogous reaction to that described in example 290, but starting with N-(3-chlorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide (2.13 g, 5.5 mmol) yielded title compound (1.02 g, 65 %).

^{1}HNMR (DMSOd$_6$): 5.15 (d, 1H) ; 6.45 (d, 1H) ; 6.90 (m, 3H) ; 7.12 (dd, 1H) ; 7.33 (t, 1H) ; 7.62 (d, 1H) ; 7.89 (m, 1H).

N-(3-chlorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide.

An analogous reaction to that described in example 290, but starting with N-(3-chlorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl) (oxo) acetamide (2.5 g, 6.5 mmol) yielded title compound (2.23 g, 89 %).

^{1}HNMR (DMSOd$_6$): 1.48 (s, 9H) ; 5.34 (d, 1H) ; 6.74 (d, 1H) ; 7.14 (m, 1H) ; 7.34 (m, 2H) ; 7.65 (m, 1H) ; 7.92 (m, 1H).

N-(3-chlorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl) (oxo) acetamide.

An analogous reaction to that described in example 290, but starting with 3-chloroaniline (1.84 g, 14 mmol) yielded title compound (3.6 g, 79 %).

^{1}HNMR (DMSOd$_6$): 1.54 (s, 9H) ; 7.24 (d, 1H) ; 7.43 (t, 1H) ; 7.79 (d, 1H) ; 8.03 (s, 1H) ; 8.61 (s, 1H).

Example 414. Preparation of compound 592 in Table 22

N'-(2(cyano-4-methoxy-5-(N-methyl-3-piperazinylpropoxyphenyl)-N,N-dimethylimidoformamide (140 mg, 0.39 mmol) in acetic acid (0.5 ml) in presence of N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)-2-(hydroxyimino)acetamide (116 mg, 0.39 mmol) was heated at 110°C for 16 hours. The mixture was concentrated and purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH, HN_3 3N 95/5 to 90/10, to give title compound (23 mg, 10 %).

MS ES^+: 613.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.0 (m, 2H) ; 2.22 (s, 3H) ; 2.47 (m, 10H) ; 4.0 (s, 3H) ; 4.22 (t, 2H) ; 7.29 (m, 1H) ; 7.47 (m, 1H) ; 7.57 (m, 1H) ; 7.97 (m, 1H) ; 8.2 (s, 1H) ; 8.38 (s, 1H) ; 8.80 (s, 1H).

N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazol-5-yl)-2-(hydroxyimino)acetamide.

N-(3,4-difluorophenyl)-2-(2-tert-butoxycarbonyl-amino-1,3-thiazol-5-yl)-2-(hydroxyimino)acetamide (600 mg, 1.5 mmol) in CH_2Cl_2 (12 ml) and TFA (4 ml) was stirred at room temperature for 2 hours. The mixture was evaporated, dissolved in methanol, the pH adjusted to 6 with sodium bicarbonate, water was added, the precipitate recovered, dried to give title compound (388 mg, 86 %).

MS ES^+ : 299.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) mixture of isomers 7.05, 7.8 (2s, 1H) ; 7.43 (m, 4H) ; 7.88 (m, 1H).

N-(3,4-difluorophenyl)-2-(2-tert-butoxycarbonyl-amino-1,3-thiazole-5-yl)-2-(hydroxyimino)acetamide.

N-(3,4-difluorophenyl)-2-(2-tert-butoxycarbonyl-amino-1,3-thiazole-5-yl) (oxo) acetamide (100 mg, 0.26 mmol) in pyridine (8 ml) was reacted with hydroxylamine hydrochloride (27 mg, 0.39 mmol) at 70°C for 15 hours. The solvent was evaporated, water was added to the residue, the solid was filtered, washed with water, dried to give title compound (84 mg, 81 %).

^{1}HNMR ($DMSOd_6$) mixture of isomers 7.41, 8.18 (2s, 1H) ; 7.50 (m, 2H) ; 7.90 (m, 1H).

Example 415. Preparation of compound 593 in Table 23

5-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)thiophene-2-carboxylic acid (80 mg, 0.18 mmol) in DMF (2 ml) was reacted with 2-aminopyridine (17 mg, 0.18 mmol) in presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (70 mg, 0.18 mmol) and DIEA (80 µl, 0.46 mmol), at 50°C for 6 hours. A saturated solution

of sodium bicarbonate (2 ml) was added and the mixture stirred for 0.5 hour. A solid is recovered by filtration, washed with water, dried to give title compound (15 mg, 16 %).

MS ES$^+$: 521 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.32 (t, 2H) ; 7.43 (m, 2H) ; 7.53 (t, 1H) ; 7.94 (d, 1H) ; 8.21 (m, 2H) ; 8.35 (t, 1H) ; 8.49 (d, 1H) ; 9.30 (s, 1H).

Example 416. Preparation of compound 594 in Table 23

An analogous reaction to that described in example 293, but starting with 4-methylaniline (19 mg, 0.18 mmol) yielded title compound (69 mg, 72 %).

MS ES$^+$: 535 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.34 (s, 3H) ; 2.40 (t, 2H) ; 3.11 (t, 2H) ; 3.38 (t, 2H) ; 3.60 (d, 2H) ; 3.90 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.35 (t, 2H) ; 7.15 (d, 2H) ; 7.27 (d, 1H) ; 7.52 (s, 1H) ; 7.62 (d, 2H) ; 7.85 (d, 1H) ; 8.15 (s, 1H) ; 8.87 (s, 1H).

Example 417. Preparation of compound 595 in Table 23

An analogous reaction to that described in example 293, but starting 2-methylaniline (19 mg, 0.18 mmol) yielded title compound (28 mg, 29 %).

MS ES$^+$: 535 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2/28 (s, 3H) ; 2.32 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.05 (d, 2H) ; 4.07 (s, 3H) ; 7.30 (m, 4H) ; 7.35 (d, 1H) ; 7.41 (s, 1H) ; 7.96 (d, 1H) ; 8.22 (s, 1H) ; 9.26 (s, 1H).

Example 418. Preparation of compound 596 in Table 23

An analogous reaction to that described in example 293, but starting 3-methoxyaniline (22 mg, 0.18 mmol) yielded title compound (14 mg, 14 %).

MS ES$^+$: 550.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 3.78 (s, 3H) ; 4.04 (d, 2H) ; 4.06 (s, 3H) ; 4.33 (t, 2H) ; 6.7 (d, 1H) ; 7.28 (s, 1H) ; 7.35 (s, 1H) ; 7.36 (d, 1H) ; 7.41 (s, 1H) ; 7.45 (s, 1H) ; 8.01 (d, 1H) ; 8.22 (s, 1H) ; 9.27 (s, 1H).

Example 419. Preparation of compound 597 in Table 23

An analogous reaction to that described in example 293, but starting 2-hydroxymethyl-aniline (22 mg, 0.18 mmol) yielded title compound (7 mg, 7 %).

MS ES$^+$: 550.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.31 (m, 2H) ; 3.18 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.06 (m, 5H) ; 4.32 (t, 2H) ; 4.65 (s, 2H) ; 7.22 (t, 1H) ; 7.32 (t, 1H) ; 7.37 (d, 1H) ; 7.40 (s, 1H) ; 7.46 (d, 1H) ; 7.72 (d, 1H) ; 7.81 (d, 1H) ; 8.22 (s, 1H) ; 9.27 (s, 1H).

Example 420. Preparation of compound 598 in Table 23

An analogous reaction to that described in example 293, but starting 3-nitroaniline (25 mg, 0.18 mmol) yielded title compound (6 mg, 6 %).

MS ES$^+$: 565.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.70 (t, 2H) ; 4.05 (d, 2H) ; 4.07 (s, 3H) ; 4.33 (t, 2H) ; 7.39 (d, 1H) ; 7.42 (s, 1H) ; 7.68 (t, 1H) ; 7.98 (d, 1H) ; 8.08 (d, 1H) ; 8.20 (m, 1H) ; 8.23 (s, 1H) ; 8.77 (s, 1H) ; 9.3 (s, 1H).

Example 421. Preparation of compound 599 in Table 23

An analogous reaction to that described in example 293, but starting 4-trifluoromethylaniline (29 mg, 0.18 mmol) yielded title compound (8 mg, 8 %).

MS ES$^+$: 588.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (m, 2H) ; 3.19 (t, 2H) ; 3.41 (t, 2H) ; 3.61 (d, 2H) ; 3.75 (t, 2H) ; 4.05 (d, 2H) ; 4.08 (s, 1H) ; 4.37 (t, 2H) ; 7.39 (d, 1H) ; 7.43 (s, 1H) ; 7.72 (d, 2H) ; 8.03 (d, 2H) ; 8.10 (d, 1H) ; 8.23 (s, 1H) ; 9.29 (s, 1H).

Example 422. Preparation of compound 600 in Table 23

An analogous reaction to that described in example 293, but starting 3-chloroaniline (23 mg, 0.18 mmol) yielded title compound (21 mg, 21 %).

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (m, 2H) ; 3.19 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 4.03 (d, 2H) ; 4.07 (s, 3H) ; 4.34 (t, 2H) ; 7.17 (d, 1H) ; 7.37 (t, 1H) ; 7.40 (m, 2H) ; 7.70 (d, 1H) ; 7.95 (m, 1H) ; 8.02 (d, 1H) ; 8.22 (s, 1H) ; 9.29 (s, 1H).

Example 423. Preparation of compound 601 in Table 23

An analogous reaction to that described in example 293, but starting 2-methoxyaniline (22 mg, 0.18 mmol) yielded title compound (32 mg, 32 %).

^{1}HNMR (DMSOd_6, TFA): 2.35 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 3.87 (s, 3H) ; 4.05 (d, 2H) ; 4.06 (s, 3H) ; 4.34 (t, 2H) ; 6.99 (t, 1H) ; 7.11 (d, 1H) ; 7.20 (s, 1H) ; 7.33 (d, 1H) ; 7.40 (s, 1H) ; 7.73 (dd, 1H) ; 7.97 (d, 1H) ; 8.22 (s, 1H) ; 9.27 (s, 1H).

Example 424. Preparation of compound 602 in Table 23

An analogous reaction to that described in example 293, but starting 3-(2-hydroxyethyl) aniline (25 mg, 0.18 mmol) yielded title compound (27 mg, 26 %).

MS ES$^+$: 564.7 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.37 (d, 3H) ; 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.62 (t, 2H) ; 4.06 (d, 2H) ; 4.08 (s, 3H) ; 4.36 (t, 2H) ; 4.76 (q, 1H) ; 7.08 (d, 1H) ; 7.29 (t, 1H) ; 7.35 (d, 1H) ; 7.42 (s, 1H) ; 7.70 (d, 1H) ; 7.76 (s, 1H) ; 8.05 (d, 1H) ; 8.23 (s, 1H) ; 9.28 (s, 1H).

Example 425. Preparation of compound 603 in Table 23

An analogous reaction to that described in example 293, but starting 3-fluoro-4-methoxyaniline (25 mg, 0.18 mmol) yielded title compound (14 mg, 14 %).

MS ES$^+$: 568.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.38 (t, 2H) ; 3.57 (d, 2H) ; 3.72 (t, 2H) ; 3.85 (s, 3H) ; 4.04 (d, 2H) ; 4.07 (s, 3H) ; 4.35 (t, 2H) ; 7.17 (t, 1H) ; 7.36 (d, 1H) ; 7.42 (s, 1H) ; 7.47 (dd, 1H) ; 7.73 (dd, 1H) ; 7.98 (d, 1H) ; 8.24 (s, 1H) ; 9.27 (s, 1H).

Example 426. Preparation of compound 604 in Table 23

An analogous reaction to that described in example 293, but starting 2-methyl-4-fluoroaniline (23 mg, 0.18 mmol) yielded title compound (27 mg, 27 %).

MS ES$^+$: 552.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.28 (s, 3H) ; 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.57 (d, 2H) ; 3.71 (t, 2H) ; 4.05 (d, 2H) ; 4.07 (s, 3H) ; 7.07 (dt, 1H) ; 7.15 (dd, 1H) ; 7.35 (d, 1H) ; 7.36 (m, 1H) ; 7.41 (s, 1H) ; 7.95 (d, 1H) ; 8.23 (s, 1H) ; 9.26 (s, 1H).

Example 427. Preparation of compound 605 in Table 23

An analogous reaction to that described in example 293, but starting 2-fluoro-5-methylaniline (23 mg, 0.18 mmol) yielded title compound (9 mg, 9 %).

MS ES$^+$: 552.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.33 (m, 5H) ; 3.19 (t, 2H) ; 3.38 (t, 2H) ; 3.56 (d, 2H) ; 3.71 (t, 2H) ; 4.04 (d, 2H) ; 4.07 (s, 3H) ; 4.35 (t, 2H) ; 7.09 (m, 1H) ; 7.18 (m, 1H) ; 7.35 (d, 1H) ; 7.40 (s, 1H) ; 7.41 (m, 1H) ; 8.0 (d, 1H) ; 8.23 (s, 1H) ; 9.27 (s, 1H).

Example 428. Preparation of compound 606 in Table 23

An analogous reaction to that described in example 293, but starting 3-cyanoaniline (21 mg, 0.18 mmol) yielded title compound (9 mg, 9 %).

MS ES$^+$: 545.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (t, 2H) ; 3.21 (t, 2H) ; 3.39 (t, 2H) ; 3.60 (d, 2H) ; 3.72 (t, 2H) ; 4.07 (d, 2H) ; 4.10 (s, 3H) ; 4.37 (t, 2H) ; 7.40 (d, 1H) ; 7.44 (s, 1H) ; 7.62 (s, 1H) ; 7.63 (m, 1H) ; 8.06 (m, 1H) ; 8.06 (d, 1H) ; 8.26 (s, 1H) ; 8.30 (s, 1H) ; 9.32 (s, 1H).

Example 429. Preparation of compound 607 in Table 23

An analogous reaction to that described in example 293, but starting isoamylamine (16 mg, 0.18 mmol) yielded title compound (15 mg, 17 %).

MS ES$^+$: 514.7 $(M+H)^+$

^{1}HNMR ($CDCl_3$) : 0.96 (d, 6H) ; 1.77 (m, 5H) ; 2.11 (m, 2H) ; 2.5 (m, 4H) ; 2.56 (t, 2H) ; 3.73 (m, 4H) ; 4.03 (s, 3H) ; 4.22 (t, 2H) ; 6.05 (t, 1H) ; 6.88 (d, 1H) ; 7.24 (s, 1H) ; 7.39 (d, 1H) ; 7.58 (s, 1H) ; 8.70 (s, 1H).

Example 430. Preparation of compound 608 in Table 23

An analogous reaction to that described in example 293, but starting 2-chloroaniline (23 mg, 0.18 mmol) yielded title compound (5 mg, 5 %).

MS ES$^+$: 554.5, 556.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 4.04 (d, 2H) ; 4.07 (s, 3H) ; 4.34 (t, 2H) ; 7.32 (t, 1H) ; 7.36 (d, 1H) ; 7.41 (s, 1H) ; 7.41 (t, 1H) ; 7.57 (d, 1H) ; 7.63 (d, 1H) ; 8.0 (d, 1H) ; 8.23 (s, 1H) ; 9.27 (s, 1H).

Example 431. Preparation of compound 609 in Table 24

An analogous reaction to that described in example 293, but starting with 5-((6-methox-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)thiophene-3-carboxylic acid (80 mg, 0.18 mmol) and aniline (20 µl, 0.22 mmol) yielded title compound (28 mg, 30 %).

MS ES$^+$: 520 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.56 (d, 2H) ; 3.71 (t, 2H) ; 4.05 (d, 2H) ; 4.06 (s, 3H) ; 4.34 (t, 2H) ; 7.12 (t, 1H) ; 7.37 (t, 2H) ; 7.40 (s, 1H) ; 7.76 (d, 1H) ; 7.79 (d, 2H) ; 8.18 (s, 1H) ; 8.21 (d, 1H) ; 9.17 (s, 1H).

5-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)thiophene-3-carboxylic acid.

Ethyl-5-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino thiophene-3-carboxylate (1.05 g, 2.2 mmol) in methanol (10 ml) was treated with sodium hydroxyde (2N, 10 ml) at 75°C for 1.5 hour. Methanol was evaporated, HCl (2N) was added (pH 3) the solid filtered, redissolved in CH_2Cl_2 / MeOH 1/1, DIEA (1.5 ml, 8.8 mmol) was added the solid removed by filtration, the filtrate was concentrated, and the residue dissolved in ethanol, title material was obtained as a solid (0.7 g, 71 %).

MS ES$^+$: 445 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.36 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.79 (t, 2H) ; 4.03 (d, 2H) ; 4.08 (s, 3H) ; 4.35 (t, 2H) ; 7.45 (s, 1H) ; 7.81 (s, 1H) ; 8.03 (s, 1H) ; 8.50 (s, 1H) ; 9.15 (s, 1H).

Ethyl-5-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)aminothiophene-3-carboxylate.

4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (1 g, 3 mmol) in isopropanol (25 ml) and isopropanol HCl (0.5 ml) was reacted with ethyl 5-aminothiophene-3-carboxylate (0.6 g, 3.3 mmol) at 110°C for 1 hour. The mixture was cooled, diluted with EtOAc, filtered to give title compound (1.58 g, 99 %).

MS ES$^+$: 473 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.33 (t, 3H) ; 2.33 (t, 2H) ; 3.17 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.75 (t, 2H) ; 4.03 (d, 2H) ; 4.06 (s, 3H) ; 4.30 (q, 2H) ; 4.33 (t, 2H) ; 7.42 (s, 1H) ; 7.73 (s, 1H) ; 8.09 (s, 1H) ; 8.35 (s, 1H) ; 9.15 (s, 1H).

Example 432. Preparation of compound 610 in Table 24

An analogous reaction to that described in example 309, but starting with 4-fluoroaniline (24 mg, 0.18 mmol) yielded title compound (20 mg, 22 %).

MS ES$^+$: 538.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 3.20 (t, 2H) ; 3.40 (t, 2H) ; 3.60 (d, 2H) ; 3.72 (t, 2H) ; 4.04 (d, 2H) ; 4.07 (s, 3H) ; 4.34 (t, 2H) ; 7.9 (s, 1H) ; 7.20 (m, 2H) ; 7.41 (s, 1H) ; 7.76 (d, 1H) ; 7.82 (m, 1H) ; 8.19 (s, 1H) ; 8.21 (d, 1H) ; 9.17 (s, 1H).

Example 433. Preparation of compound 611 in Table 24

An analogous reaction to that described in example 309, but starting with 3-hydroxyaniline (24 mg, 0.18 mmol) yielded title compound (15 mg, 17 %).

MS ES$^+$: 536.6 $(M+H)^+$

Example 434. Preparation of compound 612 in Table 24

An analogous reaction to that described in example 309, but starting with 3-(methylthio)aniline (30 mg, 0.18 mmol) yielded title compound (23 mg, 24 %).

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (m, 5H) ; 4.33 (t, 2H) ; 7.24 (t, 1H) ; 7.32 (t, 1H) ; 7.41 (s, 1H) ; 7.43 (m, 2H) ; 7.72 (d, 2H) ; 8.16 (m, 2H) ; 9.17 (s, 1H).

Example 435. Preparation of compound 613 in Table 24

An analogous reaction to that described in example 309, but starting with 4-fluoro-3-chloroaniline (32 mg, 0.18 mmol) yielded title compound (21 mg, 21 %).

MS ES$^+$: 577 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.71 (t, 2H) ; 4.06 (m, 5H) ; 4.34 (t, 2H) ; 7.41 (m, 2H) ; 7.75 (m, 2H) ; 8.11 (m, 1H) ; 8.18 (s, 1H) ; 8.21 B(s, 1H) ; 9.18 (s, 1H).

Example 436. Preparation of compound 614 in Table 24

An analogous reaction to that described in example 309, but starting with 2,4-difluorobenzylamine (31 mg, 0.18 mmol) yielded title compound (22 mg, 22 %).

MS ES$^+$: 570.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.34 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.06 (m, 5H) ; 4.34 (t, 2H) ; 4.51 (s, 2H) ; 7.06 (t, 1H) ; 7.15 (t, 1H) ; 7.40 (s, 1H) ; 7.48 (m, 1H) ; 7.69 (d, 1H) ; 8.03 (d, 1H) ; 8.17 (s, 1H) ; 9.14 (s, 1H).

Example 437. Preparation of compound 615 in Table 24

An analogous reaction to that described in example 309, but starting with 3-fluoroaniline (24 mg, 0.18 mmol) yielded title compound (27 mg, 29 %).

MS ES$^+$: 538.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.33 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (d, 2H) ; 4.04 (d, 2H) ; 4.07 (s, 3H) ; 4.35 (t, 2H) ; 6.91 (m, 1H) ; 7.42 (m, 2H) ; 7.59 (d, 1H) ; 7.78 (d, 1H) ; 7.79 (m, 1H) ; 8.19 (s, 1H) ; 8.24 (d, 1H) ; 9.18 (s, 1H).

Example 438. Preparation of compound 616 in Table 25

2-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)imidazole-5-carboxylic acid (200 mg, 0.47 mmol) in DMF (3 ml) was reacted with aniline (43 µl, 0.47 mmol) in presence of O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (178 mg, 0.47 mmol) and DIEA (120 µl, 0.7 mmol) at 40°C for 3 hours. A solution of dimethylamine in methanol (2M, 1 ml) was added and stirring was carried on for 3 hours. The solvent was evaporated, and the mixture was purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH NH_3 (sat.) 95/5 to give title compound (80 mg, 34 %).

MS ES$^+$: 504.1 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.29 (t, 2H) ; 3.18 (t, 2H) ; 3.35 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.96 (s, 3H) ; 4.04 (d, 2H) ; 4.27 (t, 2H) ; 7.15 (t, 1H) ; 7.25 (s, 1H) ; 7.40 (t, 2H) ; 7.74 (d, 2H) ; 7.81 (s, 1H) ; 8.09 (s, 1H) ; 8.75 (s, 1H).

Example 439. Preparation of compound 617 in Table 25

An analogous reaction to that described in example 316, but starting with 4-fluoroaniline (60 µl, 0.58 mmol) yielded title compound (120 mg, 39 %).

MS ES+ : 522.1 (M+H)+

^{1}HNMR ($DMSOd_6$, TFA) : 2.29 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 1H) ; 3.69 (t, 2H) ; 3.96 (s, 3H) ; 4.04 (d, 2H) ; 4.27 (t, 2H) ; 7.22 (m, 3H) ; 7.74 (m, 2H) ; 7.82 (s, 1H) ; 8.07 (s, 1H) ; 8.76 (s, 1H).

Example 440. Preparation of compound 618 in Table 25

An analogous reaction to that described in example 316, but starting with allylamine 50 µl, 0.7 mmol) yielded title compound (133 mg, 40 %).

MS ES$^+$: 468.1 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.28 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.94 (m, 5H) ; 4.04 (d, 2H) ; 4.26 (t, 2H) ; 5.14 (dd, 1H) ; 5.23 (dd, 1H) ; 5.88 (m, 1H) ; 7.23 (s, 1H) ; 7.77 (s, 1H) ; 7.86 (s, 1H) ; 8.71 (s, 1H).

2 -((6-methoxy-7-(3-morpholinoporpoxy)quinazolin-4-yl)amino)imidazole-5-carboxylic acid.

ethyl-2((4-imino-6-methoxy-7-(3-morpholinopropoxy)quinazolin-3-(4H)-yl)imidazole-5-carboxylate (650 mg, 1.42 mmol) in methanol (14 ml) was treated with sodium hydroxyde (2N, 14 ml) at 80°C for 1.5 hour. Methanol was evaporated, hydrochloric acid (6N) was added (pH 2.5), the precipitate was recovered by filtration, dried to give title compound (650 mg, 100 %).

^{1}HNMR (DMSOd_6, TFA) : 2.35 (t, 2H) ; 3.13 (t, 2H) ; 3.32 (t, 2H) ; 3.5 (d, 2H) ; 3.95 (m, 7H) ; 4.28 (t, 2H) ; 7.42 (s, 1H) ; 7.8 (s, 1H) ; 7.86 (s, 1H) ; 8.72 (s, 1H).

Example 441. Preparation of compound 619 in Table 26

4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (265 mg, 0.79 mmol) in 2-propanol (14 ml) was reacted with 4-amino-N-phenylthiophene-3-carboxamide hydrochloride (210 mg, 0.82 mmol) at 100°C for 2 hours. The solvent was evaporated and the residue purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH, NH_3 sat. 95/5 to give title compound (330 mg, 81 %).

MS ES$^+$: 520.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.30 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (s, 3H) ; 4.04 (d, 2H) ; 4.32 (t, 2H) ; 7.13 (t, 1H) ; 7.35 (t, 2H) ; 7.39 (s, 1H) ; 7.69 (d, 2H) ; 7.79 (s, 1H) ; 8.13 (d, 1H) ; 8.58 (d, 1H) ; 8.95 (s, 1H).

4-(tert-butoxycarbotylamino-N-phenylthiophene-3-carboxamide

4-(tert-butoxycarbonylamino)thiophene-3-carboxylic acid obtained by a literature procedure, Tetrahedron Letters 1997, 2637, (385 mg, 1.58 mmol) in DMF (5 ml) was reacted with aniline (140 µl, 1.58 mmol) in presence of 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (602 mg, 1.58 mmol) at 40°C for 7 hours. The solvent was evaporated,

and the residue purified by silica gel chromatography, Eluant petroleum ether / AcOEt : 80/20 to give title compound (348 mg, 70 %).

^{1}HNMR ($CDCl_3$) : 1.50 (s, 9H) ; 7.19 (t, 1H) ; 7.39 (t, 2H) ; 7.54 (d, 2H) ; 7.69 (s, 2H) ; 7.71 (s, 1H) ; 9.45 (s, 1H).

4-amino-N-phenylthiophene-3-carboxamide

4-(tert-butoxycarbonylamino)-N-phenylthiophene-3-carboxamide (300 mg, 0.94 mmol) in CH_2Cl_2 (3 ml) was treated with TFA (0.36 ml, 4.71 mmol) at room temperature for 2.5 hours. The solvent was evaporated, the residue was dissolved in methanol / HCl, ether was added to the solution, the precipitate was recovered to give title compound (210 mg, 87 %) which was used as is in the next step.

Example 442. Preparation of compound 620 in Table 26

An analogous reaction to that described in example 319, but starting with 4-amino-N-allylthiophene-3-carboxamide (218 mg, 1.06 mmol) yielded title compound (366 mg, 75 %).

MS ES$^+$: 484.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.28 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.95 (d, 2H) ; 4.03 (m, 5H) ; 4.32 (t, 2H) ; 5.14 (dd, 1H) ; 5.24 (dd, 1H) ; 5.91 (m, 1H) ; 7.41 (s, 1H) ; 7.59 (s, 1H) ; 8.28 (d, 1H) ; 8.51 (d, 1H) ; 9.04 (s, 1H).

4-tert-butoxycarbonylamino)-N-allylthiophene-3-carboxamide

An analogous reaction to that described in example 319, but starting with allylamine (150 µl, 2.06 mmol) yielded title compound (385 mg, 66 %).

^{1}HNMR ($CDCl_3$) : 1.51 (s, 9H) ; 4.04 (m, 2H) ; 5.21 (dd, 1H) ; 5.29 (dd, 1H) ; 5.92 (m, 1H) ; 6.1 (m, 1H) ; 7.54 (d, 1H) ; 7.64 (m, 1H) ; 9.64 (s, 1H).

4-amino-N-allylthiophene-3-carboxamide

An analogous reaction to that described in example 319, but starting with 4-tert-butoxycarboxylamino-N-allyl-thiophene-3-carboxamide (320 mg, 1.13 mmol) yielded title compound (218 mg, 94 %) which was used as is in the next step.

Example 443. Preparation of compound 621 in Table 27

4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinzaoline (100 mg, 0.29 mmol) in isopropanol (5 ml) was reacted with methyl-4-amino-thiophene-4-carboxylate hydrochloride (63.6 mg, 0.33 mmol) at reflux for 1 hour. Ethyl acetate was added to the reaction mixture, the solid was recovered by filtration, dried, to give title compound (140 mg, 89 %).

MS ES$^+$: 459.1 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.39 (t, 2H) ; 3.19 (t, 2H) ; 3.40 (t, 2H) ; 3.58 (d, 2H) ; 3.77 (m, 5H) ; 4.06 (m, 5H) ; 4.37 (t, 2H) ; 7.42 (s, 1H) ; 7.95 (s, 1H) ; 8.01 (d, 1H) ; 8.49 (d, 1H) ; 8.93 (s, 1H).

Example 444. Preparation of compound 622 in Table 28

4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (110 mg, 0.3 mmol) in 2-pentanol (5 ml) and isopropanol / HCl (55 µl) was reacted with 2-amino-5-isopropylthiophene-3-carboxamide (60 mg, 0.33 mmol) at 100°C for 1 hour, ether and ethylacetate was added to the mixture, the precipitate was filtered to give title compound (155 mg, 93 %).

MS ES$^+$: 486.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) ; 1.38 (d, 6H) ; 2.38 (t, 2H) ; 3.20 (m, 3H) ; 3.38 (t, 2H) ; 3.57 (d, 2H) ; 3.82 (t, 2H) ; 4.05 (d, 2H) ; 4.08 (s, 3H) ; 4.39 (t, 2H) ; 7.40 (s, 1H) ; 7.47 (s, 1H) ; 7.52 (s, 1H) ; 9.23 (s, 1H).

Example 445. Preparation of compound 623 in Table 28

An analogous reaction to that described in example 322 but starting with allyl-5-aminothiophene-2-carboxylate (67 mg, 0.33 mmol) at 100°C for 2 hours yielded title compound (151 mg, 85 %).

MS ES$^+$: 485.6 $(M+H)^+$

^{1}HNMR (DMSOd_6,TFA) : 2.38 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.57 (d, 2H) ; 3.80 (t, 2H) ; 4.06 (d, 2H) ; 4.12 (s, 3H) ; 4.38 (t, 2H) ; 4.84 (d, 2H) ; 5.33 (d, 1H) ; 5.45 (d, 1H) ; 6.10 (m, 1H) ; 7.48 (s, 1H) ; 7.65 (d, 1H) ; 7.84 (d, 1H) ; 8.64 (s, 1H) ; 9.30 (s, 1H).

Example 446. Preparation of compound 624 in Table 28

An analogous reaction to that described in example 322 but starting with 2-aminothiophene-3-carboxamide (46 mg, 0.33 mmol) yielded title commound (154 mg, 99 %).

MS ES$^+$: 444.6 $(M+H)^+$

^{1}HNMR (DMSOd_6,TFA) : 2.34 (t, 2H) ; 3.15 (t, 2H) ; 3.36 (t, 2H) ; 3.54 (d, 2H) ; 3.76 (t, 2H) ; 4.02 (d, 2H) ; 4.05 (s, 3H) ; 4.36 (t, 2H) ; 7.32 (d, 1H) ; 7.41 (s, 1H) ; 7.48 (s, 1H) ; 7.66 (d, 1H) ; 9.23 (s, 1H).

Example 447. Preparation of compound 625 in Table 28

An analogous reaction to that described in example 322 but starting with 2-amino-5-ethylthiophene-3-carboxamide (55 mg, 0.33 mmol) yielded title compound (147 mg, 90 %).

MS ES$^+$: 472.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.34 (t, 3H) ; 2.38 (t, 2H) ; 2.86 (q, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.57 (d, 2H) ; 3.80 (t, 2H) ; 4.05 (d, 2H) ; 4.07 (s, 3H) ; 4.38 (t, 2H) ; 7.40 (s, 1H) ; 7.43 (s, 1H) ; 7.52 (s, 1H) ; 9.21 (s, 1H).

Example 448. Preparation of compound 626 in Table 29

Methyl-2-cyano-4-methoxy-5-(3-morpholinopropoxy)phenylimidoformate (100 mg ; 0.3 mmol) in DMF (1.5 ml) was reacted with 2-amino-4-phenyl-1,3-thiazole (58 mg ; 0.33 mmol) in presence of sodium hydride (13.2 mg ; 0.33 mmol) at 75°C for 1.5 h. Acetic acid (1.5 eq.) was added and the solvent was evaporated to give 6-methoxy-7-(3-morpholinopropoxy)-3-(4-phenyl-1,3-thiazol-2-yl)quinazolin-4(3H)-imine as an intermediate which was redissolved in DMF (1.5 ml) and ammonium acetate (95 mg ; 0.9 mmol) added. The mixture was stirred at 75°C for 1 h, the solvent was evaporated and the residue purified by silica gel chromatography, CH_2Cl_2/MeOH 95/5 → 90/10 to give title compound (44 mg, 31 %).

^{1}HNMR (DMSOd_6, TFA) : 2.30 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.05 (m, 5H) ; 4.33 (t, 2H) ; 7.42 (m, 2H) ; 7.51 (t, 2H) ; 7.90 (s, 1H) ; 8.00 (d, 2H) ; 8.35 (s, 1H) ; 9.27 (s, 1H).

Example 449. Preparation of compound 627 in Table 29

An analogous reaction to that described in example 326 but starting with 2-amino-4-methyl-5-acetyl-1,3-thiazole (103 mg, 0.66 mmol), heating at 75°C for 1 h in the first step, and stirring the intermediate in the above conditions at room temperature for 1 h, gave title compound (71 mg, 52 %).

MS ES$^+$: 458 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H) ; 2.55 (s, 3H) ; 2.67 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.0 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.37 (s, 1H) ; 7.99 (s, 1H) ; 9.26 (s, 1H).

Example 450. Preparation of compound 628 in Table 29

An analogous reaction to that described in example 326 but starting with ethyl-2-amino-4-trifluoromethyl-1,3-thiazole-5-carboxylate (79 mg, 0.33 mmol) yielded title compound (81 mg, 50 %).

MS ES$^+$: 542 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.34 (t, 3H) ; 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.03 (s, 3H) ; 4.04 (d, 2H) ; 4.36 (m, 4H) ; 7.47 (s, 1H) ; 8.41 (s, 1H) ; 9.34 (s, 1H).

Example 451. Preparation of compound 629 in Table 29

An analogous reaction to that described in example 326 but starting with ethyl-2-amino-4-phenyl-1,3-thiazole-5-carboxylate (82 mg, 0.33 mmol) yielded title compound (133 mg, 81 %).

MS ES$^+$: 550 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.25 (t, 2H) ; 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 1H) ; 4.04 (d, 2H) ; 4.26 (q, 2H) ; 4.35 (t, 2H) ; 7.45 (s, 1H) ; 7.50 (m, 3H) ; 7.79 (m, 2H) ; 8.33 (s, 1H) ; 9.37 (s, 1H).

Example 452. Preparation of compound 630 in Table 29

An analogous reaction to that described in example 326 but starting with 4,5,6,7-tetrahydro-1,3-benzothiazole-2-amine (51 mg, 0.33 mmol) yielded title compound (97 mg, 71 %).

MS ES$^+$: 456 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.83 (m, 4H) ; 2.29 (t, 2H) ; 2.61 (m, 2H) ; 2.67 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.28 (s, 1H) ; 7.84 (s, 1H) ; 9.0 (s, 1H).

Example 453. Preparation of compound 631 in Table 29

An analogous reaction to that described in example 326 but starting with N-(4-(2-amino-1,3-thiazol-4-yl)phenyl)acetamide (77 mg, 0.33 mmol) yielded title compound (58 mg, 36 %).

MS ES$^+$: 535 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.09 (s, 3H) ; 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.05 (s, 3H) ; 4.06 (d, 2H) ; 4.35 (t, 2H) ; 7.40 (s, 1H) ; 7.72 (d, 2H) ; 7.77 (s, 1H) ; 7.92 (d, 2H) ; 8.33 (s, 1H) ; 9.25 (s, 1H).

Example 454. Preparation of compound 632 in Table 29

An analogous reaction to that described in example 326 but starting with 5-phenyl-4-(trifluoromethyl)-1,3-thiazole-2-amine (81 mg, 0.33 mmol) yielded title compound (144 mg, 88 %).

MS ES$^+$: 546 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (d, 2H) ; 4.05 (s, 3H) ; 4.36 (t, 2H) ; 7.49 (s, 1H) ; 7.54 (s, 5H) ; 8.46 (s, 1H) ; 9.30 (s, 1H).

Example 455. Preparation of compound 633 in Table 29

An analogous reaction to that described in example 326 but starting with 4-(trifluoromethyl)-1,3-thiazole-2-amine (55 mg, 0.33 mmol) yielded title compound (62 mg, 44 %).

MS ES$^+$: 470 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (s, 3H) ; 4.05 (d, 2H) ; 4.36 (t, 2H) ; 7.49 (s, 1H) ; 8.23 (s, 1H) ; 8.44 (s, 1H) ; 9.34 (s, 1H).

Example 456. Preparation of compound 634 in Table 29

An analogous reaction to that described in example 326 but starting with 4-tert-butyl-1,3-thiazole-2-amine (52 mg, 0.33 mmol) yielded title compound (90 mg, 65 %).

MS ES$^+$: 458 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.46 (s, 9H) ; 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (d, 2H) ; 7.38 (s, 1H) ; 7.95 (s, 1H) ; 9.18 (s, 1H).

Example 457. Preparation of compound 635 in Table 29

An analogous reaction to that described in example 326 but starting with 4,5-dimethyl-1,3-thiazole-2-amine (42 mg, 0.33 mmol) yielded title compound (61 mg, 47 %).

MS ES$^+$: 430 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.25 (s, 3H) ; 2.30 (m, 5H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.96 (s, 3H) ; 4.04 (d, 2H) ; 4.28 (t, 1H) ; 7.28 (s, 1H) ; 7.82 (s, 1H) ; 8.98 (s, 1H).

Example 458. Preparation of compound 636 in Table 29

An analogous reaction to that described in example 326 but starting with 4-methyl-1,3-thiazole-2-amine (38 mg, 0.33 mmol) yielded title compound (40 mg, 32 %).

MS ES$^+$: 415 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (t, 2H) ; 2.34 (s, 3H) ; 3.15 (t, 2H) ; 3.37 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.03 (s, 1H) ; 7.29 (s, 1H) ; 7.87 (s, 1H) ; 9.05 (s, 1H).

Example 459. Preparation of compound 637 in Table 29

1-(2-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)-4-methyl-1,3-thiazole-5-yl)ethanone (50 mg, 0.11 mmol) in ethanol (4 ml) and pyridine (1 ml) was reacted with hydroxylamine hydrochloride (19.5 mg, 0.27 mmol) at reflux for 3 h. The solvent was evaporated, water was added to the residue and a solid was recovered, washed with water to give title compound (14 mg, 27 %)

MS ES$^+$: 473 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.25 (s, 3H) ; 2.30 (t, 2H) ; 2.53 (s, 3H) ; 3.17 (t, 2H) ; 3.38 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.05 (d, 2H) ; 4.32 (t, 2H) ; 7.32 (s, 1H) ; 7.88 (s, 1H) ; 9.12 (s, 1H).

Example 460. Preparation of compound 638 in Table 29

2-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)-1,3-thiazole-5-carboxylic acid (89 mg, 0.2 mmol) in DMF (1.5 ml) was treated with diphenylphosporyl azide (66 mg, 0.24 mmol) and triethylamine (26 mg, 0.26 mmol). The solution was stirred at room temperature for 1 h and at 45°C for 1 h. Tert-butanol (1 ml) was added, and the mixture heated at 90°C for 2 h. The mixture was diluted with ethylacetate, aqueous sodium bicarbonate, the organic phase was recovered, dried over $MgSO_4$, filtered, concentrated and purified by silica gel chromatography, eluent CH_2Cl_2/MeOH 95/5 to 85/15 to give title compound as a yellow solid (25 mg, 24 %).

MS ES$^+$: 517 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.50 (s, 9H) ; 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.13 (s, 1H) ; 7.26 (s, 1H) ; 7.94 (s, 1H) ; 9.11 (s, 1H).

Example 461. Preparation of compound 639 in Table 29

An analogous reaction to that described in example 337 but starting with O-methylhydroxylamine hydrochloride (18 mg, 0.22 mmol) and heating at reflux for 72 h yielded title compound (39 mg, 63 %).

MS ES$^+$: 487 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.26 (s, 3H) ; 2.31 (t, 2H) ; 3.53 (s, 3H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.76 (s, 2H) ; 3.94 (s, 3H) ; 3.99 (s, 3H) ; 4.02 (d, 2H) ; 4.33 (t, 2H) ; 7.35 (s, 1H) ; 7.89 (s, 1H) ; 9.11 (s, 1H).

Example 462. Preparation of compound 640 in Table 29

An analogous reaction to that described in example 339 but starting with O-phenylhydroxylamine hydrochloride (32 mg, 0.22 mmol) yielded title compound (8 mg, 12 %).

MS ES$^+$: 549 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.28 (t, 2H) ; 3.12 (t, 2H) ; 3.32 (t, 2H) ; 3.52 (d, 2H) ; 3.65 (t, 2H) ; 3.96 (s, 3H) ; 4.0 (d, 2H) ; 4.27 (t, 2H) ; 7.06 (t, 1H) ; 7.20 (d, 2H) ; 7.28 (s, 1H) ; 7.34 (t, 2H) ; 7.91 (s, 1H) ; 9.17 (s, 1H).

Example 463. Preparation of compound 641 in Table 29

An analogous reaction to that described in example 326 but starting with 2-amino-5-(4-methoxyphenyl)-1,3-thiazole, HBr (86 mg, 0.33 mmol) yielded title compound (105 mg, 77 %).

MS ES$^+$: 508.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.33 (t, 2H) ; 3.20 (t, 2H) ; 3.40 (t, 2H) ; 3.60 (d, 2H) ; 3.73 (t, 2H) ; 3.86 (s, 3H) ; 4.08 (s, 3H) ; 4.09 (d, 2H) ; 4.36 (t, 2H) ; 7.10 (d, 2H) ; 7.44 (s, 1H) ; 7.76 (s, 1H) ; 7.96 (d, 2H) ; 8.33 (s, 1H) ; 9.26 (s, 1H).

Example 464. Preparation of compound 642 in Table 29

An analogous reaction to that described in example 326 but starting with 2-amino-5-phenyl)-1,3-thiazole (58 mg, 0.33 mmol) yielded title compound (120 mg, 84 %).

MS ES$^+$: 478.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.01 (s, 3H) ; 4.05 (d, 2H) ; 4.32 (t, 2H) ; 7.34 (s, 1H) ; 7.41 (t, 1H) ; 7.51 (t, 2H) ; 7.72 (d, 2H) ; 7.97 (s, 1H) ; 8.24 (s, 1H) ; 9.16 (s, 1H).

Example 465. Preparation of compound 643 in Table 29

Methyl-2-cyano-4-methoxy-5-(3-morpholinopropoxy)phenyl-imidoformate (300 mg, 0.9 mmol) in DMF (4.5 ml) was reacted with 2-amino-5-ethyl-1,3-thiazole (127 mg, 0.99 mmol) in presence of sodium hydride (39.6 mg, 0.99 mmol) at 75°C for 2 h. Acetic acid (77 µl, 1.35 mmol) was added to the mixture at room temperature, followed by MeOH/Me_2NH (2M) (90 µl, 0.18 mmol) and the mixture was stirred at 75°C for 1 h. The solvent was evaporated and the mixture was purified by silica gel chromatography, eluent CH_2Cl_2/MeOH 95/5 → 90/10 to give title compound (193 mg, 50 %).

MS ES$^+$: 430.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.29 (t, 3H) ; 2.32 (t, 2H) ; 2.81 (q, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.98 (s, 3H) ; 4.05 (d, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.50 (s, 1H) ; 7.87 (s, 1H) ; 9.04 (s, 1H).

Example 466. Preparation of compound 644 in Table 29

An analogous reaction to that described in example 343 but starting with 2-amino-5-isopropyl)-1,3-thiazole (141 mg, 0.99 mmol) yielded title compound (107 mg, 26 %).

MS ES$^+$: 444.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.33 (d, 6H) ; 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.29 (s, 1H) ; 7.49 (s, 1H) ; 7.87 (s, 1H) ; 9.05 (s, 1H).

Example 467. Preparation of compound 645 in Table 29

An analogous reaction to that described in example 343 but starting with 2-amino-5-benzyl)-1,3-thiazole (188 mg, 0.99 mmol) yielded title compound (370 mg, 84 %).

MS ES$^+$: 492.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.18 (s, 2H) ; 4.29 (t, 2H) ; 7.27 (s, 1H) ; 7.28 (m, 1H) ; 7.35 (m, 4H) ; 7.61 (s, 1H) ; 7.88 (s, 1H) ; 9.02 (s, 1H).

Example 468. Preparation of compound 646 in Table 29

An analogous reaction to that described in example 343 but starting with 2-amino-5-methyl)-1,3-thiazole (113 mg, 0.99 mmol) yielded title compound (300 mg, 80 %).

MS ES$^+$: 416.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (t, 2H) ; 2.42 (s, 3H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.30 (s, 1H) ; 7.48 (s, 1H) ; 7.86 (s, 1H) ; 9.03 (s, 1H).

Example 469. Preparation of compound 647 in Table 29

An analogous reaction to that described in example 343 but starting with 2-amino-5-butyl)-1,3-thiazole (155 mg, 0.99 mmol) yielded title compound (385 mg, 93 %).

MS ES$^+$: 458.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 0.93 (t, 3H) ; 1.36 (m, 2H) ; 1.64 (m, 2H) ; 2.29 (t, 2H) ; 2.79 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.51 (s, 1H) ; 7.86 (s, 1H) ; 9.03 (s, 1H).

Example 470. Preparation of compound 648 in Table 29

An analogous reaction to that described in example 343 but starting with 2-amino-5-formyl-1,3-thiazole (499.4 mg, 3.9 mmol) yielded title compound (244 mg, 39 %).

MS ES$^+$: 430.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 4.03 (s, 3H) ; 4.06 (d, 2H) ; 4.35 (t, 2H) ; 7.45 (s, 1H) ; 8.12 (s, 1H) ; 8.71 (s, 1H) ; 9.32 (s, 1H).

Example 471. Preparation of compound 649 in Table 29

An analogous reaction to that described in example 337 but starting with 2-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino-1,3-thiazol-5-carbaldehyde (100 mg, 0.23 mmol) and heating at 80°C for 4 h, yielded title compound (21 mg, 20 %).

MS ES^+ : 445.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (s, 3H) ; 4.05 (d, 2H) ; 4.32 (t, 2H) ; 7.36 (s, 1H) ; 7.92 (s, 1H) ; 7.98 (s, 1H) ; 8.33 (s, 1H) ; 9.20 (s, 1H).

Example 472. Preparation of compound 650 in Table 30

An analogous reaction to that described in example 326, but starting with 2-amino-5-tert-butyl-1,3,4-thiadiazol (52 mg, 0.33 mmol) yielded title compound (80 mg, 58 %).

MS ES^+ : 458 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.45 (s, 9H) ; 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.38 (s, 1H) ; 7.95 (s, 1H) ; 9.18 (s, 1H).

Example 473. Preparation of compound 651 in Table 30

An analogous reaction to that described in example 326, but starting with 2-amino-5-cyclopropyl-1,3,4-thiadiazol (47 mg, 0.33 mmol) yielded title compound (105 mg, 83 %).

MS ES^+ : 443 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.08 (m, 2H) ; 1.23 (m, 3H) ; 2.32 (t, 2H); 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.32 (t, 2H) ; 7.38 (s, 1H) ; 7.93 (s, 1H) ; 9.14 (s, 1H).

Example 474. Preparation of compound 652 in Table 30

An analogous reaction to that described in example 326, but starting with 2-amino-5-ethylthio-1,3,4-thiadiazol (53 mg, 0.33 mmol) yielded title compound (103 mg, 75 %).

MS ES^+ : 463 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA) : 1.41 (t, 3H) ; 2.31 (t, 2H); 3.15 (t, 2H) ; 3.31 (q, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.41 (s, 1H) ; 8.08 (s, 1H) ; 9.19 (s, 1H).

Example 475. Preparation of compound 653 in Table 30

An analogous reaction to that described in example 326, but starting with 2-amino-5-phenyl-1,3,4-thiadiazol (91 mg, 0.33 mmol) yielded title compound (110 mg, 76 %).

MS ES$^+$: 479 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA) : 2.32 (t, 2H); 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.69 (t, 2H) ; 4.03 (s, 3H) ; 4.05 (d, 2H) ; 4.34 (t, 2H) ; 7.42 (s, 1H) ; 7.61 (m, 3H) ; 7.99 (m, 2H) ; 8.06 (s, 1H) ; 9.25 (s, 1H).

Example 476. Preparation of compound 654 in Table 30

An analogous reaction to that described in example 326, but starting with N-phenyl-4H-1,2,4-triazole-3,5-diamine (58 mg, 0.33 mmol) yielded title compound (70 mg, 49 %).

MS ES$^+$: 477 $(M+H)^+$

^{1}HNMR (DMSOd$_6$, TFA) : 2.32 (t, 2H); 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 4.02 (s, 3H) ; 4.05 (d, 2H) ; 4.34 (t, 2H) ; 6.92 (t, 1H) ; 7.30 (t, 1H) ; 7.42 (s, 1H) ; 7.58 (d, 2H) ; 8.19 (s, 1H) ; 8.95 (s, 1H).

Biological Data

The compounds of the invention inhibit the serine/threonine kinase activity of the aurora2 kinase and thus inhibit the cell cycle and cell proliferation. These properties may be assessed, for example, using one or more of the procedures set out below:

(a) In Vitro aurora2 kinase inhibition test

This assay determines the ability of a test compound to inhibit serine/threonine kinase activity. DNA encoding aurora2 may be obtained by total gene synthesis or by cloning. This DNA may then be expressed in a suitable expression system to obtain polypeptide with serine/threonine kinase activity. In the case of aurora2, the coding sequence was isolated from cDNA by polymerase chain reaction (PCR) and cloned into the BamH1 and Not1 restriction endonuclease sites of the baculovirus expression vector pFastBac HTc (GibcoBRL/Life

technologies). The 5' PCR primer contained a recognition sequence for the restriction endonuclease BamH1 5' to the aurora2 coding sequence. This allowed the insertion of the aurora2 gene in frame with the 6 histidine residues, spacer region and rTEV protease cleavage site encoded by the pFastBac HTc vector. The 3' PCR primer replaced the aurora2 stop codon with additional coding sequence followed by a stop codon and a recognition sequence for the restriction endonuclease Not1 . This additional coding sequence (5' TAC CCA TAC GAT GTT CCA GAT TAC GCT TCT TAA 3') encoded for the polypeptide sequence YPYDVPDYAS. This sequence, derived from the influenza hemagglutin protein, is frequently used as a tag epitope sequence that can be identified using specific monoclonal antibodies. The recombinant pFastBac vector therefore encoded for an N-terminally 6 his tagged, C terminally influenza hemagglutin epitope tagged aurora2 protein. Details of the methods for the assembly of recombinant DNA molecules can be found in standard texts, for example Sambrook et al. 1989, Molecular Cloning - A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory press and Ausubel et al. 1999, Current Protocols in Molecular Biology, John Wiley and Sons Inc.

Production of recombinant virus can be performed following manufacturer's protocol from GibcoBRL. Briefly, the pFastBac-1 vector carrying the aurora2 gene was transformed into E. coli DH10Bac cells containing the baculovirus genome (bacmid DNA) and via a transposition event in the cells, a region of the pFastBac vector containing gentamycin resistance gene and the aurora2 gene including the baculovirus polyhedrin promoter was transposed directly into the bacmid DNA. By selection on gentamycin, kanamycin, tetracycline and X-gal, resultant white colonies should contain recombinant bacmid DNA encoding aurora2. Bacmid DNA was extracted from a small scale culture of several BH10Bac white colonies and transfected into Spodoptera frugiperda Sf21 cells grown in TC100 medium (GibcoBRL) containing 10% serum using CellFECTIN reagent (GibcoBRL) following manufacturer's instructions. Virus particles were harvested by collecting cell culture medium 72 hrs post transfection. 0.5 mls of medium was used to infect 100 ml suspension culture of Sf21s containing 1 x 10^7 cells/ml. Cell culture medium was harvested 48 hrs post infection and virus titre determined using a standard plaque assay procedure. Virus stocks were used to infect Sf9 and "High 5" cells at a multiplicity of infection (MOI) of 3 to ascertain expression of recombinant aurora2 protein.

For the large scale expression of aurora2 kinase activity, Sf21 insect cells were grown at 28°C in TC100 medium supplemented with 10% foetal calf serum (Viralex) and 0.2% F68

Pluronic (Sigma) on a Wheaton roller rig at 3 r.p.m. When the cell density reached $1.2x10^6$ cells ml^{-1} they were infected with plaque-pure aurora2 recombinant virus at a multiplicity of infection of 1 and harvested 48 hours later. All subsequent purification steps were performed at 4°C. Frozen insect cell pellets containing a total of 2.0×10^8 cells were thawed and diluted with lysis buffer (25 mM HEPES (N-[2-hydroxyethyl]piperazine-N'-[2-ethanesulphonic acid]) pH7.4 at 4°C , 100 mM KCl, 25 mM NaF, 1 mM Na_3VO_4, 1 mM PMSF (phenylmethylsulphonyl fluoride), 2 mM 2-mercaptoethanol, 2 mM imidazole, 1 μg/ml aprotinin, 1 μg/ml pepstatin, 1 μg/ml leupeptin), using 1.0 ml per 3×10^7 cells. Lysis was achieved using a dounce homogeniser, following which the lysate was centrifuged at 41,000*g* for 35 minutes. Aspirated supernatant was pumped onto a 5 mm diameter chromatography column containing 500 μl Ni NTA (nitrilo-tri-acetic acid) agarose (Qiagen, product no. 30250) which had been equilibrated in lysis buffer. A baseline level of UV absorbance for the eluent was reached after washing the column with 12 ml of lysis buffer followed by 7 ml of wash buffer (25 mM HEPES pH7.4 at 4°C , 100 mM KCl, 20 mM imidazole, 2 mM 2-mercaptoethanol). Bound aurora2 protein was eluted from the column using elution buffer (25 mM HEPES pH7.4 at 4°C , 100 mM KCl, 400 mM imidazole, 2 mM 2-mercaptoethanol). An elution fraction (2.5 ml) corresponding to the peak in UV absorbance was collected. The elution fraction, containing active aurora2 kinase, was dialysed exhaustively against dialysis buffer (25 mM HEPES pH7.4 at 4°C , 45% glycerol (v/v), 100 mM KCl, 0.25% Nonidet P40 (v/v), 1 mM dithiothreitol).

Each new batch of aurora2 enzyme was titrated in the assay by dilution with enzyme diluent (25mM Tris-HCl pH7.5, 12.5mM KCl, 0.6mM DTT). For a typical batch, stock enzyme is diluted 1 in 666 with enzyme diluent & 20μl of dilute enzyme is used for each assay well. Test compounds (at 10mM in dimethylsulphoxide (DMSO)) were diluted with water & 10μl of diluted compound was transferred to wells in the assay plates. "Total" & "blank" control wells contained 2.5% DMSO instead of compound. Twenty microlitres of freshly diluted enzyme was added to all wells, apart from "blank" wells. Twenty microlitres of enzyme diluent was added to "blank" wells. Twenty microlitres of reaction mix (25mM Tris-HCl, 78.4mM KCl, 2.5mM NaF, 0.6mM dithiothreitol, 6.25mM $MnCl_2$, 6.25mM ATP, 7.5μM peptide substrate [biotin-LRRWSLGLRRWSLGLRRWSLGLRRWSLG]) containing 0.2μCi [γ^{33}P]ATP (Amersham Pharmacia, specific activity ≥2500Ci/mmol) was then added to all test wells to start the reaction. The plates were incubated at room temperature for 60

minutes. To stop the reaction 100µl 20% v/v orthophosphoric acid was added to all wells. The peptide substrate was captured on positively-charged nitrocellulose P30 filtermat (Whatman) using a 96-well plate harvester (TomTek) & then assayed for incorporation of ^{33}P with a Beta plate counter. "Blank" (no enzyme) and "total" (no compound) control values were used to determine the dilution range of test compound which gave 50% inhibition of enzyme activity. In this test, compound 52 in Table 2 gave 50% inhibition of enzyme activity at a concentration of 0.167µM, and Compound 253 in Table 21 gave 50% inhibition of enzyme activity at 0.089µM.

(a) <u>In Vitro cell proliferation assay</u>

This assay determines the ability of a test compound to inhibit the growth of adherent mammalian cell lines, for example the human tumour cell line MCF7. MCF-7 (ATCC HTB-22) or other adherent cells were typically seeded at 1 x 10^3 cells per well (excluding the peripheral wells) in DMEM (Sigma Aldrich) without phenol red, plus 10% foetal calf serum, 1% L-glutamine and 1% penicillin/streptomycin in 96 well tissue culture treated clear plates (Costar). The following day (day 1), the media was removed from a no treatment control plate and the plate stored at -80°C. The remaining plates were dosed with compound (diluted from 10mM stock in DMSO using DMEM (without phenol red, 10% FCS, 1% L-glutamine, 1% penicillin/streptomycin). Untreated control wells were included on each plate. After 3 days in the presence / absence of compound (day 4) the media was removed and the plates stored at -80°C. Twenty four hours later the plates were thawed at room temperature and cell density determined using the CyQUANT cell proliferation assay kit (c-7026/c-7027 Molecular Probes Inc.) according to manufacturers directions. Briefly, 200µl of a cell lysis / dye mixture (10µl of 20X cell lysis buffer B, 190µl of sterile water, 0.25µl of CYQUANT GR dye) was added to each well and the plates incubated at room temperature for 5 minutes in the dark. The fluorescence of the wells was then measured using a fluorescence microplate reader (gain 70, 2 reads per well, 1 cycle with excitation 485nm and emission 530nm using a CytoFluor plate reader (PerSeptive Biosystems Inc.)). The values from day 1 and day 4 (compound treated) together with the values from the untreated cells were used to determine the dilution range of a test compound that gave 50% inhibition of cell proliferation. Compound 52 in Table 2 was effective in this test at 0.616µM and Compound 253 in Table 20 was effective at 5.9µM.

These values could also be used to calculate the dilution range of a test compound at which the cell density dropped below the day 1 control value. This indicates the cytotoxicity of the compound.

(a) <u>In Vitro cell cycle analysis assay</u>

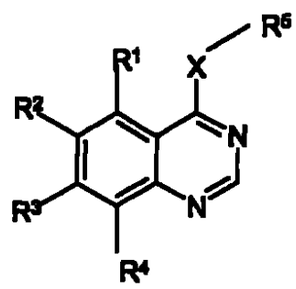
This assay determines the ability of a test compound to arrest cells in specific phases of the cell cycle. Many different mammalian cell lines could be used in this assay and MCF7 cells are included here as an example. MCF-7 cells were seeded at 3 x 10^5 cells per T25 flask (Costar) in 5 ml DMEM (no phenol red 10% FCS, 1% L-glutamine 1% penicillin / streptomycin). Flasks were then incubated overnight in a humidified 37^{0}C incubator with 5% CO_2. The following day 1ml of DMEM (no phenol red 10% FCS, 1% L-glutamine 1% penicillin / streptomycin) carrying the appropriate concentration of test compound solubilised in DMSO was added to the flask . A no compound control treatments was also included (0.5% DMSO). The cells were then incubated for a defined time (usually 24 hours) with compound. After this time the media was aspirated from the cells and they were washed with 5ml of prewarmed (37^{0}C) sterile PBSA, then detached from the flask by brief incubation with trypsin and followed by resuspension in 10ml of 1% Bovine Serum Albumin (BSA, Sigma-Aldrich Co.) in sterile PBSA. The samples were then centrifuged at 2200rpm for 10 min. The supernatant was aspirated and the cell pellet was resuspended in 200µl of 0.1% (w/v) Tris sodium citrate, 0.0564% (w/v) NaCl, 0.03% (v/v) Nonidet NP40, [pH 7.6]. Propridium Iodide (Sigma Aldrich Co.) was added to 40µg/ml and RNAase A (Sigma Aldrich Co.) to 100µg/ml. The cells were then incubated at 37^{0}C for 30 minutes. The samples were centrifuged at 2200rpm for 10 min, the supernatant removed and the remaining pellet (nuclei) resuspended in 200µl of sterile PBSA. Each sample was then syringed 10 times using 21 gauge needle. The samples were then transferred to LPS tubes and DNA content per cell analysed by Fluorescence activated cell sorting (FACS) using a FACScan flow cytometer (Becton Dickinson). Typically 25000 events were counted and recorded using CellQuest v1.1 software (Verity Software). Cell cycle distribution of the population was calculated using Modfit software (Verity Software) and expressed as percentage of cells in G0/G1, S and G2/M phases of the cell cycle.

Treating MCF7 cells with 1µM Compound 52 in Table 2 for 24 hours produced the following changes in cell cycle distribution:

Treatment	% Cells in G2/M
DMSO (control)	9.27%
10μM Compound 52	>50%

CLAIMS

1. The use of a compound of formula (I)



(I)

or a salt, ester or amide thereof;

where X is O, or S, S(O) or $S(O)_2$, or NR^6 where R^6 is hydrogen or C_{1-6}alkyl,;

R^5 is an optionally substituted 5-membered heteroaromatic ring,

R^1, R^2, R^3, R^4 are independently selected from, halo, cyano, nitro, trifluoromethyl, C_{1-3}alkyl, -NR^7R^8 (wherein R^7 and R^8, which may be the same or different, each represents hydrogen or C_{1-3}alkyl), or -X^1R^9 (wherein X^1 represents a direct bond, -O-, -CH_2-, -OCO-, carbonyl, -S-, -SO-, -SO_2-, -NR^{10}CO-, -$CONR^{11}$-, -SO_2NR^{12}-, -$NR^{13}SO_2$- or -NR^{14}- (wherein R^{10}, R^{11}, R^{12}, R^{13} and R^{14} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl), and R^9 is selected from one of the following groups:

1) hydrogen or C_{1-5}alkyl which may be unsubstituted or which may be substituted with one or more groups selected from hydroxy, fluoro or amino,

2) C_{1-5}alkylX^2COR^{15} (wherein X^2 represents -O- or -NR^{16}- (in which R^{15} represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{16} represents C_{1-3}alkyl, -$NR^{17}R^{18}$ or -OR^{19} (wherein R^{17}, R^{18} and R^{19} which may be the same or different each represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

3) C_{1-5}alkylX^3R^{20} (wherein X^3 represents -O-, -S-, -SO-, -SO_2-, -OCO-, -NR^{21}CO-, -$CONR^{22}$-, -SO_2NR^{23}-, -$NR^{24}SO_2$- or -NR^{25}- (wherein R^{21}, R^{22}, R^{23}, R^{24} and R^{25} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{20} represents hydrogen, C_{1-3}alkyl, cyclopentyl, cyclohexyl or a 5-6-membered saturated heterocyclic group with 1-2

heteroatoms, selected independently from O, S and N, which C_{1-3}alkyl group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno and C_{1-4}alkoxy and which cyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl and C_{1-4}alkoxy);

4) C_{1-5}alkylX^4C_{1-5}alkylX^5R^{26} (wherein X^4 and X^5 which may be the same or different are each -O-, -S-, -SO-, $-SO_2$-, $-NR^{27}CO$-, $-CONR^{28}$-, $-SO_2NR^{29}$-, $-NR^{30}SO_2$- or $-NR^{31}$- (wherein R^{27}, R^{28}, R^{29}, R^{30} and R^{31} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{26} represents hydrogen or C_{1-3}alkyl);

5) R^{32} (wherein R^{32} is a 5-6-membered saturated heterocyclic group (linked via carbon or nitrogen) with 1-2 heteroatoms, selected independently from O, S and N, which heterocyclic group may bear 1 or 2 substituents selected from oxo, hydroxy, halogeno, C_{1-4}alkyl, C_{1-4}hydroxyalkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkyl and C_{1-4}alkylsulphonylC_{1-4}alkyl);

6) C_{1-5}alkylR^{32} (wherein R^{32} is as defined hereinbefore);

7) C_{2-5}alkenylR^{32} (wherein R^{32} is as defined hereinbefore);

8) C_{2-5}alkynylR^{32} (wherein R^{32} is as defined hereinbefore);

9) R^{33} (wherein R^{33} represents a pyridone group, a phenyl group or a 5-6-membered aromatic heterocyclic group (linked via carbon or nitrogen) with 1-3 heteroatoms selected from O, N and S, which pyridone, phenyl or aromatic heterocyclic group may carry up to 5 substituents on an available carbon atom selected from hydroxy, halogeno, amino, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}hydroxyalkyl, C_{1-4}aminoalkyl, C_{1-4}alkylamino, C_{1-4}hydroxyalkoxy, carboxy, trifluoromethyl, cyano, $-CONR^{34}R^{35}$ and $-NR^{36}COR^{37}$ (wherein R^{34}, R^{35}, R^{36} and R^{37}, which may be the same or different, each represents hydrogen, C_{1-4}alkyl or C_{1-3}alkoxyC_{2-3}alkyl));

10) C_{1-5}alkylR^{33} (wherein R^{33} is as defined hereinbefore);

11) C_{2-5}alkenylR^{33} (wherein R^{33} is as defined hereinbefore);

12) C_{2-5}alkynylR^{33} (wherein R^{33} is as defined hereinbefore);

13) C_{1-5}alkylX^6R^{33} (wherein X^6 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{38}CO$-, $-CONR^{39}$-, $-SO_2NR^{40}$-, $-NR^{41}SO_2$- or $-NR^{42}$- (wherein R^{38}, R^{39}, R^{40}, R^{41} and R^{42} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore);

14) C_{2-5}alkenylX^7R^{33} (wherein X^7 represents -O-, -S-, -SO-, $-SO_2$-, $-NR^{43}CO$-, $-CONR^{44}$-, $-SO_2NR^{45}$-, $-NR^{46}SO_2$- or $-NR^{47}$- (wherein R^{43}, R^{44}, R^{45}, R^{46} and R^{47} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore);

15) C_{2-3}alkynylX^{8}R^{33} (wherein X^8 represents -O-, -S-, -SO-, -SO$_2$-, -NR^{48}CO-, -CONR^{49}-, -SO$_2$NR^{50}-, -NR^{51}SO$_2$- or -NR^{52}- (wherein R^{48}, R^{49}, R^{50}, R^{51} and R^{52} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore);

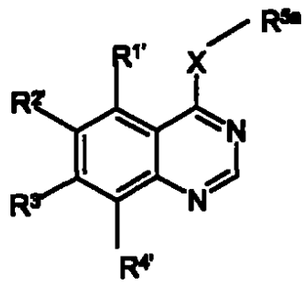
16) C_{1-3}alkylX^9C_{1-3}alkylR^{33} (wherein X^9 represents -O-, -S-, -SO-, -SO$_2$-, -NR^{53}CO-, -CONR^{54}-, -SO$_2$NR^{55}-, -NR^{56}SO$_2$- or -NR^{57}- (wherein R^{53}, R^{54}, R^{55}, R^{56} and R^{57} each independently represents hydrogen, C_{1-3}alkyl or C_{1-3}alkoxyC_{2-3}alkyl) and R^{33} is as defined hereinbefore); and

17) C_{1-3}alkylX^9C_{1-3}alkylR^{32} (wherein X^9 and R^{28} are as defined hereinbefore);

in the preparation of a medicament for use in the inhibition of aurora 2 kinase.

2. A method for inhibiting aurora 2 kinase in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I), as defined in claim 1 or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

3. A compound of formula (IA)



(IA)

or a salt, ester or amide thereof;

where X is as defined in relation to formula (I);

R$^{1'}$, R$^{2'}$, R$^{3'}$, R$^{4'}$ are equivalent to R^1, R^2, R^3, R^4 as defined in relation to formula (I) and R^{5a} is an optionally substituted 5-membered heteroaromatic ring, subject to the following provisos:

(i) that where R^{5a} is a pyrazole group, it carries a substitutent of formula (k), (II) of (VI) above,

(ii) that where X is NH and R^{5a} is a substituted pyrazolone or tetrazolyl group, at least one of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ is other than hydrogen; or

(iii) that where X is O and R^{5a} is 1-methyl-4-nitro-1H-imidazol-5-yl, at least one of $R^{1'}$, $R^{2'}$, $R^{3'}$ and $R^{4'}$ is other than hydrogen;

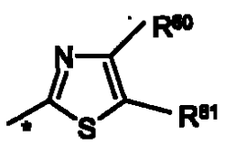
or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

4. A method for inhibiting aurora 2 kinase in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I), as defined in claim 3 or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

5. A compound according to claim 1 or 3 for use in a method of treatment of the human or animal body by therapy.

6. A pharmaceutical composition comprising a compound according to claim 1 or 3, in combination with a pharmaceutically acceptable carrier.

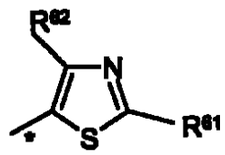
7. The composition as recited in Claim 3 wherein R^{5a} is selected from the group consisting of:



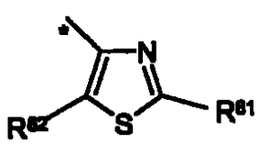
(a)



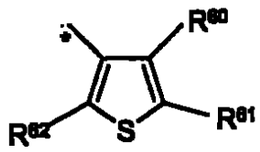
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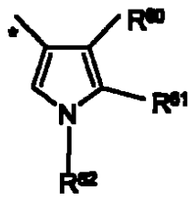
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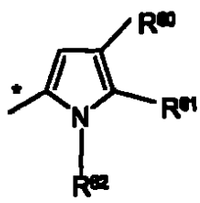


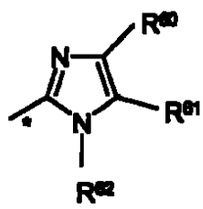
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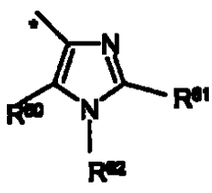


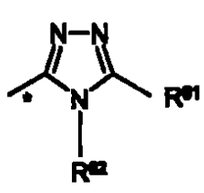
(e)


(f)


(g)

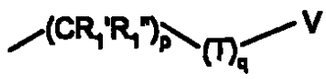

(h)


(i)


(j)

wherein where R^{60}, R^{61} and R^{62} are independently selected from hydrogen or a substituent group and * indicates the point of attachment to the group X in formula (IA).

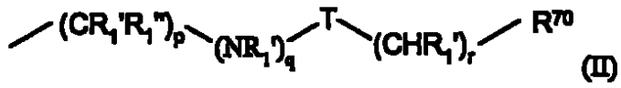
8. The composition as recited in Claim 7 wherein R^{60}, R^{61} or R^{62} is a group of sub-formula (k):



(k)

wherein p and q are independently 0 or 1 and R_1' and R_1'' are independently hydrogen, hydroxy, optionally substituted alkyl, optionally substituted cycloalkyl, halogen, cyano, optionally substituted alkyl, or optionally substituted alkyenyl, wherein R_1' can form with R_1'' a 3 to 6 membered ring; wherein T is C=O, SO_n, C(=NOR)CO, C(O)C(O), C=NCN, or CV=NO or wherein n = 0, 1 or 2 and V is independently R^{63} or $N(R^{63})R^{64}$ wherein R^{63} and R^{64} are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted heterocyclyl, or R^{63} and R^{64} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring.

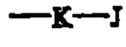
9. The composition as recited in Claim 7 wherein R^{60}, R^{61} or R^{62} is a group of sub-formula:



(II)

wherein p and q are independently 0 or 1, and r is 0, 1, 2, 3 or 4 and wherein R and R' are independently hydrogen, hydroxy, optionally substituted alkyl, optionally substituted cycloalkyl, halogen, cyano, optionally substitued alkyl, optionally substituted alkyenyl, wherein R can form with R' a 3 to 6 membered ring; wherein T is C=O, SO_n, C(=NOR)CO, C(O)C(O), C=NCN, or CV=NO or wherein n = 0, 1 or 2 and V is independently R^{63} or $N(R^{63})R^{64}$ wherein R^{63} and R^{64} are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted heterocyclyl, or R^{63} and R^{64} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring; wherein R^{70} is hydrogen, hydroxy (other than where q is 0), C_{1-6}alkyl, C_{1-6}alkoxy, amino, *N*-C_{1-6}alkylamino, *N,N*-$(C_{1-6}alkyl)_2$amino, hydroxyC_{2-6}alkoxy, C_{1-6}alkoxyC_{2-6}alkoxy, aminoC_{2-6}alkoxy, *N*-C_{1-6}alkylaminoC_{2-6}alkoxy, *N,N*-$(C_{1-6}alkyl)_2$aminoC_{2-6}alkoxy or C_{3-7}cycloalkyl,

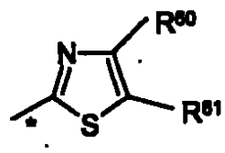
or R^{70} is of the Formula (III):



(III)

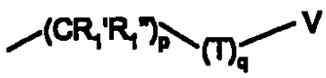
wherein J is aryl, heteroaryl or heterocyclyl and K is a bond, oxy, imino, *N*-(C_{1-6}alkyl)imino, oxyC_{1-6}alkylene, iminoC_{1-6}alkylene, *N*-(C_{1-6}alkyl)iminoC_{1-6}alkylene, -NHC(O) -, $-SO_2NH-$, $-NHSO_2-$ or -NHC(O)-C_{1-6}alkylene.

10. The composition as recited in Claim 7 wherein R^{5a} is represented by:



(a)

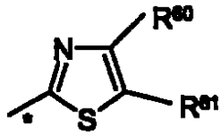
and wherein R^{60} is halogen, CN, or $CONR^{63}R^{64}$, and wherein R61 is sub-formula (k):



(k)

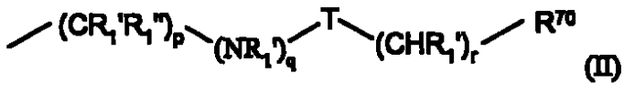
wherein p and q are independently 0 or 1 and R_1' and R_1'' are indedpendently hydrogen, hydroxy, optionally substituted alkyl, optionally substituted cycloalkyl, halogen, cyano, optionally substitued alkyl, optionally substituted alkyenyl, R_1' can form with R_1'' a 3 to 6 membered ring; wherein T is C=O, SO_n, C(=NOR)CO, C(O)C(O)), C=NCN, or V=NO or wherein n = 0, 1 or 2 and V is independently R^{63} or $N(R^{63})R^{64}$ wherein R^{63} and R^{64} are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted heterocyclyl, or R^{63} and R^{64} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring.

11. The composition as recited in Claim 7 wherein R^{5a} is represented by:



(a)

and wherein R^{60} is halogen, CN, or $CONR^{63}R^{64}$, and wherein R61 is sub-formula (k):



(II)

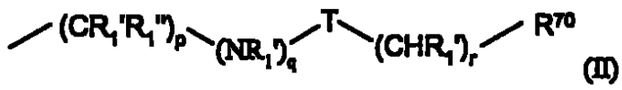
wherein p and q are independently 0 or 1, r is 0, 1, 2, 3 or 4 and R and R' are independently hydrogen, hydroxy, optionally substituted alkyl, optionally substituted cycloalkyl, halogen, cyano, optionally substituted alkyl, optionally substituted alkyenyl, R can form with the other R group a 3 to 6 membered ring; wherein T is C=O, SO_n, C(=NOR)CO, C(O)C(O)), C=NCN, or V=NO or wherein n = 0, 1 or 2 and V is independently R^{63} or $N(R^{63})R^{64}$ wherein R^{63} and R^{64} are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted heterocyclyl, or R^{63} and R^{64} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring; wherein R^{70} is hydrogen, hydroxy (other than where q is 0), C_{1-6}alkyl, C_{1-6}alkoxy, amino, *N*-C_{1-6}alkylamino, *N*,*N*-(C_{1-6}alkyl)$_2$amino, hydroxyC_{2-6}alkoxy, C_{1-6}alkoxyC_{2-6}alkoxy, aminoC_{2-6}alkoxy, *N*-C_{1-6}alkylaminoC_{2-6}alkoxy, *N*,*N*-(C_{1-6}alkyl)$_2$aminoC_{2-6}alkoxy or C_{3-7}cycloalkyl.

12. The composition as recited in Claim 7 wherein R^{5a} is represented by:



(a)

and wherein R^{60} is halogen, CN, or $CONR^{63}R^{64}$, and wherein R61 is sub-formula (k):



(II)

wherein p and q are independently 0 or 1, r is 0, 1, 2, 3 or 4 and R and R' are independently hydrogen, hydroxy, optionally substituted alkyl, optionally substituted cycloalkyl, halogen,

cyano, optionally substitued alkyl, optionally substituted alkyenyl, R can form with the other R group a 3 to 6 membered ring; wherein T is C=O, SO_n, C(=NOR)CO, C(O)C(O)), C=NCN, or V=NO or wherein n = 0, 1 or 2 and V is independently R^{63} or $N(R^{63})R^{64}$ wherein R^{63} and R^{64} are independently selected from hydrogen, optionally substituted hydrocarbyl or optionally substituted heterocyclyl, or R^{63} and R^{64} together with the nitrogen atom to which they are attached form an optionally substituted heterocyclic ring; wherein R^{70} is of the Formula (III):

—K—J (III)

wherein J is aryl, heteroaryl or heterocyclyl and K is a bond, oxy, imino, *N*-(C_{1-6}alkyl)imino, oxyC_{1-6}alkylene, iminoC_{1-6}alkylene, *N*-(C_{1-6}alkyl)iminoC_{1-6}alkylene, -NHC(O) -, -SO_2NH-, -NHSO_2- or -NHC(O)-C_{1-6}alkylene-,

and any aryl, heteroaryl or heterocyclyl group in a R^{70} group may be optionally substituted by one or more groups selected from hydroxy, halo, trifluoromethyl, cyano, mercapto, nitro, amino, carboxy, carbamoyl, formyl, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, -O-(C_{1-3}alkyl)-O-, C_{1-6}alkylS(O)$_n$- (wherein n is 0-2), *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonyl, *N*-C_{1-6}alkylcarbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{2-6}alkanoyl, C_{1-6}alkanoyloxy, C_{1-6}alkanoylamino, *N*-C_{1-6}alkylsulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, C_{1-6}alkylsulphonylamino and C_{1-6}alkylsulphonyl-*N*-(C_{1-6}alkyl)amino,

or any aryl, heteroaryl or heterocyclyl group in a R^{70} group may be optionally substituted with one or more groups of the Formula (IV):

$$—B^L—(CH_2)_p—A^1 \quad (IV)$$

wherein A^1 is halo, hydroxy, C_{1-6}alkoxy, cyano, amino, *N*-C_{1-6}alkylamino, *N,N*-(C_{1-6}alkyl)$_2$amino, carboxy, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-C_{1-6}alkylcarbamoyl or *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, p is 1 - 6, and B^1 is a bond, oxy, imino, *N*-(C_{1-6}alkyl)imino or -NHC(O)-, with the proviso that p is 2 or more unless B^1 is a bond or -NHC(O)-;

or any aryl, heteroaryl or heterocyclyl group in a R^{70} group may be optionally substituted with one or more groups of the Formula (V):

$$—E^1—D^1 \qquad (V)$$

wherein D^1 is aryl, heteroaryl or heterocyclyl and E^1 is a bond, C_{1-6}alkylene, oxyC_{1-6}alkylene, oxy, imino, *N*-(C_{1-6}alkyl)imino, iminoC_{1-6}alkylene, *N*-(C_{1-6}alkyl)-iminoC_{1-6}alkylene, C_{1-6}alkylene-oxyC_{1-6}alkylene, C_{1-6}alkylene-iminoC_{1-6}alkylene, C_{1-6}alkylene-*N*-(C_{1-6}alkyl)-iminoC_{1-6}alkylene, -NHC(O)-, -$NHSO_2$-, -SO_2NH- or -NHC(O)-C_{1-6}alkylene-, and any aryl, heteroaryl or heterocyclyl group in a substituent on D^1 may be optionally substituted with one or more groups selected from hydroxy, halo, C_{1-6}alkyl, C_{1-6}alkoxy, carboxy, C_{1-6}alkoxycarbonyl, carbamoyl, *N*-C_{1-6}alkylcarbamoyl, *N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{2-6}alkanoyl, amino, *N*-C_{1-6}alkylamino and *N*,*N*-(C_{1-6}alkyl)$_2$amino,

and any C_{3-7}cycloalkyl or heterocyclyl group in a R^{70} group may be optionally substituted with one or two oxo or thioxo substituents,

and any of the R^{70} groups defined hereinbefore which comprises a CH_2 group which is attached to 2 carbon atoms or a CH_3 group which is attached to a carbon atom may optionally bear on each said CH_2 or CH_3 group a substituent selected from hydroxy, amino, C_{1-6}alkoxy, *N*-C_{1-6}alkylamino, *N*,*N*-(C_{1-6}alkyl)$_2$amino and heterocyclyl.

13. A method for inhibiting aurora 2 kinase in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of formula (I), as defined in any one of Claims 7-12 or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

14. A compound as in any one of Claims 7-12, for use in a method of treatment of the human or animal body by therapy.

15. A pharmaceutical composition comprising a compound according to Claims 7-12 in combination with a pharmaceutically acceptable carrier.

16. A method for inhibiting aurora 2 kinase in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of

a compound of any one of Claims 7-12 or a pharmaceutically acceptable salt, or an *in vivo* hydrolysable ester thereof.

5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01450

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 403/12, C07D 409/12, C07D 413/12, A61K 31/505, A61P 35/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9935132 A1 (GLAXO GROUP LIMITED), 15 July 1999 (15.07.99) --	1-16
X	WO 9703069 A1 (GLAXO GROUP LIMITED), 30 January 1997 (30.01.97) --	1-16
X	WO 9515758 A1 (PHONEPOULEC RORER PHARMACEUTICALS INC.), 15 June 1995 (15.06.95) --	1-16
A	WO 9909016 A1 (AMERICAN CYANAMID COMPANY), 25 February 1999 (25.02.99) --	1-16

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 2001	08-11-2001
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01450

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 0121597 A1 (ASTRAZENECA AB), 29 March 2001 (29.03.01)	1-16

267

INTERNATIONAL SEARCH REPORT

Intern[illegible]al application No.
PCT/SE01/01450

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 2, 4, 13 and 16
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01450

Claims 2,4,13 and 16 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

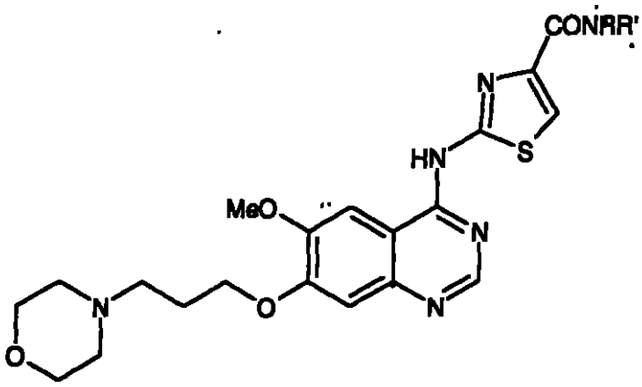
Information on patent family members

01/10/01

International application No.
PCT/SE 01/01450

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9935132 A1	15/07/99	AU 733047 B	03/05/01
		AU 1978699 A	26/07/99
		AU 6302498 A	09/09/98
		EP 0969813 A	12/01/00
		GB 9800575 D	00/00/00
		IL 131477 D	00/00/00
WO 9703069 A1	30/01/97	AU 6613996 A	10/02/97
		EP 0843671 A	27/05/98
		GB 9514265 D	00/00/00
		HR 960316 A	28/02/98
		JP 11508906 T	03/08/99
WO 9515758 A1	15/06/95	AU 1305095 A	27/06/95
		EP 0871448 A	21/10/98
		SG 54172 A	16/11/98
		US RE36256 E	20/07/99
		US 5480883 A	02/01/96
		US 5646153 A	08/07/97
		US 5710158 A	20/01/98
		US 5714493 A	03/02/98
		US 5721237 A	24/02/98
		US 5795889 A	18/08/98
		US 6057320 A	02/05/00
WO 9909016 A1	25/02/99	AU 8602398 A	08/03/99
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		CN 1271349 T	25/10/00
		EP 1000039 A	17/05/00
		HU 0002893 A	28/05/01
		NO 20000487 A	31/03/00
WO 0121597 A1	29/03/01	AU 7301900 A	24/04/01
		GB 9922171 D	00/00/00

Table 3



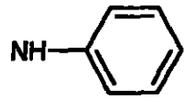
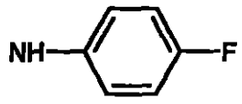
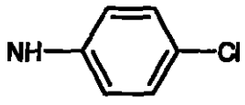
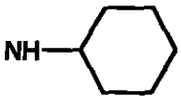
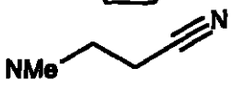
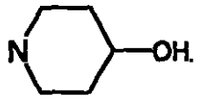
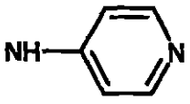
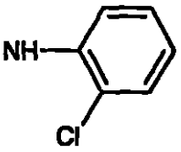
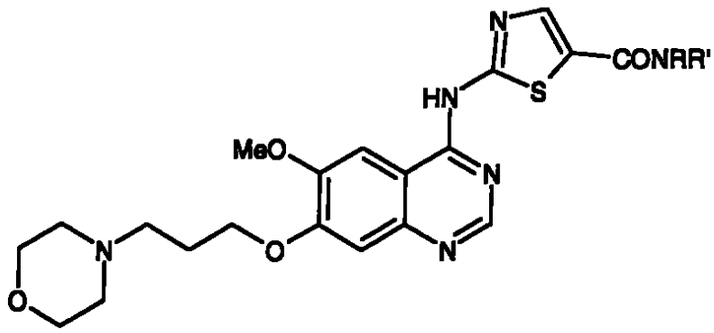
Compound No	NRR'
59	
60	
61	
62	
63	
64	
65	
66	

Table 4



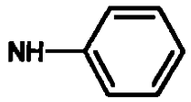
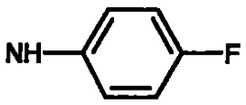
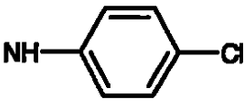
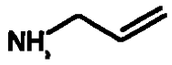
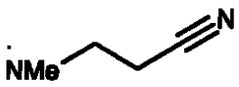
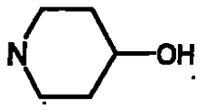
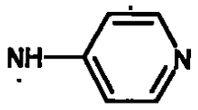
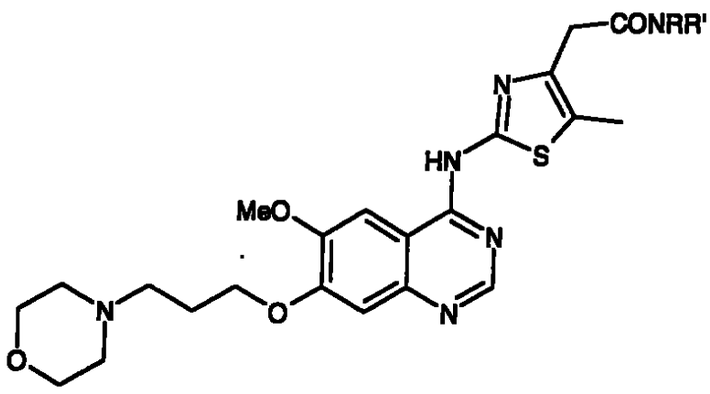
Compound No	NRR'
67	
68	
69	
70	
71	
72	
73	

Table 5



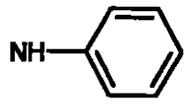
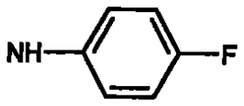
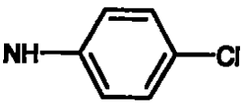
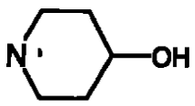
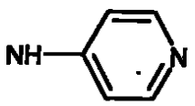
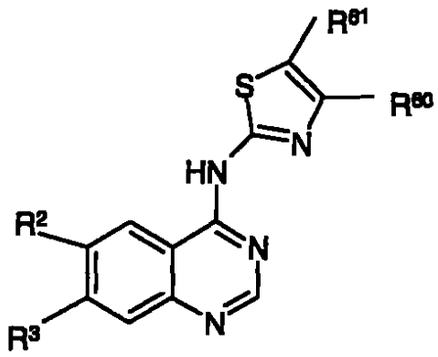
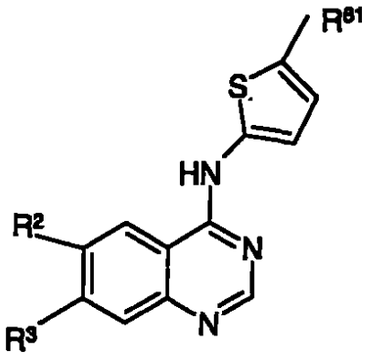
Compound No	NRR'
74	
75	
76	
77	
78	

Table 7



No.	R^2	R^3	R^{60}	R^{61}
200	OCH_3	OCH_3	$CH_2COOCH_2CH_3$	H
201	OCH_3	OCH_3	CH_2COOH	H
202	OCH_3	OCH_3	CH_3	$COOCH_2CH_3$
203	OCH_3	$O(CH_2)_3$-N-morpholino	CH_3	$COOCH_2CH_3$
204	OCH_3	$O(CH_2)_3$-N-morpholino	CH_3	COOH
205	OCH_3	$O(CH_2)_3$-N-morpholino	$CH_2COOCH_2CH_3$	H
206[1]	OCH_3	$O(CH_2)_3$-N-morpholino	$COOCH_2CH_3$	H
207	OCH_3	$O(CH_2)_3$-N-morpholino	COOH	H
208	OCH_3	$O(CH_2)_3$-N-morpholino	H	$COOCH_2CH_3$
209	OCH_3	$O(CH_2)_3$-N-morpholino	H	COOH
210	OCH_3	$O(CH_2)_3$-N-morpholino	$CH_2COOCH_2CH_3$	CH_3
211	OCH_3	$O(CH_2)_3$-N-morpholino	CH_2COOH	CH_3

Table 8



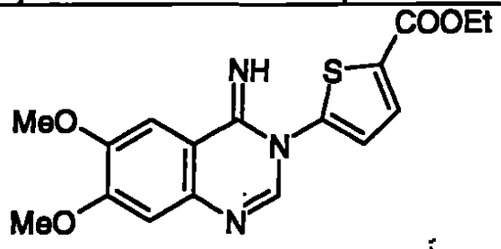
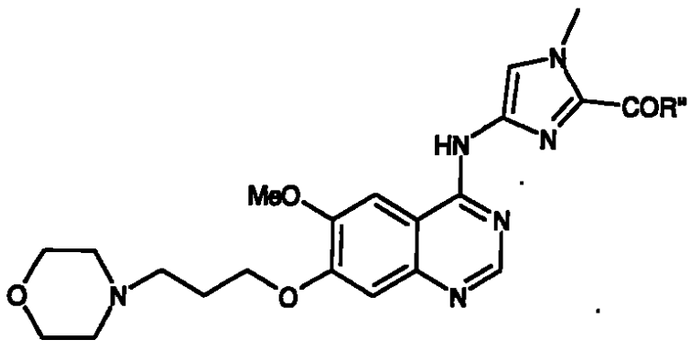
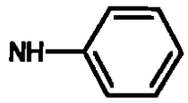
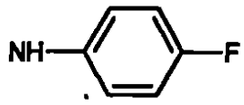
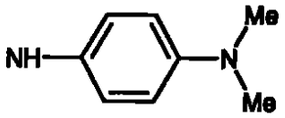
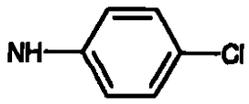
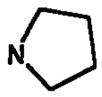
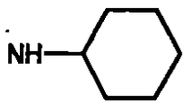
No.	R^2	R^3	R^{61}
212	OCH_3	$O(CH_2)_3$-N-morpholino	COOH
213			
214	OCH_3	OCH_3	COOH

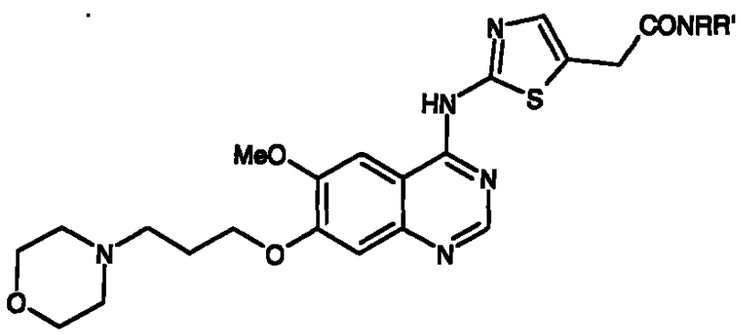
Table 10



Compound No	R"
260	$COOEt_3$
261	COOH
262	
263	
264	
265	
266	
267	

523	N,N,N'-trimethylethylenediamine	3-fluoroaniline
524	N-allylpiperazine	3-fluoroaniline
525	4-hydroxypiperidine	3-fluoroaniline
526	3-pyrrolidinol	3-fluoroaniline
527	1-(aminoethyl)pyrrolidine	3-fluoroaniline
528	N-acetylpiperazine	3-fluoroaniline
529	1-(2-hydroxyethyl)piperazine	3-fluoroaniline
530	cyclopentylamine	3-fluoroaniline
531	4-(2-hydroxyethyl)piperidine	3-fluoroaniline
532	3-hydroxypiperidine	3-fluoroaniline
533	4-hydroxymethylpiperidine	3-fluoroaniline
534	1-amino-2-propanol	3-fluoroaniline
535	(R)-(-)-2-pyrrolidinemethanol	3-fluoroaniline
536	(S)-(+)-2-pyrrolidinemethanol	3-fluoroaniline
537	piperazine	3-fluoroaniline
538	1-(2-morpholinoethyl)piperazine	3-fluoroaniline
539	2-amino-2-methyl-1-propanol	3-fluoroaniline

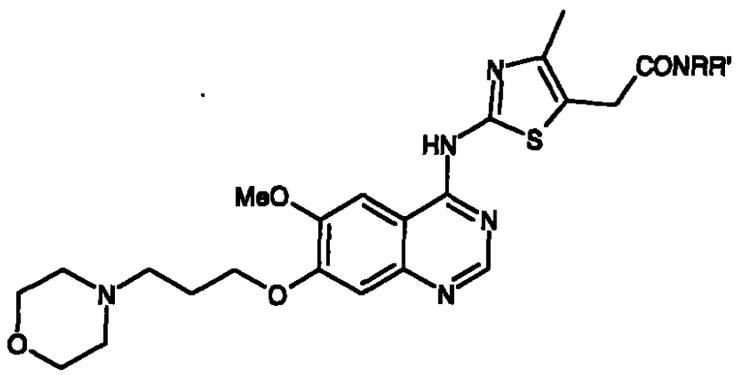
TABLE 18



N°	NRR'
540	N-ethylaniline
541	3-chloro-4-fluoro-N-methylaniline
542	ethyl-2-(3-chloro-4-fluoroanilino)acetate
543	2-anilinoacetronitrile
544	3-anilinoproponitrile
545	N-(2-tert-butoxyethyl)-3-chloro-4-fluoroaniline
546	N-allylaniline
547	N-ethyl-3,4-(methylmedioxy)aniline
548	ethyl-4-(N-butylamino)benzate
549	N-ethyl-M-toluidine
550	N-(2-hydroxy"thyl)-3-chloro-4-fluoroaniline

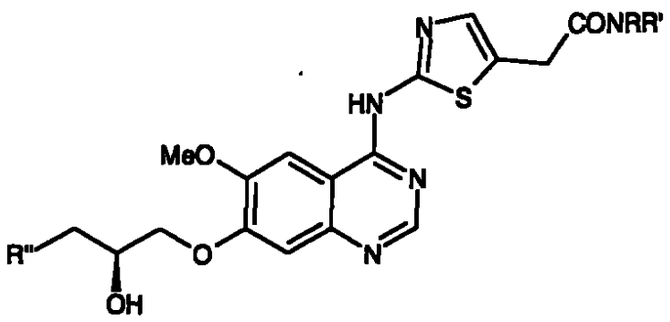
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TABLE 19



N°	NRR'
551	aniline
552	3-chloro-4-fluoroaniline
553	2-aminopyridine
554	3,4-difluoroaniline

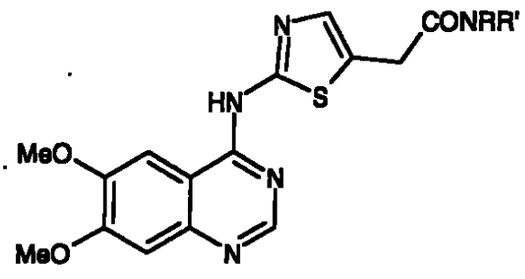
TABLE 20



N°	R"	NRR'
555	piperidine	3-chloro-4-fluoroaniline
556	pyrrolidine	3-chloro-4-fluoroaniline
557	4-hydroxypiperidine	3-chloro-4-fluoroaniline
558	piperazine	3-chloro-4-fluoroaniline
559	cyclopentylamine	3-chloro-4-fluoroaniline
560	2-amino-2-methyl-1-propanol	3-chloro-4-fluoroaniline
561	piperidine	3,4-difluoroaniline
562	pyrrolidine	3,4-difluoroaniline
563	4-hydroxypiperidine	3,4-difluoroaniline
565	cyclopentylamine	3,4-difluoroaniline

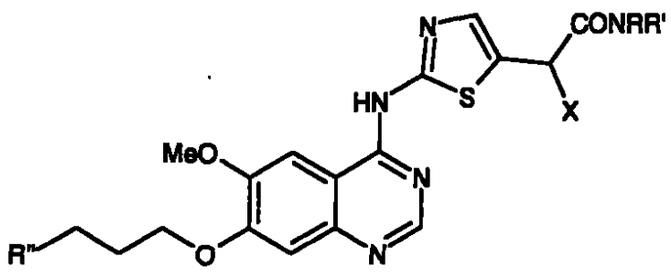
566	pyrrolidine	3-chloroaniline
567	4-hydroxypiperidine	3-chloroaniline
568	cyclopentylamine	3-chloroaniline
569	2-amino-2-methyl-1-propanol	3-chloroaniline
570	piperazine	3-chloroaniline
571	OMe	3-chloroaniline
572	piperidine	3-chloroaniline
573	piperidine	3,5-difluoroaniline
574	pyrrolidine	3,5-difluoroaniline
575	2-amino-2-methyl-1-propanol	3,5-difluoroaniline
576	piperazine (acetate)	3,5-difluoroaniline
577	piperazine	3,5-difluoroaniline
578	pyrrolidine	3-fluoroaniline
579	piperidine	3-fluoroaniline
580	piperazine	3-fluoroaniline
581	piperazine (acetate)	3-fluoroaniline
582	cyclopentylamine	3-fluoroaniline

TABLE21



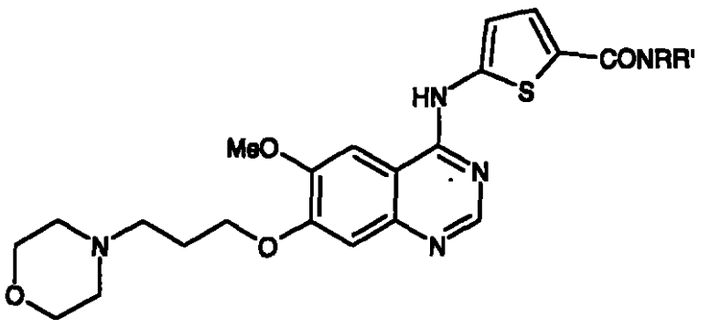
N°	NRR'
583	3,5-difluoroaniline
584	3-chloroaniline
585	3-chloro-4-fluoroaniline
586	3,4-difluoroaniline

TABLE 22



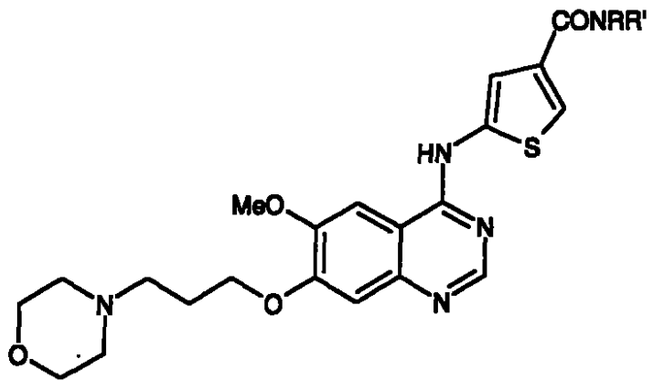
N°	R"	X	NRR'
587	morpholine	OH	aniline
588	morpholine	OH	3,4-difluoroaniline
589	N-Me-piperazine	OH	3,4-difluoroaniline
590	piperidine	OH	3-fluoroaniline
591	piperidine	OH	3-chloroaniline
592	N-Me-piperazine	=N-OH	3,4-difluoroaniline

TABLE 23



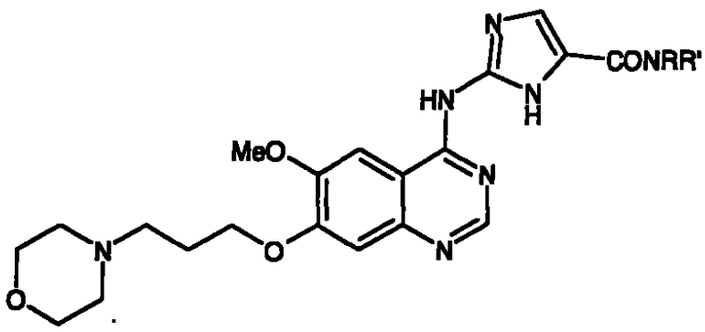
N°	NRR'	N°	NRR'
593	2-aminopyridine	601	2-methoxyaniline
594	4-methylaniline	602	3-(2-hydroxyethyl)aniline
595	2-methylaniline	603	3-fluoro-4-methoxyaniline
596	3-methoxyaniline	604	2-methyl-4-fluoroaniline
597	2-hydroxymethylaniline	605	2-fluoro-5-methylaniline
598	3-nitroaniline	606	3-cyanoaniline
599	4-trifluoromethylaniline	607	isoamylamine
600	3-chloroaniline	608	2-chloroaniline

TABLE 24



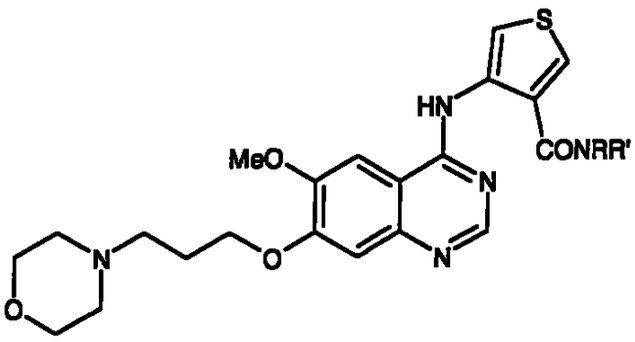
N°	NRR'
609	aniline
610	4-fluoroaniline
611	3-hydroxyaniline
612	3-(methylthio)aniline
613	4-fluoro-3-chloroaniline
614	2,4-difluorobenzylamine
615	3-fluoroaniline

TABLE 25



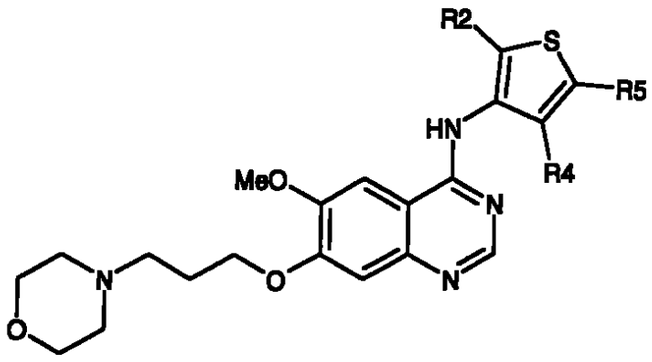
N°	NRR'
616	aniline
617	4-fluoroaniline
618	allylamine

TABLE 26



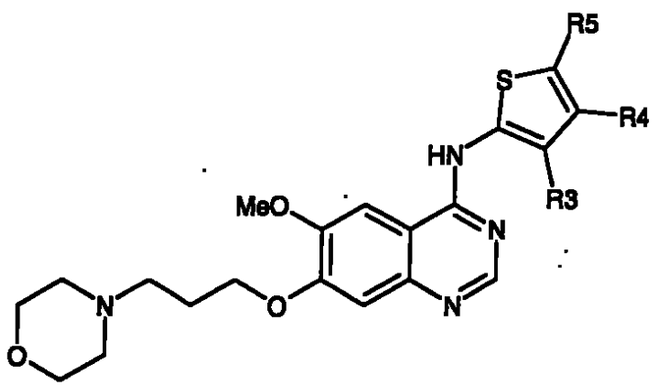
N°	NRR'
619	aniline
620	allylamine

TABLE 27



N°	R_2	R_4	R_5
621	COOMe	H	H

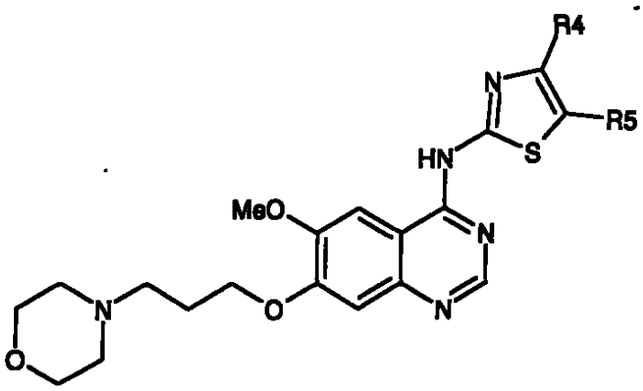
TABLE 28



N°	R_3	R_4	R_5
622	CONH2	H	isopropyl
623	H	H	COO allyl

624	CONH2	H	H
625	CONH2	H	ethyl

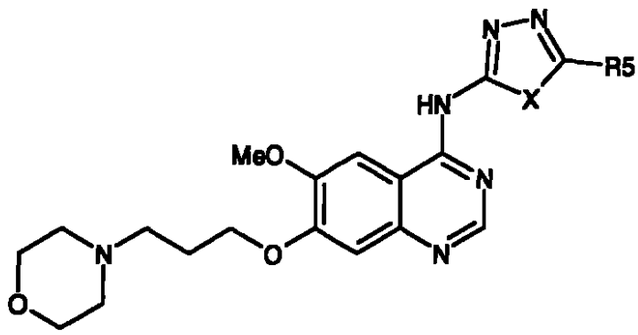
TABLE 29



	R4	R5
626	Ph	H
627	Me	COCH3
628	CF3	COOEt
629	Ph	COOEt
630	-(CH2)4-	
631	4-acetylaminophenyl	H
632	CF3	Ph
633	CF3	H
634	tert-butyl	H
635	Me	Me
636	Me	H
637	Me	-C(=N-OH)-Me
638	H	-NHCOO-tert-butyl
639	Me	-C(=NOMe)-Me
640	Me	-C(=NOPh)-Me
641	H	4-methoxyphenyl
642	H	Ph
643	H	Et
644	H	isopropyl

645	H	-CH2Ph
646	H	Me
647	H	n-butyl
648	H	CHO
649	H	-CH=N-OH

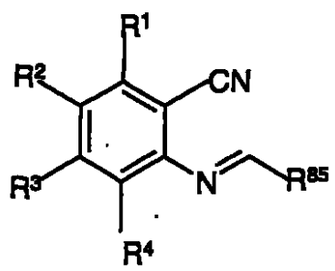
TABLE 30



	X	R5
650	S	tert-butyl
651	S	cyclopropyl
652	S	-S-CH2-CH3
653	S	-Ph
654	NH	-NH-Ph

Other compounds of Formula (I) or Formula (IA), in particular those in which R^5 carries a carboxy or carboxyl ester substituent are described below in the Examples.

Compounds of Formula (I) or Formula (IA) may be prepared by various methods which would be apparent from the literature. For example compounds of formula (I) where X is NH may be prepared by reacting a compound of formula (VII)



(VII)

^{1}HNMR ($CDCl_3$) : 3.08 (s, 6H) ; 3.86 (s, 3H) ; 3.91 (s, 3H) ; 6.48 (s, 1H) ; 6.94 (s, 1H) ; 7.58 (s, 1H).

MS ES$^+$: 234 $(M,H)^+$

Compound 200

A mixture of amidine B (1.4 g, 6 mmol), ethyl 2-amino-4-thiazoleacetate (1.4 g, 7.5 mmol) in acetic acid (14 ml) was heated at 130°C for 3 hours. The solvent was removed under vacuum, the residue was triturated in ethanol (5 ml) and a solution of $NaHCO_3$ (pH 8) for 10 minutes. The solid was recovered by filtration, washed with water, dissolved in CH_2Cl_2, and dried over $MgSO_4$. CH_2Cl_2 was evaporated, the residual oil treated with ether and pet. ether to give title compound (1.8 g, 80 %).

^{1}H NMR (DMSO-d_6) : 1.2 (t, 3H) ; 3.74 (s, 2H) ; 3.95 (s, 6H) ; 4.1 (q, 2H) ; 7.02 (s, 1H) ; 7.26 (s, 1H) ; 8.14 (s, 1H) ; 8.68 (s, 1H).

Compound 201

Ester 200 (1.8 g, 4.8 mmol) was reacted with 2N NaOH (4.8 ml, 9.6 mmol) in ethanol (20 ml) at room temperature for 2 hours. The mixture was cooled to room temperture, acidified with EtOH, HCl (2N) to pH 3. Stirring was carried on for 15 minutes, and a yellow solid of title compound was recovered by filtration (1.7 g, 100 %).

^{1}HNMR (DMSO-d_6) : 3.71 (s, 2H) ; 3.96 (s, 3H) ; 3.97 (s, 3H) ; 7.11 (s, 1H) ; 7.28 (s, 1H) ; 8.3 (brs, 1H) ; 8.88 (s, 1H).

Synthesis of amide c, general procedure

The acid 201 (86.5 mg, 0.25 mmol) in DMF (1 ml) was reacted with various amines (2.6 mmol) in presence of O-(7-azabenzotriazol-1yl) N,N,N',N',-tetramethyluronium hexafluorophosphate (98 mg, 0.26 mmol), DIEA (33 mg, 0.26 mmol) at room temperature for 0.5 hour. A solution of $NaHCO_3$ (1 ml) and water (7 ml) was added to the mixture. The mixture was left overnight, and the precipitated solid was then recovered by filtration, washed with water and dried under vacuum in presence of P_2O_5, to give compounds of formula C as listed below.

^{1}HNMR (DMSO-d_6, TFA) : 1.82 (m, 2H) ; 1.93 (m, 2H) ; 2.28 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (m, 4H) ; 3.55 (m, 4H) ; 3.68 (t, 2H) ; 3.71 (s, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.3 (t, 2H) ; 7.17 (s, 1H) ; 7.3 (s, 1H) ; 7.94 (s, 1H) ; 9.08 (s, 1H).

MS ES$^+$: 513 $(M,H)^+$

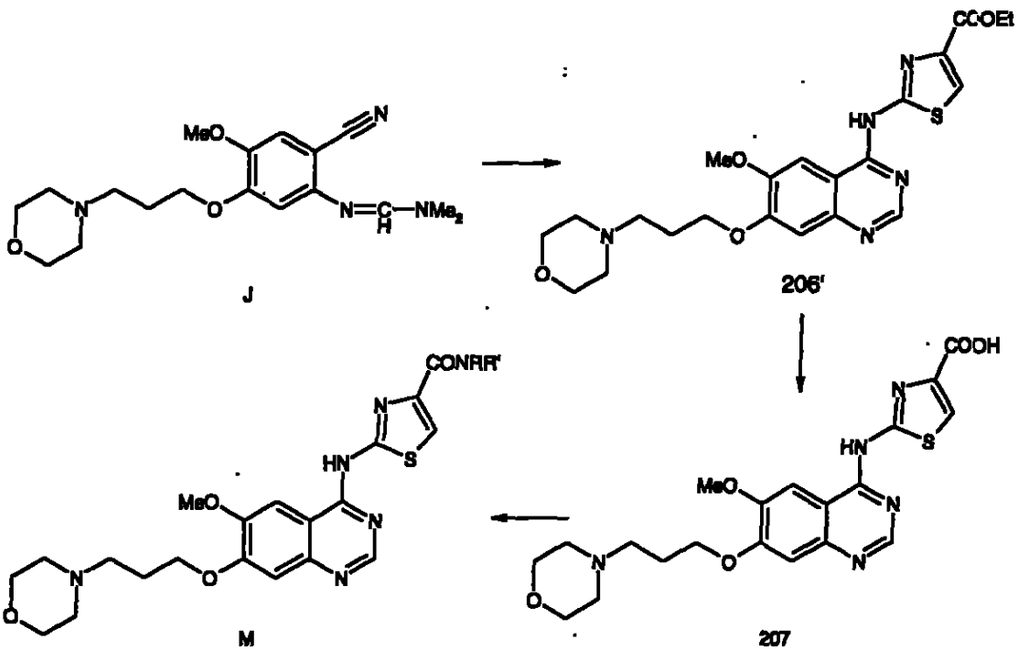
Example 58.

An analogous reaction to that described in General Scheme 3, starting with cyclohexylamine (20 mg, 0.2 mmol) yielded Compound 58 in Table 2 (80 mg, 87 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.25 (m, 4H) ; 1.75 (m, 4H) ; 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.56 (d, 2H) ; 3.6 (s, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.3 (t, 2H) ; 7.15 (s, 1H) ; 7.97 (s, 1H) ; 9.09 (s, 1H);

MS ES$^+$: 541 $(M,H)^+$

General Scheme 4



Compound 206^1

The amidine J (1.38 g, 4 mmol) in acetic acid (14 ml) was reacted with ethyl 2-amino-4-thiazolcarboxylate (0.72 g, 4.2 mmol) at 130°C for 6 hours. The solvent was evaporated, the residue dissolved in ethanol, and stirred with a saturated solution of $NaHCO_3$. The mixture

was extracted with CH_2Cl_2, dried, and purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH 98/2 → 90/10, to give title compound (0.738 g, 52 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.34 (t, 3H) ; 2.28 (m, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (s, 3H) ; 4.04 (d, 2H) ; 4.34 (m, 4H) ; 7.45 (s, 1H) ; 8.33 (s, 1H) ; 8.44 (s, 1H) ; 9.26 (s, 1H).

MS ES$^+$: 474 $(M,H)^+$

Compound 207

Ester **206**[1] (946 mg, 2 mmol) in suspension in ethanol (20 ml) was treated with sodium hydroxide (6N, 4 ml) at 75°C for 45 minutes. The reaction mixture was then cooled to room temperature, acidified (pH 3) with 6N HCl. The precipitate was filtered, washed with ethanol, triturated with ether, dried under vacuum, to give title compound (795 mg, 80 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.34 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.76 (t, 2H) ; 4.03 (m, 5H) ; 4.35 (t, 2H) ; 7.48 (s, 1H) ; 8.26 (s, 1H) ; 8.41 (s, 1H) ; 9.29 (s, 1H).

Synthesis of amides of general structure M, general procedure

The acid **207** (79 mg, 0.16 mmol) in DMF (1 ml) was reacted with amine (0.19 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (73 mg, 0.19 mmol), DIEA (52 mg, 0.4 mmol), for 1 hour at room temperature. The reaction mixture was then treated with a solution of $NaHCO_3$ (5 ml) with stirring for 0.5 hour, and the solid filtered, dried under vacuum over P_2O_5. For the compounds which did not precipitate, the solution was concentrated to dryness, the residues were washed with methylene chloride / methanol, filtered. Alumine was added to the methylene chloride / methanol solution and the solvent evaporated. Purification of the compounds was carried out by chromatography over alumine, eluent CH_2Cl_2 ; CH_2Cl_2 / MeOH : 95/5, to give title compounds.

Example 59.

An analogous reaction to that described in General Scheme 4, starting with aniline (18 mg, 0.19 mmol) yielded Compound 59 in Table 3(50 mg, 60 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.34 (t, 2H) ; 7.14 (t, 1H) ; 7.39 (t, 2H) ; 7.45 (s, 1H) ; 7.3 (d, 2H) ; 8.29 (s, 1H) ; 8.41 (s, 1H) ; 9.29 (s, 1H).

^{1}HNMR (DMSO-d_6, TFA) : 2.34 (m, 5H) ; 3.13 (t, 2H) ; 3.32 (t, 2H) ; 3.52 (d, 2H) ; 3.74 (s, 2H) ; 3.78 (t, 2H) ; 3.98 (s, 3H) ; 4.01 (d, 2H) ; 4.31 (t, 2H) ; 7.37 (s, 1H) ; 7.91 (s, 1H) ; 9.03 (s, 1H).

MS ES$^+$: 474 $(M,H)^+$

Synthesis of amides of general structure O, general procedure

The acid 211 (87 mg, 0.13 mmol) in DMF (1 ml) was reacted with amine (0.169 mmol) in presence of O-(7-azabensotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (69 mg, 0.182 mmol), diisopropylethylamine (84 mg, 0.65 mmol) over night, at room temperature. The reaction mixture was diluted with water (5 ml) and a concentrated solution of sodium bicarbonate (1 ml). The solid was filtered, washed with water, ethanol, ether, and dried under vacuum, to give title compounds. For the compounds which did not precipitate, the solution was concentrated to dryness, the residues were washed with methylene chloride, methanol, filtered. Alumine was added to the methylene chloride / methanol solution, and the solvent was evaporated. Purification of the compounds was carried out by chromatography over alumine, eluent CH_2Cl_2 / MeOH : 98/2 to 95/5, to give title compounds.

Example 74.

An analogous reaction to that described in General Scheme 6, starting with aniline (16 mg, 0.17 mmol) yielded Compound 74 in Table 5 (50 mg, 70 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.28 (m, 2H) ; 2.37 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.56 (d, 2H) ; 3.68 (t, 2H) ; 3.84 (s, 2H) ; 3.96 (s, 3H) ; 4.03 (d, 2H) ; 4.28 (t, 2H) ; 7.07 (t, 1H) ; 7.29 (s, 1H) ; 7.3 (t, 2H) ; 7.61 (d, 2H) ; 7.89 (s, 1H) ; 9.02 (s, 1H).

MS ES$^+$: 549 $(M,H)^+$

Example 75.

An analogous reaction to that described in General Scheme 6, starting with 4-fluoroaniline (19 mg, 0.17 mmol) yielded Compound 75 in Table 5 (50 mg, 67 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 2.38 (s, 3H) ; 3.16 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.84 (s, 2H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.16 (t, 2H) ; 7.29 (s, 1H) ; 7.64 (m, 2H) ; 7.9 (s, 1H) ; 9.03 (s, 1H).

MS ES$^+$: 567 $(M,H)^+$.

Example 76.

An analogous reaction to that described in General Scheme 6, starting with 4-chloroaniline (22 mg, 0.17 mmol) yielded Compound 76 in Table 5(45 mg, 59 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.28 (m, 2H) ; 2.37 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.85 (s, 2H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.37 (d, 2H) ; 7.65 (d, 2H) ; 7.9 (s, 1H) ; 9.03 (s, 1H).

MS ES$^+$: 583 $(M,H)^+$

Example 77.

An analogous reaction to that described in General Scheme 6, starting with 4-hydroxypiperidine (17 mg, 0.17 mmol) yielded Compound 77 in Table 5(45 mg, 62 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.42 (m, 2H) ; 1.82 (m, 2H) ; 2.31 (m, 5H) ; 3.08 (m, 1H) ; 3.16 (t, 2H) ; 3.27 (m, 1H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.78 (m, 2H) ; 3.83 (s, 2H) ; 3.92 (m, 1H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.28 (s, 1H) ; 7.85 (s, 1H) ; 9.0 (s, 1H).

MS ES$^+$: 557 $(M,H)^+$.

Example 78.

An analogous reaction to that described in General Scheme 6, starting with 4-aminopyridine (16 mg, 0.17 mmol) yielded Compound 78 in Table 5(35 mg, 49 %).

^{1}HNMR (DMSO-d6, TFA) : 2.29 (m, 2H) ; 2.39 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.96 (s, 3H) ; 4.02 (d, 2H) ; 4.04 (s, 2H) ; 4.29 (t, 2H) ; 7.33 (s, 1H) ; 7.92 (s, 1H) ; 8.1 (d, 2H) ; 8.76 (d, 2H) ; 9.06 (s, 1H).

MS ES$^+$: 550 $(M,H)^+$.

^{1}HNMR (DMSO-d_6, TFA) : 1.33 (t, 3H) ; 2.28 (m, 2H) ; 3.12 (t, 2H) ; 3.32 (t, 2H) ; 3.53 (d, 2H) ; 3.73 (t, 2H) ; 3.96 (s, 3H) ; 4.02 (d, 2H) ; 4.37 (m, 4H) ; 7.45 (s, 1H) ; 7.67 (d, 1H) ; 7.95 (d, 1H) ; 8.12 (s, 1H) ; 8.52 (s, 1H).

MS ES$^+$: 473 $(M,H)^+$

Compound 212

Ester V (1.1 g, 2.3 mmol) in methanol (20 ml) was treated with sodium hydroxide (2N, 20 ml) at 75°C for 4 hours, and at room temperature over night. Methanol was evaporated, and the remaining aqueous solution was kept for 24 hours at 5°C. The solid was filtered, washed with water, MeOH / CH_2Cl_2 : 1/1, dried under vacuum to give title compound (0.9 g, 87 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.31 (m, 2H) ; 3.14 (t, 2H) ; 3.33 (t, 2H) ; 3.53 (d, 2H) ; 3.76 (t, 2H) ; 4.01 (d, 2H) ; 4.07 (s, 3H) ; 4.33 (t, 2H) ; 7.44 (s, 1H) ; 7.54 (d, 1H) ; 7.68 (d, 1H) ; 8.54 (s, 1H) ; 9.22 (s, 1H).

MS ES$^+$: 445 $(M,H)^+$

Synthesis of amides of general structure W, general procedure

Acid 212 (80 mg, 0.18 mmol) in DMF (1.5 ml) was reacted with amine (0.216 mmol) in presence of O-(7-azabenzotriazol-1-yl) N,N,N',N'-tetramethyluronium hexafluorophosphate (80 mg, 0.21 mmol), DIEA (80 µl, 0.46 mmol), for 3 hours at room temperature. The reaction mixture was then treated with a solution of $NaHCO_3$ (2 ml) with stirring for 0.5 hour, the solid filtered, washed with water, ether, dried under vacuum over P_2O_5, to give title compound.

Example 79.

An analogous reaction to that described in General Scheme 7, starting with aniline (17 µl, 0.186 mmol) yielded Compound 79 in Table 6 (80 mg, 86 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.32 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.53 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (d, 2H) ; 4.03 (s, 3H) ; 4.3 (t, 2H) ; 7.7 (t, 1H) ; 7.32 (m, 4H) ; 7.73 (d, 2H) ; 7.98 (d, 1H) ; 8.18 (s, 1H) ; 9.22 (s, 1H).

MS ES$^+$: 520 $(M,H)^+$

Example 80.

An analogous reaction to that described in General Scheme 7, starting with 4-fluoroaniline (24 mg, 0.216 mmol) yielded Compound 80 in Table 6 (62 mg, 64 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 4.05 (m, 5H) ; 4.33 (t, 2H) ; 7.21 (t, 2H) ; 7.33 (d, 1H) ; 7.4 (s, 1H) ; 7.77 (m, 2H) ; 7.98 (d, 1H) ; 8.2 (s, 1H) ; 9.25 (s, 1H).

MS ES$^+$: 538 $(M,H)^+$.

Example 81.

An analogous reaction to that described in General Scheme 7, starting with 3-aminophenol (24 mg, 0.216 mmol) yielded Compound 81 in Table 6 (60 mg, 66 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.7 (t, 2H) ; 4.04 (d, 2H) ; 4.06 (s, 3H) ; 4.33 (t, 2H) ; 6.53 (m, 1H) ; 7.13 (m, 2H) ; 7.3 (d, 1H) ; 7.36 (d, 1H) ; 7.4 (s, 1H) ; 7.96 (s, 1H) ; 8.0 (d, 1H) ; 8.26 (s, 1H) ; 9.25 (s, 1H).

MS ES$^+$: 536 $(M,H)^+$.

Example 82.

An analogous reaction to that described in General Scheme 7, starting with 4-aminopyridine (20 mg, 0.216 mmol) yielded Compound 82 in Table 6 (16 mg, 19 %).

^{1}HNMR (DMSO-d6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.32 (t, 2H) ; 7.01 (d, 1H) ; 7.03 (s, 1H) ; 8.18 (d, 1H) ; 8.22 (s, 1H) ; 8.3 (d, 2H) ; 8.76 (d, 2H) ; 9.3 (s, 1H).

MS ES$^+$: 521 $(M,H)^+$.

Example 83.

An analogous reaction to that described in General Scheme 7, starting with 4-amino-1-butanol (19 mg, 0.216 mmol) yielded Compound 83 in Table 6 (22 mg, 28 %).

^{1}HNMR (DMSO-d_6, TFA) : 1.46 (m, 2H) ; 1.58 (m, 2H) ; 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.26 (t, 2H) ; 3.36 (t, 2H) ; 3.44 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (m, 5H) ; 4.32 (t, 2H) ; 7.26 (d, 1H) ; 7.39 (s, 1H) ; 7.7 (d, 1H) ; 8.19 (s, 1H) ; 9.21 (s, 1H).

MS ES$^+$: 516 $(M,H)^+$

Example 84.

An analogous reaction to that described in General Scheme 7, starting with 3-aminobenzamide (29 mg, 0.216 mmol) yielded Compound 84 in Table 6 (60 mg, 77 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.67 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.32 (t, 2H>) ; 7.34 (d, 1H) ; 7.39 (s, 1H) ; 7.42 (t, 1H) ; 7.62 (d, 1H) ; 7.96 (d, 1H) ; 8.05 (d, 1H) ; 8.21 (m, 2H) ; 9.27 (s, 1H).

MS ES$^+$: 563 $(M,H)^+$.

Example 85.

An analogous reaction to that described in General Scheme 7, starting with allylamine (12 mg, 0.216 mmol) yielded title Compound 85 in Table 6 (20 mg,, 43 %).

^{1}HNMR (DMSO-d6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.91 (d, 2H) ; 4.04 (m, 5H) ; 4.32 (t, 2H) ; 5.12 (d, 1H) ; 5.2 (d, 1H) ; 5.91 (m, 1H) ; 7.26 (d, 1H) ; 7.38 (s, 1H) ; 7.75 (d, 1H) ; 8.19 (s, 1H) ; 9.22 (s, 1H).

MS ES$^+$: 484 $(M,H)^+$.

Example 86.

An analogous reaction to that described in General Scheme 7, starting with Methyl-4-aminobutyrate (25 mg, 0.216 mmol) yielded Compound 86 in Table 6 (18 mg, 23 %).

^{1}HNMR : 1.8 (t, 2H) ; 2.3 (m, 2H) ; 2.39 (t, 2H) ; 3.16 (t, 2H) ; 3.28 (t, 2H) ; 3.35 (t, 2H) ; 3.56 (d, 2H) ; 3.6 (s, 3H) ; 3.67 (t, 2H) ; 4.04 (m, 5H) ; 4.32 (t, 2H) ; 7.26 (d, 1H) ; 7.38 (s, 1H) ; 7.69 (d, 1H) ; 8.19 (s, 1H) ; 9.22 (s, 1H).

MS ES$^+$: 544 $(M,H)^+$.

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (m, 5H) ; 4.3 (t, 2H) ; 7.19 (s, 1H) ; 7.32 (s, 1H) ; 7.62 (s, 1H) ; 8.17 (s, 1H) ; 8.93 (s, 1H).

MS ES$^+$: 428 $[M,H]^+$

Example 91. Synthesis of amides N, general procedure

Acid 251 (79 mg, 0.15 mmol) in DMF (1 ml) was reacted with O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (62 mg, 0.165 mmol), the appropriate amine (1.65 mmol) and DIEA (68 mg, 0.525 mmol) at room temperature for 1.5 hour. The reaction mixture was then diluted with water (4 ml) and an aqueous solution of sodium bicarbonate (1 ml). The solid was recovered by filtration, redissolved in tetrahydrofuran, methylene chloride, and concentrated, the precipitated solid was recovered, washed with ether, dried under vacuum, to give title compound.

Example 92. Preparation of Compound 252 in Table 9

Compound 252 was obtained by reaction of the N-hydroxybenzotriazol ester of 251 (56 mg, 0.1 mmol) with aniline (11 mg, 0.12 mmol) in DMF (1 ml) at 105°C for 3 hours. Water was added to the cooled reaction mixture, which was extracted with ethylacetate, the organic phase was washed with water, dried over $MgSO_4$, filtered and concentrated to give title compound (12 mg, 23 %). The N-hydroxybenzotriazol ester was obtained as described in the general procedure of Example 91.

^{1}HNMR (DMSOd_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.08 (t, 1H) ; 7.33 (m, 3H) ; 7.4 (s, 1H) ; 7.63 (s, 1H) ; 7.74 (d, 2H) ; 8.1 (s, 1H) ; 8.93 (s, 1H).

MS ES+ : 517 $[M,H]^+$

Example 93. Preparation of Compound 253 in Table 9

An analogous reaction to that described in Example 92, but starting with 4-fluoroaniline (22 mg, 0.195 mmol) yielded title compound (40 mg, 57 %).

^{1}H NMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.72 (t, 2H) ; 3.97 (s, 3H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.3 (t, 2H) ; 7.18 (t, 2H) ; 7.34 (s, 1H) ; 7.4 (d, 1H) ; 7.63 (d, 1H) ; 7.76 (m, 1H) ; 8.11 (s, 1H) ; 8.94 (s, 1H).

the solid recovered by filtration and washed with ether. This solid was then treated with a diluted solution of sodium bicarbonate, filtered, washed with water and dried under vacuum over P_2O_5 to give title compound (1.34 g, 73 %).

^{1}H NMR (DMSO-d_6) : 1.3 (t, 3H) ; 1.95 (t, 2H) ; 2.38 (m, 4H) ; 2.44 (t, 2H) ; 3.58 (m, 4H) ; 3.94 (s, 3H) ; 4.16 (d, 2H) ; 4.23 (q, 2H) ; 7.05 (d, 1H) ; 7.14 (s, 1H) ; 7.59 (d, 1H) ; 7.75 (s, 1H) ; 8.46 (s, 1H) ; 9.53 (s, 1H) ; 11.72 (s, 1H).

MS ES$^+$: 456 $[M+H]^+$

Example 96[1]. Preparation of Compound 257 in Table 9

Ester 256 (1.34 g, 3 mmol) in ethanol (25 ml) was treated with sodium hydroxide (6N, 3 ml) at 75°C for 2 hours. The solution was cooled, and acidified with hydrochloric acid (6N) to pH 3. The precipitate was filtered, washed with ethanol, ether, dried under vacuum over P_2O_5, to give title compound (0.63 g, 42 %).

^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (s, 3H) ; 4.03 (d, 2H) ; 4.3 (t, 2H) ; 7.19 (d, 1H) ; 7.32 (s, 1H) ; 7.62 (d, 1H) ; 8.17 (s, 1H) ; 8.93 (s, 1H).

MS ES$^+$: 428 $[M+H]^+$

Example 97. Preparation of Compound 258 in Table 9

Acid 257 (75 mg, 0.15 mmol) in DMF (0.7 ml) was reacted with O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (68 mg, 0.18 mmol), aniline (17 mg, 0.18 mmol) and DIEA (62 mg, 0.48 mmol) at room temperature over night. The reaction mixture was then diluted with a saturated solution of sodium bicarbonate (5 ml), and stirred for 1 hour. The solid was filtered, washed with water, dried under vacuum over P_2O_5, to give title compound (30 mg, 40 %).

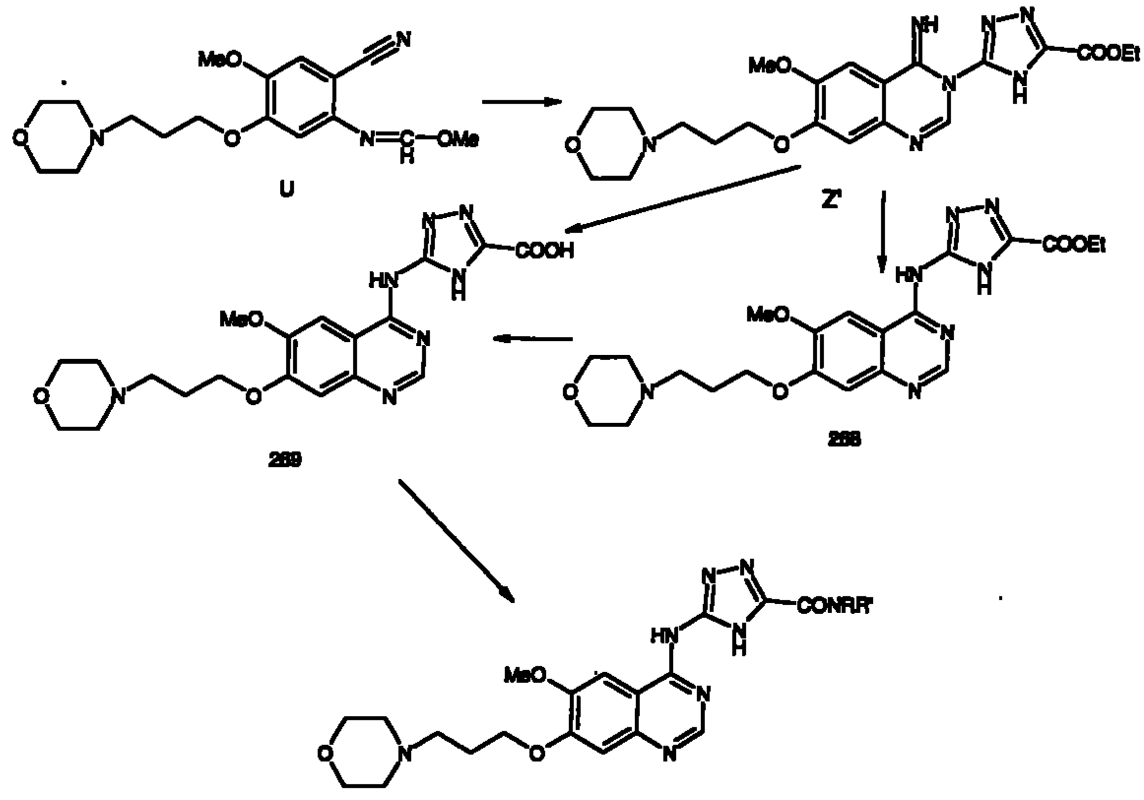
^{1}HNMR (DMSO-d_6, TFA) : 2.3 (m, 2H) ; 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.54 (d, 2H) ; 3.69 (t, 2H) ; 4.01 (s, 3H) ; 4.03 (d, 2H) ; 4.31 (t, 2H) ; 7.08 (t, 1H) ; 7.35 (m, 3H) ; 7.46 (d, 1H) ; 7.56 (d, 1H) ; 7.77 (d, 1H) ; 8.1 (s, 1H) ; 8.93 (s, 1H).

MS ES$^+$: 503 $[M+H]^+$

Example 98. Preparation of Compound 259 in Table 9

An analogous reaction to that described for the Example 97, but starting with cyclohexylamine (18 mg, 0.18 mmol) yielded title compound (30 mg, 39 %).

General Scheme 12



Example 108.

Step (a) .Preparation of Intermediates of General formula Z^1

Imidate U (2 g, 6 mmol) in dimethylformamide (40 ml) was reacted with ethyl 5-amino-4H-1,2,4-triazole-3-carboxylate hydrochloric acid (1.16 g, 6 mmol) in presence of sodium hydride (60 %, 504 mg, 12.6 mmol) at 110°C for 7 hours, under argon. The mixture was then cooled to room temperature, and acetic acid (1.03 ml, 18 mmol) was added, the solvent was evaporated under vacuum, the residue purified by silica gel chromatography, eluent : CH_2Cl_2 / MeOH, 90/10 to give title compound (1.07 g, 39 %).

^{1}H NMR (DMSO-d_6, TFA) : 1.39 (t, 3H) ; 2.28 (m, 2H) ; 3.15 (t, 2H) ; 3.32 (t, 2H) ; 3.56 (d, 2H) ; 3.68 (t, 2H) ; 3.98 (s, 3H) ; 4.05 (d, 2H) ; 4.37 (t, 2H) ; 4.52 (q, 2H) ; 7.49 (s, 1H) ; 8.12 (s, 1H) ; 8.71 (s, 1H).

MS ES$^+$: 458 [M,H]$^+$

Step (b) : Preparation of Compound 268 in Table 11

Triazole ester Z^1 (80 mg, 0.17 mmol) in dimethylformamide (3 ml) was treated with dimethylamine acetate (0.52 mmol) at 70°C for 20 minutes. The mixture was cooled, the

^{1}HNMR (DMSOd_6) : 1.22 (t, 3H) ; 1.96 (t, 2H) ; 2.37 (m, 4H) ; 2.35 (t, 2H) ; 3.58 (m, 4H) ; 3.91 (s, 2H) ; 3.95 (s, 3H) ; 4.13 (q, 2H) ; 4.20 (t, 2H) ; 7.25 (s, 1H) ; 7.36 (s, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H).

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.

4-(ethyl(2-amino-1,3-thiazole-5-yl)acetate)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (4.38 g, 8 mmol) in ethanol (44 ml) was treated with sodium hydroxyde (2N, 10 ml) at 50°C for 4 hours. The mixture was cooled to room temperature and the pH adjusted to 3.5 with 2N HCl. The residue was dissolved in CH_2Cl_2 / MeOH, 60/40, DIEA (3 g, 24 mmoles) was added, the mixture was stirred for 10 minutes, filtered, and the solution was concentrated to give an oily residue. This residue was dissolved in ethanol, and the solvent was partially evaporated. A cristalin solid was recovered, suspended in ethanol, washed with ether and dried under vacuum to give title compound (3.7 g, 100 %).

^{1}HNMR (DMSOd_6, TFA) : 2.28 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.70 (t, 2H) ; 3.92 (s, 2H) ; 3.99 (s, 3H) ; 4.03 (d, 2H) ; 4.30 (t, 2H) ; 7.32 (s, 1H) ; 7.60 (s, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 161. Preparation of compound 338 in Table 14

An analogous reaction to that described in example 160 but starting with 3-chloro-4-fluoroaniline (30 mg, 0.2 mmol) yielded the title compound (24 mg, 24 %).

MS ES$^+$: 587 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.34 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (m, 5H) ; 4.03 (d, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.65 (s, 1H) ; 7.85 (s, 1H) ; 7.97 (d, 1H) ; 9.09 (s, 1H).

Example 162. Preparation of compound 339 in Table 14

An analogous reaction to that described in example 160 but starting with 4-chloroaniline (26 mg, 0.2 mmol) yielded title compound (73 mg, 76 %).

MS ES$^+$: 569 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.89 (m, 5H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.39 (d, 2H) ; 7.64 (s, 1H) ; 7.65 (d, 2H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 163. Preparation of compound 340 in Table 14

An analogous reaction to that described in example 160 but starting with 3,4-difluoroaniline (26 mg, 0.2 mmol) yielded title compound (75 mg, 77 %).

MS ES$^+$: 571(M+H)$^+$

^{1}HNMR (DMSOd$_6$, TFA) 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.72 (t, 2H) ; 3.99 (m, 5H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.31 (s, 1H) ; 7.32 (m, 1H) ; 7.41 (q, 1H) ; 7.65 (s, 1H) ; 7.81 (m, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 164. Preparation of compound 341 in Table 14

An analogous reaction to that described in example 160 but starting with 3-methoxyaniline (25 mg, 0.2 mmol) yielded title compound (40 mg, 42 %).

MS ES$^+$: 565 (M+H)$^+$

^{1}HNMR (DMSOd$_6$, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.70 (t, 2H) ; 3.74 (s, 3H) ; 3.97 (s, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.31 (t, 2H) ; 6.68 (d, 1H) ; 7.15 (d, 1H) ; 7.23 (t, 1H) ; 7.29 (s, 1H) ; 7.33 (s, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 165. Preparation of compound 342 in Table 14

An analogous reaction to that described in example 160 but starting with 2-chloroaniline (26 mg, 0.2 mmol) yielded title compound (15 mg, 16 %).

MS ES$^+$: 569 (M+H)$^+$

^{1}HNMR (DMSOd$_6$, TFA) : 2.30 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.05 (m, 4H) ; 4.31 (t, 2H) ; 7.22 (t, 1H) ; 7.30 (s, 1H) ; 7.35 (t, 1H) ; 7.51 (d, 1H) ; 7.65 (s, 1H) ; 7.75 (d, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 166. Preparation of compound 343 in Table 14

An analogous reaction to that described in example 160 but starting with 4-methoxyaniline (26 mg, 0.21 mmol) yielded title compound (55 mg, 57 %).

MS ES$^+$: 565.6 (M+H)$^+$

^{1}HNMR (DMSOd$_6$, TFA) : 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.73 (t, 2H) ; 3.80 (s, 3H) ; 3.97 (s, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 6.93 (d, 2H) ; 7.09 (s, 1H) ; 7.33 (s, 1H) ; 7.56 (d, 2H) ; 7.66 (s, 1H) ; 7.94 (s, 1H) ; 9.12 (s, 1H).

Example 167. Preparation of compound 344 in Table 14

An analogous reaction to that described in example 160 but starting with 4-methylaniline (23 mg, 0.21 mmol) yielded title compound (51 mg, 54 %).

MS ES$^+$: 549.7 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.29 (s, 3H) ; 2.31 (t, 2H) ; 3.19 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 3.99 (s, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.16 (d, 2H) ; 7.33 (s, 1H) ; 7.54 (d, 2H) ; 7.67 (s, 1H) ; 7.94 (s, 1H) ; 9.12 (s, 1H).

Example 168. Preparation of compound 345 in Table 14

An analogous reaction to that described in example 160 but starting with 2-methylaniline (23 mg, 0.21 mmol) yielded title compound (42 mg, 45 %).

MS ES$^+$: 549.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.24 (s, 3H) ; 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 2H) ; 4.02 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.12 (t, 1H) ; 7.19 (t, 1H) ; 7.24 (d, 1H) ; 7.31 (s, 1H) ; 7.43 (t, 1H) ; 7.66 (s, 1H) ; 7.92 (s, 1H) ; 9.08 (s, 1H).

Example 169. Preparation of compound 346 in Table 14

An analogous reaction to that described in example 160 but starting with 2-aminopyridine (20 mg, 0.21 mmol) yielded title compound (12 mg, 13 %).

MS ES$^+$: 536.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (m, 5H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.34 (s, 1H) ; 7.37 (t, 1H) ; 7.68 (s, 1H) ; 7.93 (d, 1H) ; 7.94 (s, 1H) ; 8.10 (t, 1H) ; 8.42 (d, 1H) ; 9.10 (s, 1H).

Example 170. Preparation of compound 347 in Table 14

An analogous reaction to that described in example 160 but starting with 2-aminobenzylalcohol (26 mg, 0.21 mmol) yielded title compound (24 mg, 24 %).

MS ES$^+$: 565.7 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.97 (t, 2H) ; 2.41 (m, 6H) ; 3.59 (m, 4H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.21 (t, 2H) ; 4.50 (d, 2H) ; 5.27 (t, 1H) ; 7.18 (t, 1H) ; 7.25 (d, 1H) ; 7.26 (s, 1H) ; 7.42 (m, 2H) ; 7.52 (d, 1H) ; 8.67 (s, 1H) ; 9.59 (s, 1H).

Example 171. Preparation of compound 348 in Table 14

An analogous reaction to that described in example 160 but starting with 2-amino-3-methyl-1-butanol (22 mg, 0.21 mmol) yielded title compound (25 mg, 27 %).

MS ES$^+$: 545.7 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 0.87 (d, 3H) ; 0.89 (d, 3H) ; 1.86 (m, 1H) ; 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.44 (2s, 2H) ; 3.57 (d, 2H) ; 3.63 (q, 1H) ; 3.70 (t, 2H) ; 3.80 (d, 2H) ; 4.01 (t, 3H) ; 4.07 (d, 2H) ; 4.31 (t, 2H) ; 7.32 (s, 1H) ; 7.58 (s, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 172. Preparation of compound 349 in Table 14

An analogous reaction to that described in example 160 but starting with 2-anilinoethanol (29 mg, 0.21 mmol) yielded title compound (11 mg, 11 %).

MS ES$^+$: 579.7 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.38 (t, 2H) ; 3.40 (m, 2H) ; 3.50 (t, 2H) ; 3.54 (d, 2H) ; 3.67 (m, 2H) ; 3.75 (t, 2H) ; 3.98 (s, 3H) ; 4.07 (d, 2H) ; 4.31 (t, 2H) ; 7.30 (s, 1H) ; 7.40 (s, 1H) ; 7.45 (m, 2H) ; 7.52 (m, 3H) ; 7.89 (s, 1H) ; 9.08 (s, 1H).

Example 173. Preparation of compound 350 in Table 14

An analogous reaction to that described in example 160 but starting with 3-chloro-4-methylamine (30 mg, 0.21 mmol) yielded title compound (3 mg, 3 %).

MS ES$^+$: 583.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (m, 5H) ; 3.20 (t, 2H) ; 3.40 (t, 2H) ; 3.60 (d, 2H) ; 3.72 (t, 2H) ; 4.01 (s, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 7.32 (m, 2H) ; 7.42 (d, 1H) ; 7.68 (s, 1H) ; 7.87 (s, 1H) ; 7.95 (s, 1H) ; 9.13 (s, 1H).

Example 174. Preparation of compound 351 in Table 14

An analogous reaction to that described in example 160 but starting with 3-nitroaniline (29 mg, 0.21 mmol) yielded title compound (20 mg, 21 %).

MS ES$^+$: 580.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.33 (t, 2H) ; 3.20 (t, 2H) ; 3.39 (t, 2H) ; 3.60 (d, 2H) ; 3.73 (t, 2H) ; 4.02 (s, 3H) ; 4.06 (d, 2H) ; ';4.09 (s, 2H) ; 4.34 (t, 2H) ; 7.34 (s, 1H) ; 7.67 (d, 1H) ; 7.70 (s, 1H) ; 7.95 (s, 1H) ; 7.98 (m, 2H) ; 8.74 (s, 1H) ; 9.15 (s, 1H).

Example 175. Preparation of compound 352 in Table 14

An analogous reaction to that described in example 160 but starting with aminoacetonitrile (19 mg, 0.21 mmol) yielded title compound (28 mg, 31 %).

MS ES$^+$: 498.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 3.84 (s, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.21 (s, 2H) ; 4.31 (t, 2H) ; 7.31 (s, 1H) ; 7.60 (s, 1H) ; 9.10 (s, 1H).

Example 176. Preparation of compound 353 in Table 14

An analogous reaction to that described in example 160 but starting with 2-methyl-5-nitroaniline (32 mg, 0.21 mmol) yielded title compound (11 mg, 11 %).

MS ES$^+$: 594.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 2.44 (s, 3H) ; 3.19 (t, 2H) ; 3.40 (t, 2H) ; 3.59 (d, 2H) ; 3.73 (t, 2H) ; 4.03 (s, 3H) ; 4.07 (d, 2H) ; 4.16 (s, 2H) ; 4.34 (t, 2H) ; 7.34 (s, 1H) ; 7.57 (d, 1H) ; 7.71 (s, 1H) ; 7.95 (s, 1H) ; 8.01 (d, 1H) ; 8.58 (s, 1H) ; 9.13 (s, 1H).

Example 177. Preparation of compound 354 in Table 14

An analogous reaction to that described in example 160 but starting with 2-amino-5-chloropyridine (27 mg, 0.21 mmol) yielded title compound (13 mg, 13 %).

MS ES$^+$: 570.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.07 (s, 2H) ; 4.31 (t, 2H) ; 7.02 (d, 1H) ; 7.36 (s, 1H) ; 7.64 (s, 1H) ; 7.92 (s, 1H) ; 7.98 (dd, 1H) ; 8.21 (d, 1H) ; 9.1 (s, 1H).

Example 178. Preparation of compound 355 in Table 14

An analogous reaction to that described in example 160 but starting with 4-trifluoromethylaniline (34 mg, 0.21 mmol) yielded title compound (26 mg, 25 %);

MS ES$^+$: 603.7 $(M+H)^+$

^{1}H NMR ($DMSOd_6$, TFA): 2.30 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.72 (t, 2H) ; 3.99 (s, 3H) ; 4.05 (m, 4H) ; 4.31 (t, 2H) ; 7.31 (s, 1H) ; 7.66 (s, 1H) ; 7.70 (d, 2H) ; 7.84 (d, 2H) ; 7.92 (s, 1H) ; 9.10 (s, 1H).

Example 179. Preparation of compound 356 in Table 14

An analogous reaction to that described in example 160 but starting with 3-chloroaniline (27 mg, 0.21 mmol) yielded title compound (47 mg, 48 %).

MS ES$^+$: 569.7 $(M+H)^+$

^{1}H NMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2 H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.04 (d, 2H) ; 4.31 (t, 2H) ; 7.14 (d, 1H) ; 7.30 (s, 1H) ; 7.37 (t, 1H) ; 7.47 (d, 1H) ; 7.65 (s,1H) ; 7.87 (s, 1H) ; 7.92 (s, 1H) ; 9.10 (s, 1H).

Example 180. Preparation of compound 357 in Table 14

An analogous reaction to that described in example 160 but starting with 2-methoxyaniline (26 mg, 0.21 mmol) yielded title compound (44 mg, 46 %).

MS ES$^+$: 565.7 $(M+H)^+$

^{1}H NMR ($DMSOd_6$, TFA): 2.33 (t, 2H) ; 3.20 (t, 2H) ; 3.40 (t, 2H) ; 3.60 (d, 2H) ; 3.73 (t, 2H) ; 3.91 (s, 3H) ; 4.03 (s, 3H) ; 4.08 (d, 2H) ; 4.11 (s, 2H) ; 4.34 (t, 2H) ; 6.96 (t, 1H) ; 7.12 (m, 2H) ; 7.34 (s, 1H) ; 7.66 (s, 1H) ; 7.95 (s, 1H) ; 8.01 (d, 1H) ; 9.12 (s, 1H).

Example 181. Preparation of compound 358 in Table 14

An analogous reaction to that described in example 160 but starting with 2-fluoroaniline (23 mg, 0.21 mmol) yielded title compound (43 mg, 46 %).

MS ES$^+$: 553.7 $(M+H)^+$

^{1}H NMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (s, 3H) ; 4.05 (d, 2H) ; 4.08 (s, 2H) ; 4.31 (t, 2H) ; 7.19 (m, 2H) ; 7.28 (m, 1H) ; 7.31 (s, 1H) ; 7.64 (s, 1H) ; 7.93 (m, 2H) ; 9.06 (, 1H).

Example 182. Preparation of compound 359 in Table 14

An analogous reaction to that described in example 160 but starting with thiphene-2-methylamine (24 mg, 0.21 mmol) yielded title compound (50 mg, 53 %).

MS ES$^+$: 555.7 $(M+H)^+$

^{1}H NMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 3.80 (s, 2H) ; 4.01 (s, 3H) ; 4.06 (d, 2H) ; 4.33 (t, 2H) ; 4.52 (s, 2H), 6.98 (dd, 1H) ; 7.02 (dd, 1H) ; 7.32 (s, 1H) ; 7.41 (dd, 1H) ; 7.60 (sq, 1H) ; 7.93 (s, 1H) ; 9.11 (s, 1H).

Example 183. Preparation of compound 360 in Table 14

An analogous reaction to that described in example 160 but starting with 2-amino-1-phenylethanol (29 mg, 0.21 mmol) yielded title compound (32 mg, 33 %).

MS ES^+: 579.7 $(M+H)^+$

^1H NMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 3.18 (m, 3H) ; 3.36 (m, 3H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.74 (s, 2H) ; 3.99 (s, 3H) ; 4.05 (d, 2H) ; 4.30 (t, 2H) ; 4.66 (m, 1H) ; 7.3 (m, 6H) ; 7.53 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 184. Preparation of compound 361 in Table 14

An analogous reaction to that described in example 160 but starting with 3-(1-hydroxyethyl)aniline (29 mg, 0.21 mmol) yielded title compound (50 mg, 50 %).

MS ES^+ : 579.7 $(M+H)^+$

^1H NMR ($DMSOd_6$, TFA): 1.34 (d, 3H) ; 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.00 (s, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 4.72 (q, 1H) ; 7.07 (d, 1H) ; 7.29 (t, 1H) ; 7.33 (s, 1H) ; 7.53 (d, 1H) ; 7.67 (s, 2H) ; 7.93 (s, 1H) ; 9.12 (s, 1H).

Example 185. Preparation of compound 362 in Table 14

An analogous reaction to that described in example 160 but starting with neopentylamine (18 mg, 0.21 mmol) yielded title compound (57 mg, 64 %).

MS ES^+ : 529.7 $(M+H)^+$

^1H NMR ($DMSOd_6$, TFA) : 0.89 (s, 9H) ; 2.33 (t, 2H) ; 2.97 (s, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.59 (d, 2H) ; 3.80 (s, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.32 (t, 2H) ; 7.33 (s, 1H) ; 7.60 (s, 1H) ; 7.93 (s, 1H) ; 9.11 (s, 1H).

Example 186. Preparation of compound 363 in Table 14

An analogous reaction to that described in example 160 but starting with 3-fluoro-4-methoxyaniline (30 mg, 0.21 mmol) yielded title compound (64 mg, 65 %).

MS ES^+: 583.7 $(M+H)^+$

^1H NMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 3.82 (s, 3H) ; 3.96 (s, 2H) ; 4.00 (s, 3H) ; 4.04 (d, 2H) ; 4.31 (t, 2H) ; 7.15 (t, 1H) ; 7.30 (d, 1H) ; 7.31 (s, 1H) ; 7.61 (s, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.10 (s, 1H).

Example 187. Preparation of compound 364 in Table 14

An analogous reaction to that described in example 160 but starting with 2-methyl-4-fluoroaniline (26 mg, 0.21 mmol) yielded title compound (60 mg, 62 %).

MS ES$^+$: 567.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (s, 3H) ; 4.01 (s, 2H) ; 4.04 (d, 2H) ; 4.31 (t, 2H) ; 7.02 (t, 1H) ; 7.10 (d, 1H) ; 7.31 (s, 1H) ; 7.41 (q, 1H) ; 7.66 (s, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 188. Preparation of compound 365 in Table 14

An analogous reaction to that described in example 160 but starting with 2,5-difluoroaniline (27 mg, 0.21 mmol) yielded title compound (14 mg, 14 %).

MS ES$^+$: 571.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.01 (s, 3H) ; 4.06 (d, 2H) ; 4.12 (s, 2H) ; 4.33 (t, 2H) ; 7.00 (m, 1H) ; 7.33 (m, 2H) ; 7.65 (s, 1H) ; 7.95 (m, 2H) ; 9.11 (s, 1H).

Example 189. Preparation of compound 366 in Table 14

An analogous reaction to that described in example 160 but starting with 2-fluoro-4-chloroaniline (31 mg, 0.21 mmol) yielded title compound (12 mg, 12 %).

MS ES$^+$: 587.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (m, 4H) ; 4.31 (t, 2H) ; 7.29 (d, 1H) ; 7.52 (dd, 1H) ; 7.64 (s, 1H) ; 7.97 (d, 1H) ; 9.09 (s, 1H).

Example 190. Preparation of compound 367 in Table 14

An analogous reaction to that described in example 160 but starting with 2-fluoro-4-methylaniline (26 mg, 0.21 mmol) yielded title compound (20 mg, 20 %).

MS ES$^+$: 567.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (s, 3H) ; 2.32 (t, 2H) ; 3.20 (t, 2H) ; 3.39 (t, 2H) ; 3.59 (d, 2H) ; 3.73 (t, 2H) ; 4.03 (s, 3H) ; 4.07 (d, 2H) ; 4.09 (s, 2H) ; 4.34 (t, 2H) ; 7.02 (m, 1H) ; 7.18 (dd, 1H) ; 7.34 (s, 1H) ; 7.67 (s, 1H) ; 7.77 (d, 1H) ; 7.95 (s, 1H) ; 9.12 (s, 1H).

Example 191. Preparation of compound 368 in Table 14

An analogous reaction to that described in example 160 but starting with 3-methylaniline (23 mg, 0.21 mmol) yielded title compound (45 mg, 48 %).

MS ES$^+$: 549.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (m, 5H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.00 (s, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 6.93 (d, 1H) ; 7.24 (t, 1H) ; 7.33 (s, 1H) ; 7.43 (d, 1H) ; 7.51 (s, 1H) ; 7.67 (s, 1H) ; 7.94 (s, 1H) ; 9.12 (s, 1H).

Example 192. Preparation of compound 369 in Table 14

An analogous reaction to that described in example 160 but starting with 2-(methylthio)aniline (29 mg, 0.21 mmol) yielded title compound (13 mg, 13 %).

MS ES$^+$: 581.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.46 (s, 3H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.59 (d, 2H) ; 3.72 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (s, 2H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 7.22 (t, 1H) ; 7.27 (t, 1H) ; 7.34 (s, 1H) ; 7.39 (d, 1H) ; 7.45 (d, 1H) ; 7.68 (s, 1H) ; 7.93 (s, 1H) ; 9.10 (s, 1H).

Example 193. Preparation of compound 370 in Table 14

An analogous reaction to that described in example 160 but starting with 5-aminoindole (28 mg, 0.21 mmol) yielded title compound (33 mg, 34 %).

MS ES$^+$: 574.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.36 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 3.97 (s, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.31 (t, 2H) ; 7.32 (m, 6H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.10 (s, 1H).

Example 194. Preparation of compound 371 in Table 14

An analogous reaction to that described in example 160 but starting with 2,4-difluoroaniline (27 mg, 0.21 mmol) yielded title compound (28 mg, 29 %).

MS ES$^+$: 571.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.59 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.08 (s, 2H) ; 4.34 (t, 2H) ; 7.12 (t, 1H) ; 7.34 (s, 1H) ; 7.36 (m, 1H) ; 7.89 (m, 1H) ; 7.95 (s, 1H) ; 9.12 (s, 1H).

Example 195. Preparation of compound 372 in Table 14

An analogous reaction to that described in example 160 but starting with 2-fluoro-4-methylaniline (26 mg, 0.21 mmol) yielded title compound (35 mg, 37 %).

MS ES$^+$: 567.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.33 (s, 5H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (s, 3H) ; 4.07 (s, 2H) ; 4.08 (d, 2H) ; 4.33 (t, 2H) ; 7.04 (d, 1H) ; 7.12 (d, 1H) ; 7.34 (s, 1H) ; 7.66 (s, 1H) ; 7.78 (t, 1H) ; 7.94 (s, 1H) ; 9.12 (s, 1H).

Example 196. Preparation of compound 373 in Table 14

An analogous reaction to that described in example 160 but starting with 3-cyanoaniline (25 mg, 0.21 mmol) yielded title compound (21 mg, 22 %).

MS ES$^+$: 560.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (s, 3H) ; 4.06 (s, 2H) ; 4.07 (d, 2H) ; 4.33 (t, 2H) ; 7.34 (s, 1H) ; 7.6 (m, 2H) ; 7.69 (s, 1H) ; 7.85 (m, 1H) ; 7.95 (s, 1H) ; 8.18 (s, 1H) ; 9.13 (s, 1H).

Example 197. Preparation of compound 374 in Table 14

An analogous reaction to that described in example 160 but starting with 2-methyl-5-fluoroaniline (26 mg, 0.21 mmol) yielded title compound (15 mg, 16 %).

MS ES$^+$: 567.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.27 (s, 3H) ; 2.32 (t, 2H) ; 3.20 (t, 2H) ; 3.39 (t, 2H) ; 3.59 (d, 2H) ; 3.72 (t, 2H) ; 4.02 (s, 3H) ; 4.07 (d, 2H) ; 4.09 (s, 2H) ; 4.33 (t, 2H) ; 6.96 (t, 1H) ; 7.29 (t, 1H) ; 7.34 (s, 1H) ; 7.48 (d, 1H) ; 7.69 (s, 1H) ; 7.95 (s, 1H) ; 9.12 (s, 1H).

Example 198. Preparation of compound 375 in Table 14

An analogous reaction to that described in example 160 but starting with 2-methyl-5-chloroaniline (30 mg, 0.21 mmol) yielded title compound (20 mg, 21 %).

MS ES$^+$: 583.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA) : 2.26 (s, 3H) ; 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.71 (t, 2H) ; 4.01 (s, 3H) ; 4.05 (d, 2H) ; 4.07 (s, 2H) ; 4.32 (t, 2H) ; 7.16 (dd, 1H) ; 7.27 (d, 1H) ; 7.31 (s, 1H) ; 7.65 (d, 1H) ; 7.65 (s, 1H) ; 7.93 (s, 1H) ; 9.10 (s, 1H).

Example 199. Preparation of compound 376 in Table 15

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-((1-methyl-piperidine-4-yl)methoxy)quinazoline (89 mg, 0.2 mmol) in DMF (1.5 ml), was reacted with aniline (22 mg, 0.24 mmol) in presence of 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (99 mg, 0.26 mmol) and DIEA (50 mg, 0.4 mmol) at 60°C over night. After cooling to room temperature the reaction mixture was diluted with dichloromethane, and purified by silicagel chromatography, eluting successively with CH_2Cl_2, CH_2Cl_2 / MeOH 90/10, and CH_2Cl_2 / MeOH sat. NH_3 90/10 to give title compound (50 mg, 42 %).

MS ES^+: 519.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.58 (m, 2H) ; 2.02 (m, 2H) ; 2.13 (m, 1H) ; 2.80 (s, 3H) ; 3.03 (t, 2H) ; 3.52 (d, 2H) ; 3.98 (s, 2H) ; 3.98 (s, 3H) ; 4.10 (d, 2H) ; 7.06 (t, 1H) ; 7.29 (s, 1H) ; 7.33 (t, 2H) ; 7.60 (d, 2H) ; 7.61 (s, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

The NMR spectrum of example 199 in presence of acid shows the existence of 2 forms in a ratio of approximately 9 : 1. Signals due to the minor form are seen at 1.95 (m) 3.23 (m) 3.32 (m) 4.28 (d) 9.38 (m).

4-benzyloxy-3-methoxybenzonitrile.

4-benzyloxy-3-methoxybenzaldehyde (4.84 g, 20 mmol) in acetic acid (25 ml) and sodium acetate (3.3 g, 40 mmol) was reacted with hydroxylamine hydrochloride (2.8 g, 40 mmol) at reflux for 6 hours. The mixture was cooled, diluted with water, extracted with methylene chloride, dried over $MgSO_4$, concentrated to give title compound (4.8 g, 100 %).

^{1}HNMR ($DMSOd_6$): 3.83 (s, 3H) ; 5.20 (s, 2H) ; 7.21 (d, 1H) ; 7.40 (m, 7H).

2-nitro-4-benzyloxy-5-methoxybenzonitrile

4-benzyloxy-3-methoxybenzonitrile (4.78 g, 20 mmol) in acetic acid (10 ml) was slowly added to nitric acid (25 ml) at 20°C to 30°C. The mixture was stirred at room temperature for 6 hours, basified (pH 10-11) with cooling (KOH 10N), extracted with methylene chloride, dried over $MgSO_4$ evaporated. The solid was recristallysed in hot EtOAc, a yellow solid of title compound was obtained (3.62 g, 64 %).

MS ES^+: 285 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 3.97 (s, 3H) ; 5.33 (s, 2H) ; 7.40 (m, 5H) ; 7.71 (s, 1H) ; 8.01 (s, 1H).

2-nitro-4-hydroxy-5-methoxybenzonitrile

(excess) was added. The insoluble was filtered, the filtrate was concentrated, ethanol was added, the solid filtered, washed with ether, to give title compound (102 mg, 77 %).

MS ES$^+$: 444.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.61 (m, 2H) ; 2.03 (d, 2H) ; 2.16 (m, 1H) ; 2.80 (s, 3H) ; 3.03 (t, 2H) ; 3.5 (d, 2H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.10 (d, 2H) ; 7.32 (s, 1H) ; 7.59 (s, 1H) ; 7.89 (s, 1H) ; 9.07 (s, 1H).

Example 200. Preparation of compound 377 in Table 15

An analogous reaction to that described in example 199 but starting with 3-chloro-4-fluoroaniline (44 mg, 0.3 mmol) yielded compound 377 in table 15 (63 mg, 60 %)

MS ES$^+$: 571 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.64 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.8 (s, 3H) ; 3.04 (t, 2H) ; 3.51 (d, 2H) ; 3.99 (s, 3H) ; 4.0 (s, 2H) ; 4.11 (d, 2H) ; 7.34 (s, 1H) ; 7.39 (t, 1H) ; 7.5 (m, 1H) ; 7.65 (s, 1H) ; 7.91 (dd, 1H) ; 9.09 (s, 1H).

Example 201. Preparation of compound 378 in Table 15

An analogous reaction to that described in example 199 but starting with 2-aminopyridine (40 mg, 0.42 mmol) yielded compound 378 in table 15 (100 mg, 53 %)

MS ES$^+$: 520 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.65 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.78 (s, 3H) ; 3.02 (t, 2H) ; 3.48 (d, 2H) ; 3.99 (s, 3H) ; 4.1 (d, 2H) ; 4.14 (s, 2H) ; 7.32 (m, 1H) ; 7.39 (s, 1H) ; 7.66 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (d, 1H) ; 8.16 (t, 1H) ; 8.4 (d, 1H) ; 9.079 (s, 1H).

Example 202. Preparation of compound 379 in Table 15

An analogous reaction to that described in example 199 but starting with 3,4-difluoroaniline (54 mg, 0.42 mmol) yielded compound 379 in table 15 (120 mg, 72 %)

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.63 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.79 (s, 3H) ; 3.03 (t, 2H) ; 3.49 (d, 2H) ; 3.99 (s, 3H) ; 4.0 (s, 2H) ; 4.10 (d, 2H) ; 7.35 (s, 1H) ; 7.39 (m, 2H) ; 7.64 (s, 1H) ; 7.82 (dd., 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 203. Preparation of compound 380 in Table 15

An analogous reaction to that described in example 199 but starting with 2-chloroaniline (54 mg, 0.42 mmol) yielded compound 380 in table 15 (29 mg, 16 %)

MS ES^+: 553 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.62 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 1H) ; 2.81 (s, 3H) ; 3.04 (t, 2H) ; 3.51 (d, 2H) ; 4.0 (s, 3H) ; 4.08 (s, 2H) ; 4.11 (d, 2H) ; 7.24 (t, 1H) ; 7.31 (s, 1H) ; 7.34 (dd, 1H) ; 7.53 (d, 1H) ; 7.66 (s, 1H) ; 7.75 (d, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 204. Preparation of compound 381 in Table 15

An analogous reaction to that described in example 199 but starting with 4-methylaniline (45 mg, 0.42 mmol) yielded compound 381 in table 15 (155 mg, 85 %)

MS ES^+: 533 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.65 (m, 2H) ; 2.02 (m, 2H) ; 2.16 (m, 1H) ; 2.27 (s, 3H) ; 2.8 (s, 3H) ; 3.05 (t, 2H) ; 3.50 (d, 2H) ; 3.97 (s, 2H) ; 3.99 (s, 3H) ; 4.11 (d, 2H) ; 7.14 (d, 2H) ; 7.34 (s, 1H) ; 7.52 (d, 2H) ; 7.63 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 205. Preparation of compound 382 in Table 15

An analogous reaction to that described in example 199 but starting with 2-methylaniline (45 mg, 0.42 mmol) yielded compound 382 in table 15 (126 mg, 69 %)

MS ES^+: 533 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.62 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.24 (s, 3H) ; 2.8 (s, 3H) ; 3.04 (t, 2H) ; 3.51 (d, 2H) ; 3.99 (s, 3H) ; 4.02 (s, 2H) ; 4.10 (d, 2H) ; 7.11 (t, 1H) ; 7.19 (t, 1H) ; 7.24 (d, 1H) ; 7.33 (s, 1H) ; 7.43 (d, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.07 (s, 1H).

Example 206. Preparation of compound 383 in Table 15

An analogous reaction to that described in example 199 but starting with 4-chloroaniline (54 mg, 0.42 mmol) yielded compound 383 in table 15 (128 mg, 68 %)

MS ES^+: 553 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.65 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.79 (s, 3H) ; 3.04 (t, 2H) ; 3.50 (d, 2H) ; 3.99 (s, 3H) ; 4.0 (s, 2H) ; 4.1 (d, 2H) ; 7.36 (s, 1H) ; 7.38 (d, 2H) ; 7.64 (s, 1H) ; 7.68 (d, 2H) ; 7.9 (s, 1H) ; 9.08 (s, 1H).

Example 207. Preparation of compound 384 in Table 15

An analogous reaction to that described in example 199 but starting with 4-fluoroaniline (47 mg, 0.42 mmol) yielded compound 384 in table 15 (136 mg, 84 %)

MS ES$^+$: 537 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.62 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.79 (s, 3H) ; 3.03 (t, 2H) ; 3.50 (d, 2H) ; 3.97 (s, 2H) ; 3.98 (s, 3H) ; 4.1 (d, 2H) ; 7.16 (t, 2H) ; 7.34 (s, 1H) ; 7.63 (s, 1H) ; 7.65 (m, 2H) ; 7.9 (s, 1H) ; 9.07 (s, 1H).

Example 208. Preparation of compound 385 in Table 15

An analogous reaction to that described in example 199 but starting with 2-amino-6-methylpyrimidine (45 mg, 0.42 mmol) yielded compound 385 in table 15 (91 mg, 57 %)

MS ES$^+$: 534 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.61 (m, 2H) ; 2.05 (m, 2H) ; 2.15 (m, 1H) ; 2.50 (s, 3H) ; 2.8 (s, 3H) ; 3.03 (t, 2H) ; 3.52 (d, 2H) ; 4.02 (s, 3H) ; 4.1 (s, 2H) ; 4.11 (d, 2H) ; 7.15 (m, 1H) ; 7.33 (s, 1H) ; 7.65 (s, 1H) ; 7.8 (m, 2H) ; 7.91 (s, 1H) ; 9.07 (s, 1H).

Example 209. Preparation of compound 386 in Table 15

An analogous reaction to that described in example 199 but starting with 3-methoxyaniline (52 mg, 0.42 mmol) yielded compound 386 in table15 (125 mg, 67 %)

MS ES$^+$: 549 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.63 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.8 (s, 3H) ; 3.04 (t, 2H) ; 3.52 (d, 2H) ; 3.75 (s, 3H) ; 3.98 (s, 2H) ; 3.99 (s, 3H) ; 4.11 (d, 2H) ; 6.68 (m, 1H) ; 7.17 (d, 1H) ; 7.24 (t, 1H) ; 7.33 (s, 1H) ; 7.35 (d, 1H) ; 7.64 (s, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 210. Preparation of compound 387 in Table 15

An analogous reaction to that described in example 199 but starting with 2-amino-5-chloropyridine (54 mg, 0.42 mmol) yielded compound 387 in table 15 (22 mg, 11 %)

MS ES$^+$: 554$(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.61 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 1H) ; 2.8 (s, 3H) ; 3.03 (t, 2H) ; 3.5 (d, 2H) ; 3.98 (s, 3H) ; 4.07 (s, 2H) ; 4.11 (d, 2H) ; 7.30 (s, 1H) ; 7.63 (s, 1H) ; 7.9 (s, 1H) ; 7.93 (dd, 1H) ; 8.12 (d, 1H) ; 8.41 (d, 1H).

Example 211 Preparation of compound 388 in Table 15

An analogous reaction to that described in example 199 but starting with 3-chloroaniline (54 mg, 0.42 mmol) yielded compound 388 in Table 15 (130 mg, 69 %).

MS ES$^+$: 553 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.62 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.78 (s, 3H) ; 3.02 (t, 2H) ; 3.49 (d, 2H) ; 3.97 (s, 3H) ; 3.99 (s, 2H) ; 4.08 (d, 2H) ; 7.13 (d, 1H) ; 7.3 (s, 1H) ; 7.38 (t, 1H) ; 7.64 (s, 1H) ; 7.86 (s, 1H) ; 7.90 (s, 1H) ; 9.07 (s, 1H).

Example 212. Preparation of compound 389 in Table 15

An analogous reaction to that described in example 199 but starting with 2-fluoroaniline (47 mg, 0.42 mmol) yielded compound 389 in Table 15 (116 mg, 63 %).

MS ES$^+$: 537 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.64 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.79 (s, 3H) ; 3.03 (t, 2H) ; 3.50 (d, 2H) ; 3.99 (s, 3H) ; 4.07 (s, 2H) ; 4.10 (d, 2H) ; 7.19 (m, 2H) ; 7.25 (m, 1H) ; 7.35 (s, 1H) ; 7.63 (s, 1H) ; 7.90 (s, 1H) ; 7.91 (m, 1H) ; 9.07 (s, 1H).

Example 213. Preparation of compound 390 in Table 15

Analogous reaction to that described in example 199 but starting with 3-dluoro-4-methoxyaniline (59 mg, 0.42 mmol) yielded compound 390 in Table 15 (151 mg, 85 %).

MS ES$^+$: 567 $(M+H)^+$.

^{1}HNMR ($DMSOd_6$, TFA): 1.62 (m, 2H) ; 2.01 (m, 2H) ; 2.15 (m, 1H) ; 2.79 (s, 3H) ; 3.03 (t, 2H) ; 3.51 (d, 2H) ; 3.81 (s, 3H) ; 3.96 (s, 2H) ; 3.98 (s, 3H) ; 4.10 (d, 2H) ; 7.14 (t, 1H) ; 7.28 (d, 1H) ; 7.34 (s, 1H) ; 7.59 (dd, 1H) ; 7.6 (s, 1H) ; 7.90 (s, 1H) ; 9.07 (s, 1H).

Example 214. Preparation of compound 391 in Table 15

An analogous reaction to that described in example 199 but starting with 2-methyl-4-fluoroaniline (53 mg, 0.42 mmol) yielded compound 391 in Table 15 (151 mg, 81 %).

MS ES$^+$: 551 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.62 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.33 (s, 3H) ; 2.79 (s, 3H) ; 2.93 (t, 2H) ; 3.48 (d, 2H) ; 3.97 (s, 3H) ; 3.99 (s, 2H) , 4.09 (d, 2H) ; 7.01 (dt, 1H) ; 7.1 (dd, 1H) ; 7.37 (s, 1H) ; 7.39 (m, 1H) ; 7.64 (s, 1H) ; 7.89 (s, 1H) ; 9.05 (s, 1H).

Example 215. Preparation of compound 392 in Table 15

An analogous reaction to that described in example 199 but starting with 2-amino-4-methylpyridine (45 mg, 0.42 mmol) yielded compound 392 in Table 15 (119 mg, 66 %).
MS ES$^+$: 534 $(M+H)^+$
^{1}HNMR ($DMSOd_6$, TFA): 1.66 (m, 2H) ; 2.05 (m, 2H) ; 2.15 (m, 1H) ; 2.77 (s, 3H) ; 3.03 (t, 2H) ; 3.48 (d, 2H) ; 3.97 (s, 3H) ; 4.09 (d, 2H) ; 4.21 (s, 2H) ; 7.35 (m, 1H) ; 7.45 (s, 1H) ; 7.69 (s, 1H) ; 7.70 (s, 1H) ; 7.90 (s, 1H) ; 8.31 (d, 1H) ; 9.06 (s, 1H).

Example 216. Preparation of compound 393 in Table 15

An analogous reaction to that described in example 199 but starting with 2,5-difluoroaniline (54 mg, 0.42 mmol) yielded compound 393 in Table 15 (42 mg, 22 %).
MS ES$^+$: 555 $(M+H)^+$
^{1}HNMR ($DMSOd_6$, TFA): 1.60 (m, 2H) ; 2.02 (m, 2H) ; 2.15 (m, 1H) ; 2.81 (s, 3H) ; 3.04 (t, 2H) ; 3.52 (d, 2H) ; 3.99 (s, 3H) ; 4.10 (s, 2H) ; 4.11 (d, 2H) ; 7.02 (m, 2H) ; 7.32 (s, 1H) ; 7.34 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.92 (m, 1H) ; 9.08 (s, 1H).

Example 217. Preparation of compound 394 in Table 15

An analogous reaction to that described in example 199 but starting with 2-fluoro-4-chloroaniline (61 mg, 0.42 mmol) yielded compound 394 in Table 15 (97 mg, 50 %).
MS ES$^+$: 571 $(M+H)^+$
^{1}HNMR ($DMSOd_6$, TFA): 1.63 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.77 (s, 3H) ; 3.03 (t, 2H) ; 3.48 (d, 2H) ; 3.98 (s, 3H) ; 4.07 (s, 2H) ; 4.09 (d, 2H) ; 7.26 (d, 1H) ; 7.38 (s, 1H) ; 7.5 (dd, 1H) ; 7.62 (s, 1H) ; 7.89 (s, 1H) ; 7.96 (t, 1H) ; 9.06 (s, 1H).

Example 218. Preparation of compound 395 in Table 15

An analogous reaction to that described in example 199 but starting with 2-fluoro-5-methylaniline (53 mg, 0.42 mmol) yielded compound 395 in Table 15 (119 mg, 63 %).
MS ES$^+$: 551 $(M+H)^+$
^{1}HNMR ($DMSOd_6$, TFA): 1.63 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 1H) ; 2.28 (s, 3H) ; 2.77 (s, 3H) ; 3.03 (t, 2H) ; 3.49 (d, 2H) ; 3.98 (s, 3H) ; 4.05 (s, 2H) ; 4.09 (d, 2H) ; 6.98 (m, 1H) ; 7.15 (dd, 1H) ; 7.38 (s, 1H) ; 7.62 (s, 1H) ; 7.72 (m, 1H) ; 7.89 (s, 1H) ; 9.06 (s, 1H).

Example 219. Preparation of compound 396 in Table 15

An analogous reaction to that described in example 199 but starting with 3-methylaniline (45 mg, 0.42 mmol) yielded compound 396 in Table 15 (144g, 79 %).

MS ES$^+$: 533 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.64 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.3 (s, 3H) ; 2.79 (s, 3H) ; 3.04 (t, 2H) ; 3.51 (d, 2H) ; 3.98 (s, 2H) ; 3.99 (3H) ; 4.10 (d, 2H) ; 6.90 (d, 1H) ; 7.21 (t, 1H) ; 7.36 (s, 1H) ; 7.42 (d, 1H) ; 7.49 (s, 1H) ; 7.63 (s, 1H) ; 7.9 (s, 1H) ; 9.07 (s, 1H).

Example 220. Preparation of compound 397 in Table 15

An analogous reaction to that described in example 199 but starting with 2,4-difluoroaniline (54 mg, 0.42 mmol) yielded compound 397 in Table 15 (121 mg, 74 %).

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.63 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 1H) ; 2.78 (s, 3H) ; 3.03 (t, 2H) ; 3.5 (d, 2H) ; 3.98 (s, 3H) ; 4.04 (s, 2H) ; 4.1 (d, 2H) ; 7.08 (m, 1H) ; 7.33 (m, 1H) ; 7.36 (s, 1H) ; 7.63 (s, 1H) ; 7.86 (m, 1H) ; 7.90 (s, 1H) ; 9.07 (s, 1H).

Example 221. Preparation of compound 398 in Table 15

An analogous reaction to that described in example 199 but starting with 2-fluoro-4-methylaniline (53 mg, 0.42 mmol) yielded compound 398 in Table 15 (147 mg, 79 %).

MS ES$^+$: 551 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.63 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.3 (s, 3H) ; 2.79 (s, 3H) ; 3.04 (t, 2H) ; 3.51 (d, 2H) ; 3.99 (s, 3H) ; 4.04 (s, 2H) ; 4.1 (d, 2H) ; 6.99 (d, 1H) ; 7.10 (d, 1H) ; 7.35 (s, 1H) ; 7.62 (s, 1H) ; 7.75 (t, 1H) ; 7.90 (s, 1H) ; 9.07 (s, 1H).

Example 222. Preparation of compound 399 in Table 15

An analogous reaction to that described in example 199 but starting with 3-cyanoaniline (50 mg, 0.42 mmol) yielded compound 399 in Table 15 (118 mg, 71 %).

MS ES$^+$: 544 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.66 (m, 2H) ; 2.07 (m, 2H) ; 2.17 (m, 1H) ; 2.81 (s, 3H) ; 3.06 (t, 2H) ; 3.53 (d, 2H) ; 4.0 (s, 3H) ; 4.05 (s, 2H) ; 4.11 (d, 2H) ; 7.36 (s, 1H) ; 7.54 (m, 2H) ; 7.65 (s, 1H) ; 7.86 (dd, 1H) ; 7.92 (s, 1H) ; 8.18 (s, 1H) ; 9.09 (s, 1H).

Example 223. Preparation of compound 400 in Table 15

An analogous reaction to that described in example 199 but starting with 2-methyl-5-fluoroaniline (53 mg, 0.42 mmol) yielded compound 400 in Table 15 (107 mg, 57 %).

MS ES$^+$: 551 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.65 (m, 2H) ; 2.04 (m, 2H) ; 2.15 (m, 1H) ; 2.24 (s, 3H) ; 2.76 (s, 3H) ; 3.02 (t, 2H) ; 3.47 (d, 2H) ; 3.98 (s, 3H) ; 4.07 (s, 2H) ; 4.08 (d, 2H) ; 6.92 (m, 1H) ; 7.25 (t, 1H) ; 7.4 (s, 1H) ; 7.43 (m, 1H) ; 7.64 (s, 1H) ; 7.88 (s, 1H) ; 9.04 (s, 1H).

Example 224. Preparation of compound 401 in Table 15

An analogous reaction to that described in example 199 but starting with 3,5-difluoroaniline (54 mg, 0.42 mmol) yielded compound 401 in Table 15 (83 mg, 44 %).

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.66 (m, 2H) ; 2.02 (m, 2H) ; 2.16 (m, 1H) ; 2.76 (s, 3H) ; 3.03 (t, 2H) ; 3.45 (d, 2H) ; 3.97 (s, 3H) ; 4.03 (s, 2H) ; 4.08 (d, 2H) ; 6.90 (dd, 1H) ; 7.38 (m, 2H) ; 7.39 (s, 1H) ; 7.87 (s, 1H) ; 9.05 (s, 1H).

Example 225. Preparation of compound 402 in Table 15

An analogous reaction to that described in example 199 but starting with 3-fluoroaniline (47 mg, 0.42 mmol) yielded compound 402 in Table 15 (142 mg, 77 %).

MS ES$^+$: 537 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.62 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 1H) ; 2.78 (s, 3H) ; 3.02 (t, 2H) ; 3.49 (d, 2H) ; 3.98 (s, 3H) ; 4.0 (s, 2H) ; 4.1 (d, 2H) ; 6.9 (s, 1H) ; 7.35 (s, 1H) ; 7.36 (m, 2H) ; 7.62 (m, 1H) ; 7.64 (s, 1H) ; 7.9 (s, 1H) ; 9.08 (s, 1H).

Example 226. Preparation of compound 403 in Table 16

4-((2-amino-1,3-thiazol-5-yl)acetic acid)-6-methoxy-7-(3-N-methylpiperazinylpropoxy)quinazoline (142 mg, 0.3 mmol) in NMP (1.5 ml) was reacted with aniline (42 µl, 0.45 mmol) in presence of 0-(7-azabenzotriazol-1-yl)-N,N,N',N', tetramethyluronium hexafluorophosphate (173 mg, 0.45 mmol) and diisopropylethylamine (105 µl, 0.6 mmol) at 65°C under nitrogen over night. After cooling to room temperature, the reaction mixture was diluted with dichloromethane and purified by silicagel chromatography, eluant CH_2Cl_2, CH_2Cl_2 / MeOH, 9/1, CH_2Cl_2 / MeOH sat. NH_3, 9/1 to give title compound (24 mg, 15 %).

MS ES$^+$: 360.7 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.28 (t, 2H) ; 2.96 (s, 3H) ; 3.26 (s, 3H) ; 3.35 (s, 3H) ; 3.40 (t, 2H) ; 3.1-4 (m, 8H) ; 3.88 (s, 3H) ; 4.21 (t, 2H) ; 7.32 (s, 1H) ; 7.53 (s, 1H) ; 8.56 (s, 1H).

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6-methoxy-4-((3-N-methylpiperazinylpropoxy)quinazoline

N'-(2-cyano-4-methoxy-5-(3-N-piperazinylpropoxy)phenyl)-N,N-dimethylimidoformamide (9.7 g, 27 mmol) in acetic acid (100 ml) was reacted with methyl (2-amino-1,3-thiazole-5-yl)acetate (5.2 g, 30 mmol) at reflux for 4 hours. The solvent was evaporated and the residue purified by silicagel chromatography, Eluant : CH_2Cl_2 / MeOH 99/1 to 97/3 to give title compound (9.15 g, 70 %).

MS ES$^+$: 487.6$(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 2.97 (s, 3H) ; 3.2-4.2 (m, 8H) ; 3.48 (t, 2H) ; 3.97 (s, 2H) ; 4.00 (s, 3H) ; 4.33 (t, 2H) ; 7.36 (s, 1H) ; 7.61 (s, 1H) ; 7.93 (s, 1H) ; 9.10 (s, 1H).

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-(N-methylpiperazinylpropoxy) quinazoline

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6-methoxy-7-(3-(N-methylpiperazinylpropoxy) quinazoline (8.25 g, 17 mmol) in ethanol (80 ml) was treated with sodium hydroxyde (2N, 42.5 ml, 85 mmol) at room temperature for 1 hour. Hydrochloride acid (2N) was added to the solution (pH 3). The solution was evaporated, the residue dissolved in ethanol and N-ethyl diisopropyl amine (8.9 ml, 51 mmol). Ether was added to the solution, the solid was recovered, dried to give title compound (7.44 g, 93 %).

MS ES$^+$: 473.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.1 (m, 8H) ; 3.45 (t, 2H) ; 3.89 (s, 2H) ; 3.97 (s, 3H) ; 4.29 (t, 2H) ; 7.30 (s, 1H) ; 7.56 (s, 1H) ; 7.90 (s, 1H) ; 9.06 (s, 1H).

Example 227. Preparation of compound 404 in Table 16

An analogous reaction to that described in example 226 but starting with 3,4-difluoroaniline (77 mg, 0.6 mmol) yielded title compound (105 mg, 60 %).

MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.32 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 5H) ; 4.30 (t, 2H) ; 7.32 (s, 1H) ; 7.32 (m, 1H) ; 7.40 (q, 1H) ; 7.65 (s, 1H) ; 7.81 (m, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 228. Preparation of compound 405 in Table 16

An analogous reaction to that described in example 226 but starting with 2-aminopyridine (56 mg, 0.6 mmol) yielded title compound (53 mg, 36 %).

MS ES$^+$: 549.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.41 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (s, 2H) ; 4.32 (t, 2H) ; 7.21 (m, 1H) ; 7.34 (s, 1H) ; 7.64 (s, 1H) ; 7.91 (m, 2H) ; 8.03 (d, 1H) ; 8.37 (m, 1H) ; 9.98 (s, 1H).

Example 229. Preparation of compound 406 in Table 16

An analogous reaction to that described in example 226 but starting with 3-chloro-4-fluoroaniline (87 mg, 0.6 mmol) yielded title compound (134 mg, 74 %).

MS ES$^+$: 600.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.43 (t, 2H) ; 3.1-4.1 (m, 8H) ; 3.99 (s, 5H) ; 4.32 (t, 2H) ; 7.33 (s, 1H) ; 7.38 (t, 1H) ; 7.50 (m, 1H) ; 7.64 (s, 1H) ; 7.90 (s, 1H) ; 7.96 (m, 1H) ; 9.09 (s, 1H).

Example 230. Preparation of compound 407 in Table 16

An analogous reaction to that described in example 226 but starting with 3-chloroaniline (77 mg, 0.6 mmol) yielded title compound (46 mg, 26 %).

MS ES$^+$: 582.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.2-4.1 (m, 8H) ; 3.45 (t, 2H) ; 3.99 (s, 3H) ; 4.07 (s, 2H) ; 4.30 (t, 2H) ; 7.22 (t, 1H) ; 7.31 (s, 1H) ; 7.35 (t, 1H) ; 7.53 (d, 1H) ; 7.65 (s, 1H) ; 7.74 (d, 1H) ; 7.92 (s, 1H) ; 9.08 (s, 1H).

Example 231. Preparation of compound 408 in Table 16

An analogous reaction to that described in example 226 but starting with 4-methylaniline (64 mg, 0.6 mmol) yielded title compound (105 mg, 62 %).

MS ES$^+$: 562.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.26 (s, 3H) ; 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.43 (t, 2H) ; 3.95 (s, 2H) ; 3.98 (s, 3H) ; 4.30 (t, 2H) ; 7.12 (d, 2H) ; 7.31 (s, 1H) ; 7.50 (d, 2H) ; 7.63 (s, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 232. Preparation of compound 409 in Table 16

An analogous reaction to that described in example 226 but starting with 2-methylaniline (64 mg, 0.6 mmol) yielded title compound (127 mg, 75 %).

MS ES+ : 562.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.24 (s, 3H) ; 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.2-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (s, 2H) ; 4.31 (t, 2H) ; 7.12 (t, 1H) ; 7.19 (t, 1H) ; 7.24 (d, 1H) ; 7.33 (s, 1H) ; 7.44 (d, 1H) ; 7.66 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 233. Preparation of compound 410 in Table 16

An analogous reaction to that described in example 226 but starting with 4-chloroaniline (77 mg, 0.6 mmol) yielded title compound (101 mg, 58 %).

MS ES^+: 582.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 4.00 (s, 5H) ; 4.31 (t, 2H) ; 7.33 (s, 1H) ; 7.40 (d, 2H) ; 7.65 (s, 1H) ; 7.66 (d, 2H) ; 7.92 (s, 1H) ; 9.10 (s, 1H).

Example 234. Preparation of compound 411 in Table 16

An analogous reaction to that described in example 226 but starting with 4-fluoroaniline (67 mg, 0.6 mmol) yielded title compound (97 mg, 57 %).

MS ES^+: 566.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.97 (s, 2H) ; 3.99 (s, 3H) ; 4.30 (t, 2H) ; 7.17 (t, 2H) ; 7.34 (s 1H) ; 7.64 (m, 3H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 235. Preparation of compound 412 in Table 16

An analogous reaction to that described in example 226 but starting with 2-amino-6-methylpyridine (65 mg, 0.6 mmol) yielded title compound (70 mg, 42 %).

MS ES^+ : 563.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.30 (t, 2H) ; 2.46 (s, 3H) ; 2.94 (s, 3H) ; 3.10-4.10 (m, 8H) ; 3.43 (t, 2H) ; 3.98 (s, 3H) ; 4.06 (s, 2H) ; 4.30 (t, 2H) ; 7.08 (d, 1H) ; 7.32 (s, 1H) ; 7.63 (s, 1H) ; 7.79 (t, 1H) ; 7.88 (d, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 236. Preparation of compound 413 in Table 16

An analogous reaction to that described in example 226 but starting with 2-methoxyaniline (74 mg, 0.6 mmol) yielded title compound (99 mg, 57 %).

MS ES$^+$: 578.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.43 (t, 2H) ; 3.74 (s, 3H) ; 3.97 (s, 2H) ; 3.99 (s, 3H) ; 4.30 (t, 2H) ; 6.67 (d, 1H) ; 7.15 (d, 1H) ; 7.24 (t, 1H) ; 7.33 (s, 2H) ; 7.64 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 237. Preparation of compound 414 in Table 16

An analogous reaction to that described in example 226 but starting with 2-amino-5-chloropyridine (77 mg, 0.6 mmol) yielded title compound (23 mg, 13 %).

MS ES$^+$: 583.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.10-4.10 (m, 8H) ; 3.45 (t, 2H) ; 3.98 (s, 3H) ; 4.06 (s, 2H) ; 4.30 (t, 2H) ; 7.31 (s, 1H) ; 7.63 (s, 1H) ; 7.90 (s, 1H) ; 7.91 (dd, 1H) ; 8.11 (d, 1H) ; 8.40 (d, 1H) ; 9.09 (s, 1H).

Example 238. Preparation of compound 415 in Table 16

An analogous reaction to that described in example 226 but starting with 3-chloroaniline (77 mg, 0.6 mmol) yielded title compound (96 mg, 55 %).

MS ES$^+$: 582.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.2 (m, 8H) ; 3.45 (t, 2H) ; 3.98 (s, 5H) ; 4.28 (t, 2H) ; 7.12 (d, 1H) ; 7.31 (s, 1H) ; 7.34 (t, 1H) ; 7.46 (d, 1H) ; 7.62 (s, 1H) ; 7.85 (s, 1H) ; 7.91 (s, 1H) ; 9.07 (s, 1H).

Example 239. Preparation of compound 416 in Table 16

An analogous reaction to that described in example 226 but starting with 2-fluoroaniline (67 mg, 0.6 mmol) yielded title compound (68 mg, 40 %).

MS ES$^+$: 596.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.28 (t, 2H) ; 2.91 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.40 (t, 2H) ; 3.95 (s, 3H) ; 4.03 (s, 2H) ; 4.26 (t, 2H) ; 7.13 (m, 2H) ; 7.25 (m, 2H) ; 7.28 (s, 1H) ; 7.60 (s, 1H) ; 7.87 (s, 1H) ; 9.05 (s, 1H).

Example 240. Preparation of compound 417 in Table 16

An analogous reaction to that described in example 226 but starting with 3-cyanoaniline (71 mg, 0.6 mmol) yielded title compound (101 mg, 63 %).

MS ES$^+$: 573.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.45 (t, 2H) ; 4.00 (s, 3H) ; 4.04 (s, 2H) ; 4.31 (t, 2H) ; 7.33 (s, 1H) ; 7.56 (s, 1H) ; 7.57 (m, 1H) ; 7.66 (s, 1H) ; 7.82 (m, 1H) ; 7.92 (s, 1H) ; 8.15 (s, 1H) ; 9.10 (s, 1H).

Example 241. Preparation of compound 418 in Table 16

An analogous reaction to that described in example 226 but starting with 2-fluoro-4-methylaniline (75 mg, 0.6 mmol) yielded title compound (109 mg, 63 %).

MS ES$^+$: 580.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.29 (m, 5H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.98 (s, 3H) ; 4.03 (s, 2H) ; 4.30 (t, 2H) ; 6.98 (d, 1H) ; 7.09 (d, 1H) ; 7.32 (s, 1H) ; 7.63 (s, 1H) ; 7.74 (t, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 242. Preparation of compound 419 in Table 16

An analogous reaction to that described in example 226 but starting with 3-fluoro-4-methoxyaniline (85 mg, 0.6 mmol) yielded title compound (121 mg, 68 %).

MS ES$^+$: 596.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.81 (s, 3H) ; 3.95 (s, 2H) ; 3.99 (s, 3H) ; 4.30 (t, 2H) ; 7.13 (t, 1H) ; 7.27 (m, 1H) ; 7.31 (s, 1H) ; 7.60 (m, 1H) ; 7.64 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 243. Preparation of compound 420 in Table 16

An analogous reaction to that described in example 226 but starting with 2-methyl-4-fluoroaniline (75 mg, 0.6 mmol) yielded title compound (130 mg, 75 %).

MS ES$^+$: 580.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.23 (s, 3H) ; 2.29 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.30 (t, 2H) ; 7.01 (m, 1H) ; 7.09 (dd, 1H) ; 7.32 (s, 1H) ; 7.40 (m, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 244. Preparation of compound 421 in Table 16

An analogous reaction to that described in example 226 but starting with 2-amino-4-methylpyridine (65 mg, 0.6 mmol) yielded title compound (87 mg, 52 %).

MS ES$^+$: 563.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.29 (t, 2H) ; 2.45 (s, 3H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.15 (s, 2H) ; 4.30 (t, 2H) ; 7.24 (d, 1H) ; 7.37 (s, 1H) ; 7.67 (s, 1H) ; 7.72 (s, 1H) ; 7.92 (s, 1H) ; 8.29 (d, 1H) ; 9.08 (s, 1H);

Example 245. Preparation of compound 422 in Table 16

An analogous reaction to that described in example 226 but starting with 2,5-difluoroaniline (77 mg, 0.6 mmol) yielded title compound (56 mg, 32 %).

MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.30 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.43 (t, 2H) ; 3.98 (s, 3H) ; 4.10 (s, 2H) ; 4.30 (t, 2H) ; 7.0 (m, 1H) ; 7.32 (s, 1H) ; 7.33 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (m, 2H) ; 9.09 (s, 1H).

Example 246. Preparation of compound 423 in Table 16

An analogous reaction to that described in example 226 but starting with 2-fluoro-4-chloroaniline (87 mg, 0.6 mmol) yielded title compound (69 mg, 38 %).

MS ES$^+$: 600.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.32 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.2 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.07 (s, 2H) ; 4.30 (t, 2H) ; 7.20 (dd, 1H) ; 7.33 (s, 1H) ; 7.51 (dd, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (t, 1H) ; 9.09 (s, 1H).

Example 247. Preparation of compound 424 in Table 16

An analogous reaction to that described in example 226 but starting with 2-fluoro-5-methylaniline (75 mg, 0.6 mmol) yielded title compound (81 mg, 46 %).

MS ES$^+$: 580.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.27 (s, 3H) ; 2.32 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.44 (t, 2H) ; 3.99 (s, 3H) ; 4.05 (s, 2H) ; 4.30 (t, 2H) ; 6.97 (m, 1H) ; 7.13 (dd, 1H) ; 7.34 (s, 1H) ; 7.63 (s, 1H) ; 7.74 (d, 1H) ; 7.91 (s; 1H) ; 9.08 (s, 1H).

Example 248. Preparation of compound 425 in Table 16

An analogous reaction to that described in example 226 but starting with 3-methylaniline (64 mg, 0.6 mmol) yielded title compound (116 mg, 69 %).

MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.28 (s, 3H) ; 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.45 (t, 2H) ; 3.96 (s, 2H) ; 3.98 (s, 3H) ; 4.30 (t, 2H) ; 6.88 (d, 1H) ; 7.19 (t, 1H) ; 7.30 (s, 1H) ; 7.39 (d, 1H) ; 7.47 (s, 1H) ; 7.62 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 249. Preparation of compound 426 in Table 16

An analogous reaction to that described in example 226 but starting with 2,4-difluoroaniline (77 mg, 0.6 mmol) yielded title compound (84 mg, 48 %).

MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.99 (s, 3H) ; 4.05 (s, 2H) ; 4.30 (t, 2H) ; 7.07 (t, 1H) ; 7.32 (m, 2H) ; 7.64 (s, 1H) ; 7.86 (m, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 250. Preparation of compound 427 in Table 16

An analogous reaction to that described in example 226 but starting with 2-methyl-5-fluoroaniline (75 mg, 0.6 mmol) yielded title compound (98 mg, 57 %).

MS ES$^+$: 580.6$(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.23 (s, 3H) ; 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.43 (t, 2H) ; 3.98 (s, 3H) ; 4.05 (s, 2H) ; 4.30 (t, 2H) ; 6.91 (m, 1H) ; 7.25 (t, 1H) ; 7.32 (s, 1H) ; 7.44 (dd, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 251. Preparation of compound 428 in Table 16

An analogous reaction to that described in example 226 but starting with 3,5-difluoroaniline (77 mg, 0.6 mmol) yielded title compound (54 mg, 31 %).

MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 2.95 (s, 3H) ; 3.1-4.1 (m, 8H) ; 3.45 (t, 2H) ; 3.99 (s, 3H) ; 4.02 (s, 2H) ; 4.31 (t, 2H) ; 6.92 (m, 1H) ; 7.33 (s, 1H) ; 7.35 (m, 2H) ; 7.66 (s, 1H) ; 7.92 (s, 1H) ; 9.10 (s, 1H).

Example 252. Preparation of compound 429 in Table 16

An analogous reaction to that described in example 226 but starting with 3-fluoroaniline (67 mg, 0.6 mmol) yielded title compound (120 mg, 70 %).

MS ES$^+$: 566.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.31 (t, 2H) ; 2.94 (s, 3H) ; 3.2-4.2 (m, 8H) ; 3.44 (t, 2H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.30 (t, 2H) ; 6.90 (s, 1H) ; 7.34 (s, 1H) ; 7.36 (m, 2H) ; 7.61 (m, 1H) ; 7.64 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 253. Preparation of compound 430 in Table 17

N-(3-chlorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide (141 mg, 0.22 mmol) in acetonitrile (2 ml) was reacted with pyrrolidine (3.3 mmol) in presence of potassium iodide (100 mg, 0.6 mmol) at 80°C for 15 h / 30 hours. When the reaction was completed (tlc) DMF (2 ml), silicagel (2 g) was added, the mixture evaporated, and the residue was purified by silica gel chromatography, eluant : CH_2Cl_2 / MeOH 95/5, CH_2Cl_2 / MeOH sat. NH_3 90/10 to give title compound (81 mg, 29 %).

MS ES$^+$: 553.4, 554.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.90 (m, 2H) ; 2.06 (m, 2H) ; 2.26 (t, 2H) ; 3.09 (m, 2H) ; 3.36 (t, 2H) ; 3.67 (m, 2H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.29 (t, 2H) ; 7.14 (d, 1H) ; 7.30 (s, 1H) ; 7.37 (t, 1H) ; 7.47 (d, 1H) ; 7.65 (s, 1H) ; 7.85 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

3-methoxy-4-benzyloxybenzonitrile

3-methoxy-4-benzyloxybenzoldehyde (4.87 g, 20 mmol) in acetic acid (25 ml) was treated with hydroxylamine HCl (2.8 g, 40 mmol), sodium acetate (3.3 g, 40 mmol) at reflux for 6 hours. The mixture was cooled, extracted with water and methylenechloride, dried over $MgSO_4$, evaporated, to give title compound (4.8 g, 100 %).

^{1}HNMR ($DMSOd_6$, TFA): 3.72 (s, 3H) ; 5.15 (s, 2H) ; 7.18 (d, 1H) ; 7.39 (m, 7H).

2-nitro-4-benzyloxy-5-methoxybenzonitrile.

3-methoxy-4-benzyloxybenzonitrile (4.78 g, 20 mmol) in acetic acid (10 ml) was slowly added to nitric acid (d = 1.42, 25 ml) at 20-30° with cooling in an ice bath. The mixture was then stirred at room temperature for 6 hours. The reaction mixture was treated with potassium hydroxyde (10N) at 0°C. The basic mixture (pH 10) was extracted with CH_2Cl_2, the organic phase was dried over $MgSO_4$, concentrated to give title compound (3.62 g, 64 %).

MS ES$^+$: 285 $(M+H)^+$

MS ES$^+$: 296.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.26 (t, 2H) ; 3.26 (s, 3H) ; 3.37 (s, 3H) ; 3.81 (t, 2H) ; 3.87 (s, 3H) ; 4.23 (t, 2H) ; 7.34 (s, 1H) ; 7.53 (s, 1H) ; 8.56 (s, 1H).

g) N-(3-chlorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-ylamino)1,3-thiazol-5-yl)acetamide.

N'-(2-cyano-4-methoxy-5-(3-chloropropoxyphenyl)-N,N-dimethylimidoformamide (296 mg, 1 mmol) and 2-(2-amino-1,3-thiazol-5-yl)-N-(3-chlorophenyl)acetamide (268 mg, 1 mmol) in AcOH (1.5 ml, was irradiated in a microwave oven at 120°C for 40 minutes. The mixture was cooled, the solid was filtered to give title compound (445 mg, 72 %).

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.84 (t, 2H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.32 (t, 2H) ; 7.13 (d, 1H) ; 7.29 (s, 1H) ; 7.36 (t, 1H) ; 7.46 (d, 1H) ; 7.63 (s, 1H) ; 7.85 (s, 1H) ; 7.88 (s, 1H) ; 9.07 (s, 1H).

Example 254. Preparation of compound 431 in Table 17

An analogous reaction to that described in example 253 but starting with N-(3,4-difluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide (52 mg, 0.1 mmol) and pyrrolidine (150 µl, 1.8 mmol) yielded title compound (26 mg, 47 %).

^{1}HNMR (DMSOd_6, TFA): 1.91 (m, 2H) ; 2.07 (m, 2H) ; 2.28 (t, 2H) ; 3.10 (m, 2H) ; 3.37 (t, 2H) ; 3.67 (m, 2H) ; 3.99 (s, 5H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.33 (m, 1H) ; 7.40 (q, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Starting material N-(3,4-difluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxy quinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide was obtained by an analogous reaction to that described in example 130 but starting with 2-(2-amino-1,3-thiazol-5-yl)-N-(3,4-difluorophenyl)acetamide (540 mg, 2 mmol) to give title compound (980 mg, 78 %).

MS ES$^+$: 520.4, 522.4$(M+H)^+$

1HNMR (DMSOd6) : 1.26 (t, 2H) ; 3.82 (t, 2H) ; 3.88 (s, 2H) ; 3.97 (s, 3H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.32 (m, 1H) ; 7.36 (s, 1H) ; 7.39 (t, 1H) ; 7.80 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 255. Preparation of compound 432 in Table 17

An analogous reaction to that described in example 253 but starting with N-(3,5-difluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide (138 mg, 0.22 mmol) and dimethylamine (3.6 M in CH_2Cl_2, 3 ml, 3.6 mmol) yielded title compound (47 mg, 40 %).

MS ES$^+$: 529.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.25 (t, 2H) ; 3.28 (t, 2H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.28 (t, 2H) ; 6.93 (m, 1H) ; 7.30 (s, 1H) ; 7.34 (m, 2H) ; 7.65 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Starting material N-(3,5-difluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide was obtained by an analogous reaction to that described in example 130 but starting with 2-(2-amino-1,3-thiazole-5-yl)-N-(3,5-difluorophenyl)acetamide (810 mg, 3 mmol) to give title compound (630 mg, 40 %).

MS ES$^+$: 520.4, 522.4 $(M+H)^+$

1HNMR (DMSOd6) : 2.26 (t, 2H) ; 3.84 (t, 2H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.30 (t, 2H) ; 6.94 (m, 1H) ; 7.30 (s, 1H) ; 7.35 (m, 2H) ; 7.40 (s, 1H) ; 8.14 (s, 1H) ; 8.69 (s, 1H) ; 10.64 (s, 1H).

Example 256. Preparation of compound 433 in Table 17

An analogous reaction to that described in example 253 but starting with N-(3-chloro-4-fluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide (123 mg, 0.22 mmol) and 2-amino-2-methyl-1-propanol (89.1 mg, 3.3 mmol) yielded title compound (6 mg, 5 %).

MS ES$^+$: 589.4 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.24 (s, 6H) ; 2.22 (t, 2H) ; 3.10 (t, 2H) ; 3.45 (s, 2H) ; 3.98 (s, 3H) ; 4.31 (t, 2H) ; 7.29 (s, 1H) ; 7.38 (t, 1H) ; 7.50 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (s, 1H) ; 9.09 (s, 1H).

Starting material N-(3-chloro-4-fluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide was obtained by an analogous reaction to that described in example 130 but starting with 2-(2-amino-1,3-thiazole-5-yl)-N-(3-chloro-4-fluorophenyl)acetamide (2.29 g, 8.0 mmol) to give title compound (3.62 g, 84 %).

MS ES$^+$: 536.3, 538.3 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 2.26 (t, 2H) ; 3.82 (t, 2H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.29 (t, 2H) ; 7.28 (s, 1H) ; 7.38 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (m, 1H) ; 7.93 (m, 1H) ; 8.12 (s, 1H) ; 8.67 (s, 1H) ; 10.47 (s, 1H).

Example 257. Preparation of compound 434 in Table 17

An analogous reaction to that described in example 253, but starting with N-(3-fluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide (116 mg, 0.22 mmol) and 2-amino-2-methyl-1-propanol (89 mg, 3.3 mmol) yielded title compound (40 mg, 33 %).

MS ES$^+$: 555.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.22 (t, 2H) ; 3.09 (t, 2H) ; 3.16 (s, 2H) ; 3.97 (s, 3H) ; 4.30 (t, 2H) ; 6.86 (t, 1H) ; 7.28 (s, 1H) ; 7.33 (m, 2H) ; 7.58 (m, 1H) ; 7.62 (s, 1H) ; 7.91 (s, 1H) ; 9.07 (s, 1H).

Starting material N-(3-fluorophenyl)-2-(2-(7-(3-chloropropoxy)-6-methoxyquinazoline-4-yl-amino)1,3-thiazole-5-yl)acetamide was obtained by an analogous reaction to that described in example 253 but starting with 2-(2-amino-1,3-thiazole-5-yl)-N-(3-fluorophenyl)acetamide (2.01 g, 8 mmol) to give title compound (3.08 g, 77 %).

MS ES$^+$: 502.4, 504.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.28 (t, 2H) ; 3.84 (t, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.31 (t, 2H) ; 6.91 (t, 1H) ; 7.30 (s, 1H) ; 7.35 (m, 2H) ; 7.39 (s, 1H) ; 7.63 (d, 1H) ; 8.14 (s, 1H) ; 8.69 (s, 1H) ; 10.48 (s, 1H).

Example 258. Preparation of compound 435 in Table 17

An analogous reaction to that described in example 254 but starting with 4-hydroxyperidine (405 mg, 4.0 mmol) yielded compound 435 in Table 17 (82 mg, 70 %).

MS ES$^+$: 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.43 (m, 2H) ; 1.73 (m, 2H) ; 1.95 (m, 2H) ; 2.03 (t, 2H) ; 2.44 (t, 2H) ; 2.74 (m, 2H) ; 3.38 (m, 1H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.53 (d, 1H) ; 7.26 (s, 1H) ; 7.31 (m, 1H) ; 7.39 (s, 1H) ; 7.42 (ddd, 1H) ; 7.83 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.50 (s, 1H).

Example 259. Preparation of compound 436 in Table 17

An analogous reaction to that described in example 254 but starting with N,N-dimethylenediamine (0.44 ml, 4.0 mmol) yielded compound 436 in Table 17 (40 mg, 35 %).

MS ES^+: 572.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.95 (m, 2H) ; 2.14 (s, 6H) ; 2.33 (t, 2H) ; 2.63 (t, 2H) ; 2.73 (t, 2H) ; 3.89 (s, 2H) ; 3.97 (s, 3H) ; 4.22 (t, 2H) ; 7.26 (s, 1H) ; 7.34 (m, 1H) ; 7.38 (s, 1H) ; 7.41 (ddd, 1H) ; 7.82 (m, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.50 (s, 1H).

Example 260. Preparation of compound 437 in Table 17

An analogous reaction to that described in example 254 but starting with piperidine (0.4 ml, 3.0 mmol) yielded compound 437 in Table 17 (67 mg, 59 %).

MS ES^+: 569.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H) ; 1.52 (m, 4H) ; 1.95 (m, 2H) ; 2.42 (m, 4H) ; 2.48 (t, 2H) ; 3.89 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 7.25 (s, 1H) ; 7.33 (m, 1H) ; 7.39 (s, 1H) ; 7.41 (ddd, 1H) ; 7.82 (m, 1H) ; 8.11 (s, 1H) ; 8.68 (s, 1H) ; 10.51 (s, 1H).

Example 261. Preparation of compound 438 in Table 17

An analogous reaction to that described in example 254 but starting with 2-methylaminoethanol (248 mg, 3.3 mmol) yielded compound 438 in Table 17 (23 mg, 19 %).

MS ES^+: 559 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.95 (m, 2H) ; 2.23 (s, 3H) ; 2.47 (m, 2H) ; 3.32 (m, 2H) ; 3.49 (m, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.21 (t, 2H) ; 4.37 (m, 1H) ; 7.27 (s, 1H) ; 7.34 (m, 1H) ; 7.38 (s, 1H) ; 7.40 (dd, 1H) ; 7.82 (ddd, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.50 (s, 1H).

Example 262. Preparation of compound 439 in Table 17

An analogous reaction to that described in example 254 but starting with 1,2-diamino-2-methylpropane (291 mg, 3.3 mmol) yielded compound 439 in Table 17 (16 mg, 13 %).

MS ES^+: 572 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.10 (s, 6H) ; 1.96 (m, 2H) ; 2.48 (s, 2H) ; 2.75 (t, 2H) ; 3.89 (s, 2H) ; 3.97 (s, 3H) ; 4.26 (t, 2H) ; 7.27 (s, 1H) ; 7.34 (m, 1H) ; 7.37 (s, 1H) ; 7.42 (dd, 1H) ; 7.83 (ddd, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H) ; 10.50 (s, 1H).

Example 263. Preparation of compound 440 in Table 17

An analogous reaction to that described in example 254 but starting with cyclohexylamine (327 mg, 3.3 mmol) yielded compound 440 in Table 17 (70 mg, 55 %).

MS ES^+: 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.12 (m, 1H) ; 1.27 (m, 4H) ; 1.63 (brd, 1H) ; 1.78 (m, 2H) ; 2.04 (m, 2H) ; 2.16 (m, 2H) ; 3.03 (m, 1H) ; 3.16 (t, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.29 (t, 2H) ; 7.31 (s, 1H) ; 7.34 (m, 1H) ; 7.40 (s, 1H) ; 7.42 (dd, 1H) ; 7.82 (ddd, 1H) ; 8.16 (brs, 1H) ; 8.70 (s, 1H) ; 10.51 (s, 1H).

Example 264. Preparation of compound 441 in Table 17

An analogous reaction to that described in example 254 but starting with N,N,N'-trimethylethylenediamine (337 mg, 3.3 mmol) yielded compound 441 in Table 17 (63 mg, 49 %).

MS ES^+: 587 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.33 (m, 2H) ; 2.88 (s, 6H) ; 2.93 (s, 3H) ; 3.38 (m, 2H) ; 3.56 (m, 4H) ; 3.98 (s, 5H) ; 4.30 (t, 2H) ; 7.29 (m, 1H) ; 7.33 (s, 1H) ; 7.35 (dd, 1H) ; 7.63 (s, 1H) ; 7.80 (ddd, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 265. Preparation of compound 442 in Table 17

An analogous reaction to that described in example 254 but starting with (R)-(-)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 442 in Table 17 (90 mg, 70 %).

MS ES^+: 585 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.79 (m, 1H) ; 1.91 (m, 1H) ; 2.03 (m, 1H) ; 2.11 (m, 1H) ; 2.29 (m, 2H) ; 3.21 (m, 2H) ; 3.62 (m, 4H) ; 3.77 (m, 1H) ; 3.98 (s, 5H) ; 4.29 (t, 2H) ; 7.30 (s, 1H) ; 7.32 (m, 1H) ; 7.39 (dd, 1H) ; 7.64 (s, 1H) ; 7.80 (ddd, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 266. Preparation of compound 443 in Table 17

An analogous reaction to that described in example 254 but starting with (S)-(+)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 443 in Table 17 (82 mg, 63 %).

MS ES^+: 585 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.76 (m, 1H) ; 1.88 (m, 1H) ; 2.01 (m, 1H) ; 2.10 (m, 1H) ; 2.26 (m, 2H) ; 3.21 (m, 2H) ; 3.59 (m, 4H) ; 3.74 (dd, 1H) ; 3.95 (s, 5H) ; 4.27 (t, 2H) ; 7.27 (s, 1H) ; 7.28 (m, 1H) ; 7.34 (dd, 1H) ; 7.60 (s, 1H) ; 7.77 (ddd, 1H) ; 7.88 (s, 1H) ; 9.05 (s, 1H).

Example 267. Preparation of compound 444 in Table 17

An analogous reaction to that described in example 254 but starting with 3-pyrrolidinol (288 mg, 3.3 mmol) yielded compound 444 in Table 17 (15 mg, 12 %).

MS ES$^+$: 571 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.85-2.04 (m, 2H) ; 2.28 (m, 2H) ; 3.03-3.54 (m, 4H) ; 3.75 (m, 2H) ; 3.99 (s, 5H) ; 4.28 (m, 2H) ; 4.40-4.52 (m, 1H) ; 7.29 (s, 1H) ; 7.33 (m, 1H) ; 7.39 (dd, 1H) ; 7.64 (s, 1H) ; 7.81 (ddd, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 268. Preparation of compound 445 in Table 17

An analogous reaction to that described in example 254 but starting with 1-(2-aminoethyl)pyrrolidine (377 mg, 3.3 mmol) yielded compound 445 in Table 17 (20 mg, 15 %).

MS ES$^+$: 598 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.92 (m, 2H) ; 2.06 (m, 2H) ; 2.24 (m, 2H) ; 3.11 (m, 2H) ; 3.23 (t, 2H) ; 3.42 (m, 2H) ; 3.49 (m, 2H) ; 3.52 (m, 2H) ; 4.00 (s, 5H) ; 4.32 (t, 2H) ; 7.32 (s, 1H) ; 7.33 (m, 1H) ; 7.39 (dd, 1H) ; 7.65 (s, 1H) ; 7.81 (ddd, 1H) ; 7.92 (s, 1H) ; 9.10 (s, 1H).

Example 269. Preparation of compound 446 in Table 17

An analogous reaction to that described in example 254 but starting with 1-acetylpiperazine (423 mg, 3.3 mmol) yielded compound 446 in Table 17 (100 mg, 74 %).

MS ES$^+$: 612 $(M+H)^+$

^{1}HNMR (DMSOd_6): 2.00 (s, 5H) ; 2.35 (m, 2H) ; 2.42 (m, 2H) ; 3.92-3.06 (m, 1H) ; 3.45 (m, 4H) ; 3.56 (t, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.23 (t, 2H) ; 7.28 (s, 1H) ; 7.34 (m, 1H) ; 7.40 (s, 1H) ; 7.42 (dd, 1H) ; 7.83 (ddd, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H).

Example 270. Preparation of compound 447 in Table 17

An analogous reaction to that described in example 254 but starting with 1-(2-morpholinoethyl)-piperazine (658 mg, 3.3 mmol) yielded compound 447 in Table 17 (44 mg, 29 %).

MS ES$^+$: 683 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.98 (m, 2H) ; 2.30-2.70 (m, 18H) ; 3.58 (m, 4H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.21 (t, 2H) ; 7.26 (s, 1H) ; 7.33 (m, 1H) ; 7.40 (s, 1H) ; 7.41 (dd, 1H) ; 7.82 (ddd, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.54 (s, 1H).

Example 271. Preparation of compound 448 in Table 17

An analogous reaction to that described in example 254 but starting with 2-piperidineethanol (426 mg, 3.3 mmol) yielded compound 448 in Table 17 (19 mg, 14 %).

MS ES$^+$: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.45-1.92 (m, 7H) ; 2.00-2.15 (m, 1H) ; 2.20-2.40 (m, 2H) ; 3.10-3.70 (m, 7H) ; 3.99 (s, 5H) ; 4.30 (m, 2H) ; 7.30 (s, 1H) ; 7.34 (m, 1H) ; 7.40 (dd, 1H) ; 7.64 (s, 1H) ; 7.81 (ddd, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 272. Preparation of compound 449 in Table 17

An analogous reaction to that described in example 254 but starting with 1-(2-hydroxyethyl)piperazine (430 mg, 3.3 mmol) yielded compound 449 in Table 17 (90 mg, 66 %).

MS ES$^+$: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H) ; 2.35-2.47 (m, 12H) ; 3.49 (q, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 1H) ; 4.37 (t, 1H) ; 7.25 (s, 1H) ; 7.33 (m, 1H) ; 7.39 (s, 1H) ; 7.41 (dd, 1H) ; 7.81 (ddd, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.50 (s, 1H) ; 12.03 (brs, 1H).

Example 273. Preparation of compound 450 in Table 17

An analogous reaction to that described in example 254 but starting with cyclopentylamine (281 mg, 3.3 mmol) yielded compound 450 in Table 17 (43 mg, 34 %).

MS ES$^+$: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.53 (m, 4H) ; 1.69 (m, 2H) ; 1.93 (m, 2H) ; 2.10 (m, 2H) ; 3.00 (m, 2H) ; 3.38 (m, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.28 (t, 2H) ; 7.30 (s, 1H) ; 7.32 (m, 1H) ; 7.42 (dd, 1H) ; 7.81 (ddd, 1H) ; 8.15 (brs, 1H) ; 8.70 (s, 1H) ; 10.51 (s, 1H).

Example 274. Preparation of compound 451 in Table 17

An analogous reaction to that described in example 254 but starting with 4-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 451 IN Table 17 (53 mg, 39 %).

MS ES$^+$: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H) ; 1.36 (m, 3H) ; 1.63 (brd, 2H) ; 1.87 (m, 2H) ; 1.95 (m, 2H) ; 2.45 (m, 1H) ; 2.86 (m, 2H) ; 3.44 (m, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.32 (t, 1H) ; 7.26 (s, 1H) ; 7.31 (m, 1H) ; 7.40 (s, 1H) ; 7.42 (dd, 1H) ; 7.82 (ddd, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.50 (s, 1H) ; 12.02 (brs, 1H).

Example 275. Preparation of compound 452 in Table 17

An analogous reaction to that described in example 254 but starting with L-alanine-T-butylester hydrochloride (599 mg, 3.3 mmol) and treating the crude reaction mixture with a 1:1 solution of CH_2Cl_2-TFA (4 ml) yielded compound 452 in Table 17 (75 mg, 60 %).

MS ES$^+$: (573 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.48 (d, 3H) ; 2.24 (m, 2H) ; 3.22 (m, 2H) ; 3.97 (s, 5H) ; 4.15 (q, 1H) ; 4.30 (m, 2H) ; 7.30 (s, 1H) ; 7.34 (m, 1H) ; 7.40 (dd, 1H) ; 7.64 (s, 1H) ; 7.81 (ddd, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H) ; 10.60 (s, 1H).

Example 276. Preparation of compound 453 in Table 17

An analogous reaction to that described in example 254 but starting with 3-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 453 in Table 17 (84 mg, 65 %).

MS ES$^+$: 585 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.07 (m, 1H) ; 1.41 (m, 1H) ; 1.62 (m, 1H) ; 1.76 (m, 2H) ; 1.87 (m, 1H) ; 1.95 (m, 2H) ; 2.47 (m, 2H) ; 2.68 (m, 1H) ; 2.85 (m, 1H) ; 3.48 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.20 (t, 2H) ; 4.59 (d, 1H) ; 7.26 (s, 1H) ; 7.31 (m, 1H) ; 7.39 (s, 1H) ; 7.42 (dd, 1H) ; 7.81 (ddd, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.50 (s, 1H) ; 12.02 (brs, 1H).

Example 277. Preparation of compound 454 in Table 17

An analogous reaction to that described in example 254 but starting with 4-hydroxymethylpiperidine (380 mg, 3.3 mmol) yielded compound 454 in Table 17 (42 mg, 32 %).

MS ES$^+$: 599 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.13 (m, 2H) ; 1.33 (m, 1H) ; 1.62 (brd, 2H) ; 1.90 (m, 2H) ; 1.95 (m, 2H) ; 2.44 (m, 2H) ; 2.88 (m, 2H) ; 3.22 (t, 2H) ; 3.86 (s, 2H) ; 3.93 (s, 3H) ; 4.17 (t, 2H) ; 4.38 (t, 1H) ; 7.22 (s, 1H) ; 7.31 (m, 1H) ; 7.36 (s, 1H) ; 7.38 (dd, 1H) ; 7.80 (ddd, 1H) ; 8. 09 (brs, 1H) ; 8.65 (s, 1H) ; 10.46 (s, 1H) ; 12.00 (brs, 1H).

Example 278. Preparation of compound 455 in Table 17

An analogous reaction to that described in example 254 but starting with 1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 455 in Table 17 (52 mg, 42 %).

MS ES$^+$: 573 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H) ; 1.95 (m, 2H) ; 2.48 (m, 2H) ; 2.72 (t, 2H) ; 3.68 (m, 1H) ; 3.89 (s, 2H) ; 3.97 (s, 3H) ; 4.23 (t, 2H) ; 4.46 (m, 1H) ; 7.26 (s, 1H) ; 7.32 (m, 1H) ; 7.38 (s, 1H) ; 7.41 (dd, 1H) ; 7.81 (ddd, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.49 (s, 1H).

Example 279. Preparation of compound 456 in Table 17

An analogous reaction to that described in example 253 but starting with L-alamine-t-butylester hydrochloride (599 mg, 3.3 mmol) and treating the crude reaction mixture with CH_2Cl_2-TFA (1/1, 4 ml) yielded compound 456 in Table 17 (106 mg, 84 %).

MS ES$^+$: 571 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.40 (d, 3H) ; 2.25 (m, 2H) ; 3.20 (m, 2H) ; 3.98 (s, 3H) ; 4.00 (s, 2H) ; 4.14 (m, 1H) ; 4.31 (t, 2H) ; 7.13 (dd, 1H) ; 7.32 (s, 1H) ; 7.35 (t, 1H) ; 7.47 (dd, 1H) ; 7.63 (s, 1H) ; 7.86 (t, 1H) ; 7.90 (s, 1H) ; 8.30 (m, 1H) ; 9.08 (s, 1H) ; 10.60 (s, 1H).

Example 280. Preparation of compound 457 in Table 17

An analogous reaction to that described in example 253 but starting with2-methylaminoethanol (248 mg, 3.3 mmol) yielded compound 457 in Table 17 (86 mg, 70 %).

MS ES$^+$: 557 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.93 (m, 2H) ; 2.20 (s, 3H) ; 2.43 (t, 2H) ; 2.48 (m, 1H) ; 2.55 (m, 1H) ; 3.47 (dd, 2H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.19 (t, 2H) ; 4.34 (t, 1H) ; 7.13 (brd, 1H) ; 7.25 (s, 1H) ; 7.35 (t, 1H) ; 7.38 (s, 1H) ; 7.47 (s, 1H) ; 7.84 (s, 1H) ; 8.11 (dd, 1H) ; 8.66 (s, 1H) ; 10.44 (s, 1H) ; 12.00 (dd, 1H).

Example 281. Preparation of compound 458 in Table 17

An analogous reaction to that described in example 253 but starting with 1,2-diamino-2-methylpropane (291 mg, 3.3 mmol) yielded compound 458 in Table 17 (21 mg, 17 %).

MS ES$^+$: 570 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.39 (s, 1H) ; 2.28 (m, 2H) ; 3.23 (m, 4H) ; 3.98 (s, 3H) ; 4.00 (s, 2H) ; 4.32 (m, 2H) ; 7.14 (ddd, 1H) ; 7.31 (s, 1H) ; 7.36 (t, 1H) ; 7.47 (ddd, 1H) ; 7.64 (s, 1H) ; 7.86 (t, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 282. Preparation of compound 459 in Table 17

An analogous reaction to that described in example 253 but starting with cyclohexylamine (327 mg, 3.3 mmol) yielded compound 459 in Table 17 -85 mg, 66 %).

MS ES$^+$: 581 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.13 (m, 1H) ; 1.26 (m, 4H) ; 1.62 (brd, 1H) ; 1.77 (m, 2H) ; 2.03 (m, 2H) ; 2.15 (m, 2H) ; 3.07 (m, 1H) ; 3.14 (t, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.29 (t, 2H) ; 7.13 (brd, 1H) ; 7.29 (s, 1H) ; 7.36 (t, 1H) ; 7.39 (s, 1H) ; 7.46 (dd, 1H) ; 8.16 (dd, 1H) ; 8.26 (brs, 1H) ; 8.69 (s, 1H) ; 10.45 (s, 1H).

Example 283. Preparation of compound 460 in Table 17

An analogous reaction to that described in example 253 but starting with N,N-dimethylethylenediamine (291 mg, 3.3 mmol) yielded compound 460 in Table 17 (41 mg, 32 %).

MS ES$^+$: 570 $(M+H)^+$

^{1}HNMR (DMSOd_6): 2.00 (m, 1H) ; 2.17 (s, 6H) ; 2.38 (t, 2H) ; 2.72 (t, 2H) ; 2.81 (t, 2H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.24 (t, 2H) ; 7.14 (dd, 1H) ; 7.27 (s, 1H) ; 7.37 (t, 1H) ; 7.40 (s, 1H) ; 7.49 (dd, 1H) ; 7.86 (t, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H) ; 10.50 (s, 1H).

Example 284. Preparation of compound 461 in Table 17

An analogous reaction to that described in example 253 but starting with N,N,N'-trimethylethylenediamine (337 mg, 3.3 mmol) yielded compound 461 in Table 17 (11 mg, 8 %).

MS ES$^+$: 584 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.91 (m, 2H) ; 2.12 (s, 6H) ; 2.20 (s, 3H) ; 2.33 (m, 3H) ; 2.42 (m, 3H) ; 3.76 (s, 2H) ; 3.91 (s, 3H) ; 4.12 (t, 2H) ; 6.98 (s, 1H) ; 7.11 (dd, 1H) ; 7.16 (s, 4H) ; 7.35 (t, 1H) ; 7.52 (dd, 1H) ; 7.83 (s, 1H) ; 7.88 (t, 1H) ; 8.37 (s, 1H) ; 10.56 (s, 1H).

Example 285. Preparation of compound 462 in Table 17

An analogous reaction to that described in example 253 but starting with (R)-(-)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 462 in Table 17 (76 mg, 59 %).

MS ES$^+$: 583 $((M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.77 (m, 1H) ; 1.89 (m, 1H) ; 2.02 (m, 1H) ; 2.4 (m, 1H) ; 2.29 (m, 2H) ; 3.21 (m, 2H) ; 3.62 (m, 4H) ; 3.76 (m, 1H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.29 (t, 2H) ; 7.13 (dd, 1H) ; 7.29 (s, 1H) ; 7.35 (t, 1H) ; 7.46 (dd, 1H) ; 7.63 (s, 1H) ; 7.85 (t, 1H) ; 7.90 (s, 1H) ; 9.08 (s, 1H).

Example 286. Preparation of compound 463 in Table 17

An analogous reaction to that described in example 253 but starting with (S)-(+)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 463 in Table 17 (72 mg, 56 %).

MS ES$^+$: 583 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.78 (m, 1H) ; 1.90 (m, 1H) ; 2.03 (m, 1H) ; 2.13 (m, 1H) ; 2.30 (m, 2H) ; 3.23 (m, 2H) ; 3.62 (m, 4H) ; 3.77 (m, 1H) ; 3.98 (s, 3H) ; 4.00 (s, 2H) ; 4.30 (t, 2H) ; 7.14 (dd, 1H) ; 7.30 (s, 1H) ; 7.36 (t, 1H) ; 7.46 (dd, 1H) ; 7.64 (s, 1H) ; 7.85 (s, 1H) ; 7.90 (s, 1H) ; 9.09 (s, 1H).

Example 287. Preparation of compound 464 in Table 17

An analogous reaction to that described in example 253 but starting with 4-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 464 in Table 17 (63 mg, 49 %).

MS ES$^+$: 583 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.41 (m, 2H) ; 1.73 (m, 2H) ; 1.96 (m, 2H) ; 2.04 (m, 2H) ; 2.74 (m, 2H) ; 2.50 (m, 2H) ; 3.43 (s, 1H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.54 (d, 1H) ; 7.14 (d,

1H) ; 7.26 (s, 1H) ; 7.37 (t, 1H) ; 7.40 (s, 1H) ; 7.49 (d, 1H) ; 7.86 (t, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.46 (s, 1H).

Example 288. Preparation of compound 465 in Table 17

An analogous reaction to that described in example 253 but starting with 3-pyrrolidinol (288 mg, 3.3 mmol) yielded compound 465 in Table 17 (57 mg, 45 %).

MS ES$^+$: 569 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.56 (m, 1H) ; 1.99 (m, 4H) ; 2.36 (m, 1H) ; 2.56 (m, 4H) ; 2.74 (m, 1H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.21 (t, 2H) ; 4.70 (d, 1H) ; 7.14 (dd, 1H) ; 7.26 (s, 1H) ; 7.37 (t, 1H) ; 7.40 (s, 1H) ; 7.49 (dd, 1H) ; 7.86 (t, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.47 (s, 1H) ; 12.03 (brs, 1H).

Example 289. Preparation of compound 466 in Table 17

An analogous reaction to that described in example 253 but starting with 1-(2-aminoethyl)pyrrolidine (377 mg, 3.3 mmol) yielded compound 466 in Table 17 (39 mg, 29 %).

MS ES$^+$: 596 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.91 (m, 2H) ; 2.06 (m, 2H) ; 2.24 (m, 2H) ; 3.11 (m, 2H) ; 3.23 (t, 2H) ; 3.42 (m, 2H) ; 3.48 (m, 2H) ; 3.67 (m, 2H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ;4.31 (t, 2H) ; 7.14 (d, 1H) ; 7.31 (s, 1H) ; 7.35 (t, 1H) ; 7.47 (d, 1H) ; 7.64 (s, 1H) ; 7.85 (t, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 290. Preparation of compound 467 in Table 17

An analogous reaction to that described in example 253 but starting with 4-hydroxymethylpiperidine (380 mg, 3.3 mmol) yielded compound 467 in Table 17 (64 mg, 49 %).

MS ES$^+$: 597 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H) ; 1.35 (m, 1H) ; 1.65 (brd, 2H) ; 1.88 (m, 2H) ; 1.97 (m, 2H) ; 2.47 (m, 2H) ; 2.90 (brd, 2H) ; 3.25 (t, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.41 (t, 1H) ; 7.14 (d, 1H) ; 7.25 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (s, 1H) ; 7.86 (s, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.46 (s, 1H) ; 12.03 (s, 1H).

Example 291. Preparation of compound 468 in Table 17

An analogous reaction to that described in example 253 but starting with 1-(2-hydroxyethyl)piperazine (430 mg, 3.3 mmol) yielded compound 468 in Table 17 (63 mg, 47 %).

MS ES$^+$: 612 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H) ; 2.41 (m, 12H) ; 3.50 (q, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.37 (t, 1H) ; 7.14 (dd, 1H) ; 7.25 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (d, 1H) ; 7.86 (t, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.46 (s, 1H) ; 12.04 (s, 1H).

Example 292. Preparation of compound 469 in Table 17

An analogous reaction to that described in example 253 but starting with cyclopentylamine 281 mg, 3.3 mmol) yielded compound 469 in Table 17 (77 mg, 61 %).

MS ES$^+$: 567 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.58 (m, 4H) ;1.73 (m, 2H) ; 2.00 (m, 2H) ; 2.17 (m, 2H) ; 3.12 (t, 2H) ; 3.56 (m, 1H) ; 3.92 (s, 3H) ; 3.99 (s, 3H) ; 4.31 (t, 2H) ; 7.15 (d, 1H) ; 7.31 (s, 1H) ; 7.37 (t, 1H) ; 7.41 (s, 1H) ; 7.48 (d, 1H) ; 7.86 (s, 1H) ; 8.16 (brs, 1H) ; 8.71 's, 1H) ; 10.47 (s, 1H) ; 12.03 (brs, 1H).

Example 293. Preparation of compound 470 in Table 17

An analogous reaction to that described in example 253 but starting with 4-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 470 in Table 17 (78 mg, 58 %).

MS ES$^+$: 611 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.16 (m, 2H) ; 1.36 (m, 3H) ; 1.63 (d, 2H) ; 1.88 (t, 2H) ; 1.96 (m, 2H) ; 2.44 (t, 2H) ; 2.87 (d, 2H) ; 3.44 (m, 2H) ; 3.9 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.33 (t, 1H) ; 7.14 (d, 1H) ; 7.25 (s, 1H) ; 7.37 (t, 1H) ; 7.40 (s, 1H) ; 7.49 (d, 1H) ; 7.86 (t, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.46 (s, 1H) ; 12.04 (s, 1H).

Example 294. Preparation of compound 471 in Table 17

An analogous reaction to that described in example 253 but starting with 3-hydroxypiperidine (339 mg, 3.3 mmol) yielded compound 471 in Table 17 (117 mg, 91 %).

MS ES$^+$: 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.07 (m, 1H) ; 1.41 (m, 1H) ; 1.62 (m, 1H) ; 1.70-1.90 (m, 3H) ; 1.95 (m, 2H) ; 2.46 (m, 2H) ; 2.67 (m, 1H) ; 2.83 (brd, 1H) ; 3.47 (m, 1H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.20 (t, 2H) ; 4.57 (d, 1H) ; 7.13 (ddd, 1H) ; 7.24 (s, 1H) ; 7.36 (t, 1H) ; 7.38 (s, 1H) ; 7.47 (d, 1H) ; 7.84 (t, 1H) ; 8.11 (brs, 1H) ; 8.67 (s, 1H) ; 10.46 (s, 1H) ; 12.00 (brs, 1H).

Example 295. Preparation of compound 472 in Table 17

An analogous reaction to that described in example 253 but starting with (S)-1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 472 in Table 17 (55 mg, 45 %).

MS ES^+: 557 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H) ; 1.96 (m, 2H) ; 2.48 (m, 2H) ; 2.73 (t, 2H) ; 3.70 (m, 1H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.24 (t, 2H) ; 4.48 (brs, 1H) ; 7.14 (d, 1H) ; 7.27 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.49 (d, 1H) ; 7.86 (t, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.46 (s, 1H).

Example 296. Preparation of compound 473 in Table 17

An analogous reaction to that described in example 253 but starting with (R)-1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 473 in Table 17 (84 mg, 68 %).

MS ES^+: 557 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.04 (d, 3H) ; 1.93 (m, 2H) ; 2.45 (m, 2H) ; 2.70 (t, 2H) ; 3.67 (m, 1H) ; 3.88 (s, 2H) ; 3.95 (s, 3H) ; 4.21 (t, 2H) ; 4.46 (brs, 1H) ; 7.12 (d, 1H) ; 7.24 (s, 1H) ; 7.35 (t, 1H) ; 7.37 (s, 1H) ; 7.47 (d, 1H) ; 7.84 (t, 1H) ; 8.09 (s, 1H) ; 8.65 (s, 1H) ; 10.45 (s, 1H).

Example 297. Preparation of compound 474 in Table 17

An analogous reaction to that described in example 253 but starting with tert-butyl-1-piperazinecarboxylate (615 mg, 3.3 mmol) and treating the crude reaction mixture with hydrochloric acid in 1,4 dioxane (4.0 M , 2 ml) yielded compound 474 (3 HCl) in Table 17 (89 mg, 61 %.

MS ES^+: 568 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.34 (m, 2H) ; 3.25-3.68 (m, 10H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.33 (t, 2H) ; 7.14 (dd, 1H) ; 7.35 (s, 1H) ; 7.37 (t, 1H) ; 7.49 (d, 1H) ; 7.65 (s, 1H) ; 7.86 (t, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H) ; 10.66 (s, 1H).

Example 298. Preparation of compound 475 in Table 17

An analogous reaction to that described in example 253 but starting with 2-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 475 in Table 17 (29 mg, 22 %).

MS ES$^+$: 611 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.30 (m, 2H) ; 1.48 (m, 4H) ; 1.60 (m ,2H) ; 1.76 (m, 1H) ; 1.93 (m, 2H) ; 2.26 (m, 1H) ; 2.48 (m, 1H) ; 2.79 (m, 2H) ; 3.46 (m, 2H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.18 (t, 2H) ; 4.40 (brs, 1H) ; 7.13 (d, 1H) ; 7.24 (s, 1H) ; 7.35 (t, 1H) ; 7.38 (s, 1H) ; 7.47 (d, 1H) ; 7.84 (s, 1H) ; 8.11 (brs, 1H) ; 8.67 (s, 1H) ; 10.44 (s, 1H).

Example 299. Preparation of compound 476 in Table 17

An analogous reaction to that described in example 253 but starting with 2-amino-2-methyl-1-propanol (294 mg, 3.3 mmol) yielded compound 476 in Table 17 (49 mg, 39 %).

MS ES$^+$: 571 $(M+H)^+$

1HNMR (DMSOd6, TFA) : 1.25 (s, 6H) ; 2.22 (m, 2H) ; 3.10 (m, 2H) ; 3.46 (s, 2H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.32 (t, 2H) ; 7.15 (d, 1H) ; 7.30 (s, 1H) ; 7.37 (t, 1H) ; 7.47 (d, 1H) ; 7.65 (s, 1H) ; 7.86 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 4H) ; 10.56 (s, 1H).

Example 300. Preparation of compound 477 in Table 17

An analogous reaction to that described in example 253 but starting with 1-(2-dimethylaminoethylpiperazine (519 mg, 3.3 mmol) yielded compound 477 in Table 17 (19 mg, 15 %).

MS ES$^+$: 639 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H) ; 2.13 (s, 6H) ; 2.30-2.52 (m, 14H) ; 3.89 (s, 2H) ; 3.95 (s, 3H) ; 4.18 (t, 2H) ; 7.13 (d, 1H) ; 7.23 (s, 1H) ; 7.35 (t, 1H) ; 7.38 (s, 1H) ; 7.84 (t, 1H) ; 8.10 (s, 1H) ; 8.67 (s, 1H) ; 10.45 (s, 1H).

Example 301. Preparation of compound 478 in Table 17

An analogous reaction to that described in example 253 but starting with a solution of dimethylamine in chloroform (3,6M, 3 ml, 3.6 mmol) yielded compound 478 in Table 17 (44 mg, 34 %).

MS ES$^+$: 527 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.95 (m, 2H) ; 2.17 (s, 6H) ; 2.41 (t, 2H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.18 (t, 2H) ; 7.12 (d, 1H) ; 7.23 (s, 1H) ; 7.35 (t, 1H) ; 7.38 (s, 1H) ; 7.47 (d, 1H) ; 7.84 (t, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.45 (s, 1H).

Example 302. Preparation of compound 479 in Table 17

An analogous reaction to that described in example 253 but starting with aminomethylcyclopropane (234 mg, 3.3 mmol) yielded compound 479 in Table 17 (88 mg, 65 %).

MS ES$^+$: 553 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 0.18 (m, 2H) ; 0.46 (m, 2H) ; 0.94 (m, 1H) ; 2.01 (m, 2H) ; 2.51 (d, 2H) ; 2.79 (t, 2H) ; 3.94 (s, 2H) ; 4.01 (s, 3H) ; 4.28 (t, 2H) ; 7.18 (d, 1H) ; 7.31 (s, 1H) ; 7.41 (t, 1H) ; 7.43 (s, 1H) ; 7.53 (d, 1H) ; 7.90 (s, 1H) ; 8.16 (s, 1H) ; 8.72 (s, 1H) ; 10.53 (s, 1H).

Example 303. Preparation of compound 480 in Table 17

An analogous reaction to that described in example 253 but starting with piperidine (344 mg, 4.0 mmol) yielded compound 480 in Table 17 (52 mg, 40 %).

MS ES- : 565 $(M-H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.43 (m, 1H) ; 1.69 (m, 3H) ; 1.87 (d, 2H) ; 2.30 (m, 2H) ; 2.96 (t, 2H) ; 3.27 (t, 2H) ; 3.55 (d, 2H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.31 (t, 2H) ; 7.15 (d, 1H) ; 7.31 (s, 1H) ; 7.37 (t, 1H) ; 7.47 (d, 1H) ; 7.65 (s, 1H) ; 7.86 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H) ; 10.56 (s, 1H).

Example 304. Preparation of compound 481 in Table 17

An analogous reaction to that described in example 255 but starting with 1-(2-dimethylaminomethyl)piperazine (281 mg, 3.3 mmol) yielded compound 481 in Table 17 (81 mg, 64 %).

MS ES$^+$: 641 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.33 (m, 2H) ; 2.80-3.70 (m, 14H) ; 2.84 (s, 6H) ; 3.98 (s, 3H) ; 4.01 (s, 2H) ; 4.30 (brt, 1H) ; 6.90 (m, 1H) ; 7.32 (s, 2H) ; 7.35 (dd, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 305. Preparation of compound 482 in Table 17

An analogous reaction to that described in example 255 but starting with (S)-(+)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 482 in Table 17 (58 mg, 45 %).

MS ES$^+$: 585 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.79 (m, 1H) ; 1.90 (m, 1H) ; 2.02 (m, 1H) ; 2.13 (m, 1H) ; 2.30 (m, 2H) ; 3.33 (m, 2H) ; 3.62 (m, 4H) ; 3.77 (dd, 1H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.30 (brt, 2H) ; 6.91 (t, 1H) ; 7.30 (s, 1H) ; 7.35 (dd, 2H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 306. Preparation of compound 483 in Table 17

An analogous reaction to that described in example 255 but starting with 4-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 483 in Table 17 (28 mg, 22 %).

MS ES$^+$: 585 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H) ; 1.73 (m, 2H) ; 1.96 (m, 2H) ; 2.03 (m, 2H) ; 2.45 (m, 2H) ; 2.74 (m, 2H) ; 3.45 (m, 1H) ; 3.92 (s, 2H) ; 3.97 (s, 3H) ; 3.97 (t, 2H) ; 4.54 (d, 1H) ; 6.95 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.14 (brs, 1H) ;8.68 (s, 1H) ; 10.65 (s, 1H) ; 12.04 (brs, 1H).

Example 307. Preparation of compound 484 in Table 17

An analogous reaction to that described in example 255 but starting with 3-pyrrolidinol (288 mg, 3.3 mmol) yielded compound 484 in Table 17 (30 mg, 23 %).

MS ES$^+$: 571 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 1.57 (m, 1H) ; 1.97 'm, 4H) ; 2.37 (m, 1H) ; 2.58 (m, 4H) ; 2.74 (m, 1H) ; 3.92 (s, 2H) ; 3.98 (s 3H) ; 4.22 (brt, 2H) ; 4.72 (brs, 1H) ; 6.95 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.65 (s, 1H) ; 12.04 (brs, 1H).

Example 308. Preparation of compound 485 in Table 17

An analogous reaction to that described in example 255 but starting with 1-(2-aminoethyl)pyrrolidine (377 mg, 3.3 mmol) yielded compound 485 in Table 17 (25 mg, 19 %).

MS ES$^+$: 598 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.91 (m, 2H) ; 2.06 (m, 2H) ; 2.24 (m, 2H) ; 3.11 (m, 2H) ; 3.23 (t, 2H) ; 3.41 (lm, 2H) ; 3.49 (m, 2H) ; 3.67 (m, 2H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.31 (t, 2H) ; 6.89 (t, 1H) ; 7.32 (s, 1H) ; 7.34 (d, 2H) ; 7.64 (s, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 309. Preparation of compound 486 in Table 17

An analogous reaction to that described in example 255 but starting with 4-hydroxymethylpyperidine (380 mg, 3.3 mmol) yielded compound 486 in Table 17 (62 mg, 47 %).

MS ES$^+$: 599 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H) ; 1.34 (m, 1H) ; 1.65 (d, 2H) ; 1.88 (t, 2H) ; 1.96 (m, 2H) ; 2.45 (t, 2H) ; 2.90 (d, 2H) ; 3.25 (t, 2H) ; 3.92 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.41 (t, 1H) ; 6.94 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.64 (s, 1H) ; 12.07 (brs, 1H).

Example 310. Preparation of compound 487 in Table 17

An analogous reaction to that described in example 255 but starting with 2-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 487 in Table 17 (61 mg, 45 %).

MS ES$^+$: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.47-1.90 (m, 7H) ; 2.09 (m, 1H) ; 2.27 (m, 2H) ; 3.08-3.70 (m, 7H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.30 (m, 2H) ; 6.84 (m, 1H) ; 7.29 (d, 1H) ; 7.34 (dd, 1H) ; 7.62 (s, 1H) ; 7.92 (s, 1H) ; 9.08 (s, 1H).

Example 311. Preparation of compound 488 in Table 17

An analogous reaction to that described in example 255 but starting with 1-(2-hydroxyethyl)piperazine (430 mg, 3.3 mmol) yielded compound 488 in Table 17 (124 mg, 92 %).

MS ES$^+$: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.96 (m, 2H) ; 2.40 (m, 12H) ; 2.70 (m, 1H) ; 3.48 (m, 2H) ; 3.90 (s, 2H) ; 3.95 (s, 3H) ; 4.18 (t, 2H) ; 4.35 (brt, 1H) ; 6.43 (m, 1H) ; 7.23 (s, 1H) ; 7.34 (dd, 2H) ; 7.38 (s, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H) ; 10.63 (s, 1H).

Example 312. Preparation of compound 489 in Table 17

An analogous reaction to that described in example 255 but starting with 4-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 489 in Table 17 (54 mg, 40 %).

MS ES$^+$: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H) ; 1.36 (m, 3H) ; 1.63 (brd, 2H) ; 1.88 (m, 2H) ; 1.96 (m, 2H) ; 2.44 (m, 2H) ; 2.87 (brd, 2H) ; 3.44 (m, 2H) ; 3.92 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.33 (t, 1H) ; 6.95 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.64 (s, 1H) ; 12.04 (brs, 1H).

Example 313. Preparation of compound 490 in Table 17

An analogous reaction to that described in example 255 but starting with 3-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 490 in Table 17 (53 mg, 41 %).

MS ES$^+$: 559 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.09 (m, 1H) ; 1.43 (m, 1H) ; 1.64 (m, 1H) ; 1.79 (m, 2H) ; 1.87 (m, 1H) ; 1.96 (m, 2H) ; 2.47 (m, 2H) ; 2.69 (m, 2H) ; 2.85 (m, 2H) ; 3.49 (m, 1H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.21 (t, 2H) ; 4.60 (d, 1H) ; 6.95 (t, 1H) ; 7.26 (s, 1H) ; 7.36 (d, 2H) ; 7.40 (s, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.65 (s, 1H) ; 12.04 (brs, 1H).

Example 314. Preparation of compound 491 in Table 17

An analogous reaction to that described in example 255 but starting with N,N,N'-trimethylethylenediamine (337 mg, 3.3 mmol) yielded compound 491 in Table 17 (54 mg, 42 %).

MS ES$^+$: 586 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.32 (m, 1H) ; 2.34 (m, 1H) ; 2.88 (s, 6H) ; 2.93 (s, 3H) ; 3.39 (m, 2H) ; 3.56 (m, 4H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.30 (t, 2H) ; 6.91 (m, 1H) ; 7.33 (s, 1H) ; 7.35 (dd, 2H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 315. Preparation of compound 492 in Table 17

An analogous reaction to that described in example 255 but starting with piperidine (281 mg, 3.3 mmol) yielded compound 492 in Table 17 (81 mg, 64 %).

MS ES$^+$: 569 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 1.38 (m, 2H) ; 1.50 (m, 4H) ; 2.34 (brs, 4H) ; 2.41 (t, 2H) ; 3.90 (s, 2H) ; 3.96 (s, 3H) ; 4.19 (t, 2H) ; 6.93 (t, 1H) ; 7.24 (s, 1H) ; 7.34 (d, 2H) ; 7.38 (s, 1H) ; 8.11 (brs, 1H) ; 8.67 (s, 1H) ; 10.63 (s, 1H) ; 11.98 (brs, 1H).

Example 316. Preparation of compound 493 in Table 17

An analogous reaction to that described in example 255 but starting with pyrrolidine (235 mg, 3.3 mmol) yielded compound 493 in Table 17 (66 mg, 54 %).

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.90 (m, 2H) ; 2.06 (m, 2H) ; 2.28 (m, 2H) ; 3.09 (m, 2H) ; 3.36 (m, 2H) ; 3.68 (m, 2H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.29 (t, 2H) ; 6.93 (m, 1H) ; 7.30 (s, 1H) ; 7.34 (dd, 2H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 317. Preparation of compound 494 in Table 17

An analogous reaction to that described in example 255 but starting with 2-amino-2-methyl-1-propanol (294 mg, 3.3 mmol) yielded compound 494 in Table 17 (28 mg, 22 %).

MS ES$^+$: 573 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.24 (s, 6H) ; 2.23 (m, 2H) ; 3.10 (t, 2H) ; 3.45 (s, 2H) ; 3.99 (s, 3H) ; 4.01 (s, 2H) ; 4.31 (t, 2H) ; 6.91 (m, 1H) ; 7.30 (s, 1H) ; 7.34 (dd, 2H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 318. Preparation of compound 495 in Table 17

An analogous reaction to that described in example 255 but starting with 2-methylaminoethanol (248 mg, 3.3 mmol) yielded compound 495 in Table 17 (33 mg, 27 %).

MS ES$^+$: 559 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 1.95 (m, 2H) ; 2.24 (s, 3H) ; 2.48 (m, 2H) ; 2.45 (m, 2H) ; 3.49 (m, 2H) ; 3.93 (s, 2H) ; 3.98 (s, 3H) ; 4.21 (t, 2H) ; 4.38 (m, 1H) ; 6.95 (m, 1H) ; 7.27 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.65 (s, 1H) ; 12.04 (brs, 1H).

Example 319. Preparation of compound 496 in Table 17

An analogous reaction to that described in example 255 but starting with N,N-dimethylethylenediamine (291 mg, 3.3 mmol) yielded compound 496 in Table 17 (22 mg, 17 %).

MS ES$^+$: 572 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.23 (m, 2H) ; 2.89 (s, 6H) ; 3.22 (m, 2H) ; 3.41 (s, 4H) ; 3.96 (s, 3H) ; 4.01 (s, 2H) ; 4.31 (t, 2H) ; 6.92 (m, 1H) ; 7.31 (s, 1H) ; 7.35 (dd, 2H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 320. Preparation of compound 497 in Table 17

An analogous reaction to that described in example 255 but starting with (S(-(+)-1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 497 in Table 17 (32 Mg, 26 %).

MS ES$^+$: 559 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.15 (d, 3H) ; 2.24 (m, 2H) ; 2.83 (dd, 1H) ; 3.06 (dd, 1H) ; 3.15 (t, 2H) ; 3.95 (m, 1H) ; 3.99 (s, 3H) ; 4.01 (s, 3H) ; 4.29 (t, 1H) ; 6.92 (m, 1H) ; 7.28 (s, 1H) ; 7.34 (dd, 2H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 321. Preparation of compound 498 in Table 17

An analogous reaction to that described in example 255 but starting with (R)-(-)-1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 498 in Table 17 (40 mg, 32 %).

MS ES$^+$: 559 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.15 (d, 3H) ; 2.24 (m, 2H) ; 2.83 (dd, 1H) ; 3.06 (dd, 1H) ; 3.15 (t, 2H) ; 3.95 (m, 1H) ; 3.99 (s, 3H) ; 4.01 (s, 3H) ; 4.29 (t, 1H) ; 6.90 (m, 1H) ; 7.28 (s, 1H) ; 7.34 (dd, 2H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 322. Preparation of compound 499 in Table 17

An analogous reaction to that described in example 255 but starting with tert-butyl-1-piperazine carboxylate (615 mg, 3.3 mmol) and treating the crude reaction mixture with hydrochloric acid in 1,4-dioxane (4M, 2 ml) yielded compound 499 in Table 17 (66 mg, 45 %, 3 HCl).

MS ES$^+$: 570 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.35 (m, 2H) ; 3.20-3.94 (m, 10H) ; 3.99 (s, 3H) ; 4.03 (s, 2H) ; 4.33 (t, 2H) ; 6.93 (m, 1H) ; 7.36 (s, 1H) ; 7.37 (dd, 2H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 323. Preparation of compound 500 in Table 17

An analogous reaction to that described in example 255 but starting with N-allylpiperazine (416 mg, 3.3 mmol) yielded compound 500 in Table 17 (33 mg, 25 %).

MS ES$^+$: 610 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 1.96 (m, 2H) ; 2.30-2.50 (m, 10H) ; 2.93 (d, 2H) ; 3.92 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 5.12 (d, 1H) ; 5.18 (d, 1H) ; 5.82 (m, 1H) ; 6.95 (m, 1H) ; 7.25 (s, 1H) ; 7.35 (dd, 2H) ; 7.40 (s, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.64 (s, 1H) ; 11.99 (brs, 1H).

Example 324. Preparation of compound 501 in Table 17

An analogous reaction to that described in example 255 but starting with (R)-(-)-2-pyrrolidinemethanol (334 mg, 3.3 mol) yielded compound 501 in Table 17 (51 mg, 40 %).

MS ES$^+$: 585 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.57 (m, 1H) ; 1.67 (m, 2H) ; 1.82 (m, 1H) ; 1.96 (m, 2H) ; 2.18 (q, 1H) ; 2.45 (m, 3H) ; 2.98 (m, 1H) ; 3.10 (m, 1H) ; 3.20 (m, 1H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.22 (t, 2H) ; 4.35 (brs, 1H) ; 6.95 (m, 1H) ; 7.27 (s, 1H) ; 7.36 (dd, 2H) ; 7.40 (s, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H) ; 10.66 (s, 1H) ; 12.00 (brs, 1H).

Example 325. Preparation of compound 502 in Table 17

An analogous reaction to that described in example 255 but starting with cyclopentylamine (281 mg, 3.3 mmol) yielded compound 502 in Table 17 (28 mg, 22 %).

MS ES$^+$: 569 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.31 (m, 2H) ; 1.47 (m, 2H) ; 1.62 (m, 2H) ; 1.73 (m, 2H) ; 1.93 (m, 2H) ; 2.70 (t, 2H) ; 3.03 (m, 1H) ; 3.92 (s, 2H) ; 3.97 (s, 3H) ; 4.23 (t, 2H) ; 6.94 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (dd, 2H) ; 7.39 (s, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.66 (s, 1H).

Example 326. Preparation of compound 503 in Table 17

An analogous reaction to that described in example 256 but starting with 2-methylaminoethanol (248 mg, 3.3 mmol) yielded compound 503 in Table 17 (31 mg, 24 %).

MS ES$^+$: 575 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (m, 2H) ; 2.88 (s, 3H) ; 3.16-3.45 (m, 4H) ; 3.77 (t, 2H) ; 3.99 (s, 5H) ; 4.29 (t, 2H) ; 7.30 (s, 1H) ; 7.38 (t, 1H) ; 7.50 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (dd, 1H) ; 9.09 (s, 1H).

Example 327. Preparation of compound 504 in Table 17

An analogous reaction to that described in example 256 but starting with N,N,N'-trimethylethylenediamine (337 mg, 3.3 mmol) yielded compound 504 in Table 17 (28 mg, 21 %).

MS ES$^+$: 602 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (m, 2H) ; 2.89 (s, 6H) ; 2.93 (s, 3H) ; 3.38 (m, 2H) ; 3.56 (brs, 4H) ; 3.99 (s, 5H) ; 4.30 (t, 2H) ; 7.35 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (dd, 1H) ; 9.09 (s, 1H).

Example 328. Preparation of compound 505 in Table 17

An analogous reaction to that described in example 256 but starting with N-allylpyperazine (416 mg, 3.3 mmol) yielded compound 505 in Table 17 (42 mg, 30 %).

MS ES$^+$: 626 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.33 (m, 2H) ; 3.20-3.80 (m, 10H) ; 3.91 (d, 2H) ; 3.99 (s, 5H) ; 4.32 (t, 2H) ; 5.60 (m, 2H) ; 5.94 (m, 1H) ; 7.33 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (dd, 1H) ; 9.09 (s, 1H).

Example 329. Preparation of compound 506 in Table 17

An analogous reaction to that described in example 256 but starting with 4-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 506 in Table 17 (32 mg, 25 %).

MS ES$^+$: 601 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 1.41 (m, 2H) ; 1.73 (m, 2H) ; 1.96 (m, 2H) ; 2.03 (m, 2H) ; 2.45 (m, 2H) ; 2.74 (m, 2H) ; 3.46 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.21 (t, 2H) ; 4.55 (brs, 1H) ; 7.26 (s, 1H) ; 7.40 (s, 1H) ; 7.41 (t, 1H) ; 7.51 (m, 1H) ; 7.97 (dd, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.49 (s, 1H) ; 12.03 (brs, 1H).

Example 330. Preparation of compound 507 in Table 17

An analogous reaction to that described in example 256 but starting with 3-pyrrolidinol (288 mg, 3.3 mmol) yielded compound 507 in Table 17 (24 mg, 19 %).

MS ES$^+$: 587 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.57 (m, 1H) ; 1.98 (m, 3H) ; 2.30-2.81 (m, 6H) ; 3.38 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.22 (t, 2H) ; 4.74 (brs, 1H) ; 7.27 (s, 1H) ; 7.39 (s, 1H) ; 7.40 (t, 1H) ; 7.50 (m, 1H) ; 7.96 (dd, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.49 (s, 1H) ; 12.05 (brs, 1H).

Example 331. Preparation of compound 508 in Table 17

An analogous reaction to that described in example 256 but starting with 1-(2-aminoethyl)pyrrolidine (377 mg, 3.3 mmol) yielded compound 508 in Table 17 (18 mg, 13 %).

MS ES$^+$: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.91 (m, 2H) ; 2.06 (m, 2H) ; 2.23 (m, 2H) ; 3.11 (m, 2H) ; 3.22 (t, 2H) ; 3.41 (m, 2H) ; 3.47 (m, 2H) ; 3.67 (m, 2H) ; 3.98 (s, 5H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.36 (t, 1H) ; 7.49 (m, 1H) ; 7.63 (s, 1H) ; 7.91 (s, 1H). 7.95 (dd, 1H) ; 9.09 (s, 1H).

Example 332. Preparation of compound 509 in Table 17

An analogous reaction to that described in example 256 but starting with N-acetylpiperazine (423 mg, 3.3 mmol) yielded compound 509 in Table 17 (113 mg, 82 %).

MS ES$^+$: 628 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.98 (m, 2H) ; 2.00 (s, 3H) ; 2.36 (t, 2H) ; 2.42 (t, 2H) ; 2.92 (t, 0.5H) ; 2.99 (t, 0.5H) ; 3.45 (m, 4H) ; 3.55 (t, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.23 (t, 2H) ; 7.27 (s, 1H) ; 7.40 (s, 1H) ; 7.41 (t, 1H) ; 7.52 (m, 1H) ; 7.97 (dd, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H) ; 10.51 (s, 1H).

Example 333. Preparation of compound 510 in Table 17

An analogous reaction to that described in example 256 but starting with 2-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 510 in Table 17 (34 mg, 24 %).

MS ES$^+$: 629 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.48-1.90 (m, 7H) ; 2.08 (m, 1H) ; 2.27 (m, 2H) ; 3.09-3.69 (m, 7H) ; 3.99 (s, 5H) ; 4.30 (m, 2H) ; 7.30 (d, 1H) ; 7.38 (t, 1H) ; 7.50 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (dd, 1H) ; 9.09 (s, 1H).

Example 334. Preparation of compound 511 in Table 17

An analogous reaction to that described in example 256 but starting with 2-(2-hydroxyethyl)piperazine (430 mg, 3.3 mmol) yielded compound 511 in Table 17 (80 mg, 58 %).

MS ES$^+$: 630 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.96 (m, 2H) ; 2.42 (m, 12H) ; 3.49 (dd, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.37 (t, 1H) ; 7.25 (s, 1H) ; 7.39 (s, 1H) ; 7.40 (t, 1H) ; 7.51 (m, 1H) ; 7.97 (dd, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.42 (s, 1H) ; 12.02 (brs, 1H).

Example 335. Preparation of compound 512 in Table 17

An analogous reaction to that described in example 256 but starting with cyclopentylamine (281 mg, 3.3 mmol) yielded compound 512 in Table 17 (12 mg, 9 %).

MS ES$^+$: 585 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.59 (m, 4H) ; 1.73 (m, 2H) ; 2.00 (m, 2H) ; 2.21 (m, 2H) ; 3.13 (t, 2H) ; 3.56 (m, 1H) ; 3.99 (s, 5H) ; 4.31 (t, 2H) ; 7.29 (s, 1H) ; 7.37 (t, 1H) ; 7.49 (m, 1H) ; 7.64 (s, 1H) ; 7.92 (s, 1H) ; 7.96 (dd, 1H) ; 9.09 (s, 1H).

Example 336. Preparation of compound 513 in Table 17

An analogous reaction to that described in example 256 but starting with 4-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 513 in Table 17 (54 mg, 39 %).

MS ES$^+$: 629 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 1.15 (m, 2H) ; 1.36 (m, 3H) ; 1.63 (d, 2H) ; 1.88 (t, 2H) ; 1.96 (m, 2H) ; 2.44 (t, 2H) ; 2.87 (d, 2H) ; 3.44 (m, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2HJ) ; 4.33 (t, 1H) ; 7.25 (s, 1H) ; 7.40 (s, 1H) ; 7.41 (t, 1H) ; 7.51 (m, 1H) ; 7.97 (dd, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.03 (brs, 1H).

Example 337. Preparation of compound 514 in Table 17

An analogous reaction to that described in example 256 but starting with 3-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 514 in Table 17 (96 mg, 73 %).

MS ES^+:601 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 1.09 (m, 1H) ; 1.43 (m, 1H) ; 1.63 (m, 1H) ; 1.78 (m, 2H) ; 1.87 (m, 1H) ; 1.96 (m, 2H) ; 2.47 (m, 2H) ; 2.68 (m, 1H) ; 2.84 (brd, 1H) ; 3.50 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.20 (t, 2H) ; 4.59 (d, 1H) ; 7.26 (s, 1H) ; 7.40 (s, 1H) ; 7.41 (t, 1H) ; 7.51 (m, 1H) ; 7.97 (dd, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.03 (brs, 1H).

Example 338. Preparation of compound 515 in Table 17

An analogous reaction to that described in example 256 but starting with 4-hydroxymethylpyperidine (380 mg, 3.3 mmol) yielded compound 515 in Table 17 (18 mg, 13 %).

MS ES^+: 615 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H) ; 1.35 (m, 1H) ; 1.65 (d, 2H) ; 1.88 (m, 2H) ; 1.97 (m, 2H) ; 2.46 (m, 2H) ; 2.91 (m, 2H) ; 3.25 (t, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.21 (t, 2H) ; 4.41 (t, 1H) ; 7.26 (s, 1H) ; 7.40 (s, 1H) ; 7.41 (t, 1H) ; 7.50 (m, 1H) ; 7.97 (dd, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.49 (s, 1H) ; 12.03 (brs, 1H).

Example 339. Preparation of compound 516 in Table 17

An analogous reaction to that described in example 256 but starting with 1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 516 in Table 17 (14 mg, 11 %).

MS ES^+: 575 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H) ; 1.96 (m, 2H) ; 2.49 (m, 2H) ; 2.74 (t, 2H) ; 3.71 (m, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.24 (t, 2H) ; 4.50 (brs, 1H) ; 7.27 (s, 1H) ; 7.39 (s, 1H) ; 7.41 (t, 1H) ; 7.51 (m, 1H) ; 7.97 (dd, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.49 (s, 1H).

Example 340. Preparation of compound 517 in Table 17

An analogous reaction to that described in example 256 but starting with tert-butyl-1-piperazinecarboxylate (615 mg, 3.3 mmol) and treating the crude reaction mixture with hydrochloric acid in 1,4-dioxane (4.M, 2 ml) yielded compound 517 in Table 17 (61 mg, 47 %).

MS ES$^+$: 586 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (m, 2H) ; 3.00-3.95 (m, 10 H) ; 3.99 (s, 5H) ; 4.31 (t, 2H) ; 7.32 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.65 (s, 1H) ; 7.91 (s, 1H) ; 7.97 (dd, 1H) ; 9.10 (s, 1H).

Example 341. Preparation of compound 518 in Table 17

An analogous reaction to that described in example 256 but starting with 1-(2-morpholinoethyl)piperazine (519 mg, 3.3 mmol) yielded compound 518 in Table 17 (69 mg, 48 %).

MS ES$^+$: 699 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (m, 2H) ; 2.98 (m, 2H) ; 3.10-37.5 (m, 16H) ; 3.86 (m, 4H) ; 3.99 (s, 5H) ; 4.31 (t, 2H) ; 7.33 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.65 (s, 1H) ; 7.92 (s, 1H) ; 7.97 (dd, 1H) ; 9.10 (s, 1H).

Example 342. Preparation of compound 519 in Table 17

An analogous reaction to that described in example 256 but starting with pyrrolidine (235 mg, 3.3 mmol) yielded compound 519 in Table 17 (55 mg, 44 %).

MS ES$^+$: 571 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.90 (m, 2H) ; 2.06 (m, 2H) ; 2.27 (m, 2H) ; 3.09 (m, 2H) ; 3.36 (t, 2H) ; 3.66 (m, 2H) ; 3.98 's, 5H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.39 (t, 1H) ; 7.50 (m, 1H) ; 7.64 (s, 1H) ; 7.90 (s,1H) ; 7.96 (dd, 1H) ; 9.09 (s, 1H).

Example 343. Preparation of compound 520 in Table 17

An analogous reaction to that described in example 257 but starting with 2-methylaminoethanol (248 mg, 3.3 mmol) yielded compound 520 in Table 17 (34 mg, 29 %).

MS ES$^+$: 541 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.30 (m, 2H) ; 3.57 (s, 3H) ; 3.16-3.45 (m, 4H) ; 3.75 (t, 2H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.29 (t, 2H) ; 6.89 (t, 1H) ; 7.29 (s, 1H) ; 7.30-7.40 (m, 2H) ; 7.62 (d, 1H) ; 7.63 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 344. Preparation of compound 521 in Table 17

An analogous reaction to that described in example 257 but starting with 1,2-diamino-2-methylpropane (291 mg, 3.3 mmol) yielded compound 521in Table 17 (10 mg, 8 %).

MS ES$^+$: 554 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.39 (s, 6H) ; 2.27 (m, 2H) ; 3.22 (m, 4H) ; 3.97 (s, 3H) ; 3.98 (s, 2H) ; 4.32 (t, 2H) ; 6.89 (m, 1H) ; 7.29-7.39 (m, 3H) ; 7.62 (d, 1H) ; 7.63 (s, 1H) ; 7.92 (s, 1H) ; 9.08 (s, 1H).

Example 345. Preparation of compound 522 in Table 17

An analogous reaction to that described in example 257 but starting with N,N-dimethylethylenediamine (291 mg, 3.3 mmol) yielded compound 522 in Table 17 (26 mg, 22 %).

MS ES$^+$: 554 $(M+H)^+$

^{1}HNMR ($DMSOd_6$)) : 1.95 (m, 2H) ; 2.15 (s, 6H) ; 2.33 (t, 2H) ; 2.63 (t, 2H) ; 2.73 (t, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.23 (t, 2H) ; 6.91 (m, 1H) ; 7.26 (s, 1H) ; 7.31-7.42 (m, 2H) ; 7.39 (s, 1H) ; 7.64 (d, 1H) ; 8.11 (s, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H).

Example 346. Preparation of compound 523 in Table 17

An analogous reaction to that described in example 257 but starting with N,N,N'-trimethylethylenediamine (337 mg, 3.3 mmol) yielded compound 523 in Table 17 (37 mg, 30 %).

MS ES$^+$: 568 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.34 (m, 2H) ; 2.88 (s, 6H) ; 2.93 (s, 3H) ; 3.38 (m, 2H) ; 3.55 (m, 4H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.29 (t, 2H) ; 6.89 (m, 1H) ; 7.29-7.41 (m, 2H) ; 7.33 (s, 1H) ; 7.63 (d, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 347. Preparation of compound 524 in Table 17

An analogous reaction to that described in example 257 but starting with N-allylpiperazine (416 mg, 3.3 mmol) yielded compound 524 in Table 17 (77 mg, 59 %).

MS ES$^+$: 592 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.34 (m, 2H) ; 3.00-3.08 (m, 8H) ; 2.86 (d, 2H) ; 3.92 (m, 2H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.31 (t, 2H) ; 5.53-5.66 (m, 2H) ; 5.60-5.87 (m, 1H) ; 6.89 (m, 1H) ; 7.31-7.40 (m, 3H) ; 7.62 (d, 1H) ; 7.63 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 348. Preparation of compound 525 in Table 17

An analogous reaction to that described in example 257 but starting with 4-hydroxypyperidine (334 mg, 3.3 mmol) yielded compound 525 in Table 17 (21 mg, 17 %).

MS ES$^+$: 567 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.59 (m, 1H) ; 1.85 (m, 2H) ; 2.01 (d, 1H) ; 2.28 (m, 2H) ; 3.03 (t, 1H) ; 3.21 (m, 1H) ; 3.28 (m, 2H) ; 3.40 (m, 1H) ; 3.57 (d, 1H) ; 3.68 (m, 1H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.28 (t, 2H) , 6.90 (t, 1H) ; 7.29 (s, 1H) ; 7.30-7.40 (m, 2H) ; 7.63 (d, 1H) ; 7.64 (s,1H) , 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 349. Preparation of compound 526 in Table 17

An analogous reaction to that described in example 257 but starting with 3-pyrrolidinol (288 mg, 3.3 mmol) yielded compound 526 in Table 17 (18 mg, 15 %).

MS ES$^+$: 553 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.84-2.03 (m, 2H) ; 2.27 (m, 2H) ; 3.02-3.79 (m, 6H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.29 (m, 2H) ; 4.41-4.51 (m, 1H) ; 6.91 (m, 1H) ; 7.28 (d, 1H) ; 7.31-7.41 (m, 2H) ; 7.63 (d, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.09 (s, 1H).

Example 350. Preparation of compound 527 in Table 17

An analogous reaction to that described in example 257 but starting with 1-(aminoethyl)pyrrolidine (377 mg, 3.3 mmol) yielded compound 527 in Table 17 (34 mg, 27 %).

MS ES$^+$: 580$(M+H)^+$

^{1}HNMR (DMSOd_6): 1.68 (m, 4H) ; 1.97 (m, 2H) ; 2.47 (m, 6H) ; 2.70 (t, 2H) ; 2.77 (t, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.24 (t, 2H) ; 6.91 (m, 1H) ; 7.27 (s, 1H) ; 7.30-7.42 (m, 2H) ; 7.39 (s, 1H) ; 7.64 (d,1H) , 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.49 (s, 1H).

Example 351. Preparation of compound 528 in Table 17

An analogous reaction to that described in example 257 but starting with N-acetylpiperazine (423 mg, 3.3 mmol) yielded compound 528 in Table 17 (93 mg, 71 %).

MS ES$^+$: 594 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.99 (m, 2H) ; 2.00 (s, 3H) ; 2.35 (t, 2H) ; 2.41 (t, 2H) ; 2.49 (m, 2H) ; 3.45 (m, 4H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.23 (t, 2H) ; 6.92 (m, 1H) ; 7.27 (s, 1H) ; 7.32-7.42 (m, 2H) ; 7.40 (s, 1H) ; 7.63 (d, 1H) ; 8.13 (brs, 1H) ; 8.69 (s, 1H) ; 10.48 (s, 1H).

Example 352. Preparation of compound 529 in Table 17

An analogous reaction to that described in example 257 but starting with 1-(2-hydroxyethyl)piperazine (430 mg, 3.3 mmol) yielded compound 529 in Table 17 (91 mg, 69 %).

MS ES$^+$: 596 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H) ; 2.41 (m, 12H) ; 3.50 (q, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.37 (t, 1H) ; 6.91 (t, 1H) ; 7.25 (s, 1H) ; 7.32-7.42 (m, 2H) ; 7.39 (s, 1H) ; 7.65 (d, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.04 (brs, 1H).

Example 353. Preparation of compound 530 in Table 17

An analogous reaction to that described in example 257 but starting cyclopentylamine (281 mg, 3.3 mmol) yielded compound 530 in Table 17 (47 mg, 39 %).

MS ES$^+$: 551 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.39 (m, 2H) ; 1.50 (m, 2H) ; 1.65 (m, 2H) ; 1.80 (m, 2H) ; 2.00 (m, 2H) ; 2.80 (t, 2H) ; 3.16 (m, 1H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.25 (t, 2H) ; 6.98 (t, 1H) ; 7.28 (s, 1H) ; 7.31-7.42 (m, 2H) ; 7.40 (s, 1H) ; 7.64 (d, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H) ; 10.49 (s, 1H).

Example 354. Preparation of compound 531 in Table 17

An analogous reaction to that described in example 257 but starting with 4-(2-hydroxyethyl)piperidine (426 mg, 3.3 mmol) yielded compound 531 in Table 17 (65 mg, 50 %).

MS ES$^+$: 595 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H) ; 1.36 (m, 3H) ; 1.63 (d, 2H) ; 1.88 (m, 2H) ; 1.96 (m, 2H) ; 2.44 (m, 2H) ; 2.87 (d, 2H) ; 3.44 (m, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.33 (t, 1H) ; 6.91 (t, 1H) ; 7.25 (s, 1H) ; 7.32-7.42 (m, 2H) ; 7.40 (s, 1H) ; 7.63 (d, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.03 (s, 1H).

Example 355. Preparation of compound 532 in Table 17

An analogous reaction to that described in example 257 but starting with 3-hydroxypiperidine (334 mg, 3.3 mmol) yielded compound 532 in Table 17 (72 mg, 58 %).

MS ES$^+$: 567 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.09 (m, 1H) ; 1.43 (m, 1H) ; 1.63 (m, 1H) ; 1.78 (m, 2H) ; 1.87 (m, 1H) ; 1.96 (t, 2H) ; 2.47 (m, 2H) ; 2.69 (m, 1H) ; 2.85 (brd, 1H) ; 3.49 (m, 1H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.20 (t, 2H) ; 4.60 (d, 1H) , 6.91 (t, 1H) ; 7.26 (s, 1H) ; 7.31-7.42 (m, 2H) ; 7.40 (s, 1H) ; 7.64 (d, 1H) ; 8.13 (brs, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.02 (brs, 1H).

Example 356. Preparation of compound 533 in Table 17

An analogous reaction to that described in example 257 but starting with 4-hydroxymethylpyperidine (380 mg, 3.3 mmol) yielded compound 533 in Table 17 (56 mg, 44).

MS ES$^+$: 581 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H) ; 1.34 (m, 1H) ; 1.65 (d, 2H) ; 1.88 (t, 2H) ; 1.97 (m, 2H) ; 2.45 (t, 2H) ; 2.90 (d, 2H) ; 3.25 (t, 2H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.20 (t, 2H) ; 4.41 (t, 1H) ; 6.93 (t, 1H) ; 7.25 (s, 1H) ; 7.32-7.42 (m, 2H) ; 7.40 (s, 1H) ; 7.63 (d, 1H) ; 8.12 (brs, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.03 (brs, 1H).

Example 357. Preparation of compound 534 in Table 17

An analogous reaction to that described in example 257 but starting with 1-amino-2-propanol (248 mg, 3.3 mmol) yielded compound 534 in Table 17 (36 mg, 30 %).

MS ES$^+$: 541 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H) ; 1.95 (m, 2H) ; 2.48 (m, 2H) ; 2.72 (t, 2H) ; 3.69 (m, 1H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.23 (t, 2H) ; 4.47 (brs, 1H) ; 6.91 (t, 1H) ; 7.26 (s, 1H) ; 7.32-7.41 (m, 2H) ; 7.39 (s, 1H) ; 7.63 (d, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.48 (s, 1H).

Example 358. Preparation of compound 535 in Table 17

An analogous reaction to that described in example 257 but starting with (R)-(-)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 535 in Table 17 (66 mg, 53 %).

MS ES$^+$: 567 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.57 (m, 1H) ; 1.67 (m, 2H) ; 2.82 (m, 1H) ; 1.96 (m, 2H) ; 2.18 (m, 1H) ; 2.45 (m, 2H) ; 2.98 (m, 1H) ; 3.10 (m, 1H) ; 3.20 (m, 1H) ; 3.41 (m, 1H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.22 (t, 2H) ; 4.35 (brs, 1H) ; 6.91 (t, 1H) ; 7.26 (s, 1H) ; 7.31-7.42 (m, 2H) ; 7.39 (s, 1H) ; 7.64 (d, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H) ; 10.48 (s, 1H) ; 12.01 (brs, 1H).

Example 359. Preparation of compound 536 in Table 17

An analogous reaction to that described in example 257 but starting with (S)-(+)-2-pyrrolidinemethanol (334 mg, 3.3 mmol) yielded compound 536 in Table 17 (59 mg, 48 %).

MS ES$^+$: 567 $(M+H)^+$

1HNMR (DMSOd6, TFA) : 1.78 (m, 1H) ; 1.90 (m, 1H) ; 2.03 (m, 1H) ; 2.13 (m, 1H) ; 2.31 (m, 2H) ; 3.23 (m, 2H) ; 3.61 (m, 4H) ; 3.77 (q, 1H) ; 3.98 (s, 3H) ; 3.99 (s, 2H) ; 4.29 (t, 2H) ; 6.89 (t, 1H) ; 7.29 (s, 1H) ; 7.30-7.40 (m, 2H) ; 7.63 (d, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 9.08 (s, 1H).

Example 360. Preparation of compound 537 in Table 17

An analogous reaction to that described in example 257 but starting with t-butyl-1-pyperazinecarboxylate (615 mg, 3.3 mmol) and treating the crude reaction mixture with hydrochloric acid in 1,4-dioxane (4M, 2 ml) yielded compound 537 in Table 17 (35 mg, 27 %).

MS ES$^+$: 552 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H) ; 2.33 (brs, 4H) ; 2.42 (t, 2H) ; 2.73 (t, 4H) ; 3.89 (s, 2H) ; 3.95 (s, 3H) ; 4.19 (t, 2H) ; 6.89 (t, 1H) ; 7.24 (s, 1H) ; 7.32-7.42 (m, 2H) ; 7.37 (s, 1H) ; 7.62 (d, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H) ; 10.47 (s, 1H).

Example 361. Preparation of compound 538 in Table 17

An analogous reaction to that described in example 257 but starting with 1-(2-morpholinoethyl)piperazine (519 mg, 3.3 mmol) yielded compound 538 in Table 17 (50 mg, 37 %).

MS ES$^+$: 665 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.33 (m, 2H) ; 2.99 (t, 2H) ; 3.05-3.75 (m, 16H) ; 3.86 (brs, 4H) ; 3.99 (s, 3H) ; 4.00 (s, 2H) ; 4.29 (t, 2H) ; 6.90 (t, 1H) ; 7.32 (s, 1H) ; 7.41-7.31 (m, 2H) ; 7.62 (d, 1H) ; 7.64 (s, 1H) ; 7.92 (s, 1H) ; 9.09 (s, 1H).

Example 362. Preparation of compound 539 in Table 17

An analogous reaction to that described in example 257 but starting with 2-amino-2-methyl-1-propanol (294 mg, 3.3 mmol) yielded compound 539 in Table 17 (40 mg, 33 %).

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 0.96 (s, 6H) ; 1.91 (m, 2H) ; 2.67 (t, 2H) ; 3.19 (s, 2H) ; 3.90 (s, 2H) ; 3.97 (s, 3H) ; 4.24 (t, 2H) ; 4.53 (brs, 1H) ; 6.91 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (m, 2H) ; 7.38 (s, 1H) ; 7.63 (d, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H) ; 10.48 (s, 1H).

Example 363. Preparation of compound 540 in Table 18

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (125 mg, 0.27 mmol) in DMF (2.5 ml) was reacted with N-ethylaniline (84.3 µl, 0.707 mmol) in presence of O-(7-azabenzotriazol-1-yl) -N,N,N',N'- tetramethyluronium hexafluorophosphate (136 mg, 0.37 mmol) and DIEA (95 µl, 0.54 mmol) at 50°C for 18 hours. The reaction mixture was cooled, sodium bicarbonate (sat., 1 ml) 3 g alumina were added, the mixture was evaporated to dryness, and the residue purified by chromatography over alumina, Eluant CH_2Cl_2, CH_2Cl_2/MeOH 99/1 to 95/5 to give title compound (68 mg, 44 %).

MS ES$^+$: 563.6 $(M+H)^+$

^{1}H NMR ($DMSOd_6$, TFA) : 1.05 (t, 3H) ; 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.65 (m, 6H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.31 (s, 1H) ; 7.38 (s, 1H) ; 7.40 (m, 2H) ; 7.46 (m, 1H) ; 7.53 (m, 2H) ; 7.87 (s, 1H) ; 9.06 (s, 1H).

Example 364. Preparation of compound 541 in Table 18

An analogous reaction to that described in example 363 but starting with 3-chloro-4-fluoro-N-methylaniline (97 mg, 0.35 mmol) yielded title compound (98 mg, 60).

MS ES$^+$: 601.5, 603.5 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA) : 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.21 (s, 3H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.7 (m, 4H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.31 (s, 1H) ; 7.41 (s, 1H) ; 7.50 (m, 2H) ; 7.80 (m, 1H) ; 7.87 (s, 1H) ; 9.06 (s, 1H).

N-(tert-butyloxycarbonyl)-3-chloro-4-fluoroaniline

3-chloro-4-fluoroaniline (2 g, 13.7 mmol) in THF (12.5 ml) under argon, was treated with NaHMDS (1 M, 27.5 ml, 27.5 mmol) at room temperature for 15 minutes. Di-tert-butyl dicarbonate in THF (10 ml) was slowly added to the reaction mixture, and the mixture stirred at room temperature for 45 minutes. The solvent was evaporated, diluted HCl (0.1 N) was added, and the mixture extracted with ethylacetate, dried, purified by silica gel chromatography, ether/petroleum ether 10-20 / 90-80 to give title compound (2.77 g, 82 %).

^{1}H NMR ($CDCl_3$) : 1.49 (s, 9H) ; 6.42 (s, 1H) ; 7.01 (t, 1H) ; 7.01 (m, 1H) ; 7.54 (m, 1H).

3-chloro-4-fluoro-N-methylaniline

To a solution of N-(tert-butyloxycarbonyl)-3-chloro-4-fluoroaniline (250 mg, 1.02 mmol) in THF (4 ml) at 0°C was added sodium hydride (60 %, 45 mg, 1.12 mmol), and the mixture was stirred for 20 minutes. Methyl iodide (70 µl, 1.12 mmol) was added to the mixture which was stirred at room temperature for 4 hours. The solvent was evaporated, a saturated solution of sodium chloride was added, and the mixture was extracted with CH_2Cl_2, dried, and purified by silica gel chromatography, ether / petroleum ether, 8/2 to give compound (235 mg). This compound was dissolved in CH_2Cl_2(2 ml) and TFA (2 ml), H_2O (200 µl) was added, the mixture was stirred for 1 hour at room temperature, the solvent was evaporated, to give title compound (256 mg, 89 %).

^{1}HNMR ($CDCl_3$) : 2.98 (s, 3H) ; 7.3 (m, 3H).

Example 365. Preparation of compound 542 in Table 18

An analogous reaction to that described in example 363 but starting with ethyl-2-(3-chloro-4-fluoroaniline)acetate (151 mg, 0.65 mmol) yielded title compound (10 mg, 4.5 %).

MS ES$^+$: 673.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 1.18 (t, 3H) ; 2.30 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.83 (s, 1H) ; 3.97 (s, 3H) ; 4.03 (m, 4H) ; 4.13 (s, 2H) ; 4.29 (t, 2H) ; 4.41 (s, 1H) ; 7.30 (s, 1H) ; 7.44 (s, 1H) ; 7.55 (m, 2H) ; 7.78 (m, 1H) ; 7.87 (s, 1H) ; 9.06 (s, 1H).

Example 366. Preparation of compound 543 in Table 18

An analogous reaction to that described in example 363 but starting with 2-anilinoacetonitrile (371 mg, 2.72 mmol) yielded title compound (110 mg, 18 %).

MS ES$^+$: 574.6 $(M+H)^+$

^{1}H NMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.77 (s, 1H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 4.81 (s, 2H) ; 7.31 (s, 1H) ; 7.43 (s, 1H) ; 7.57 (m, 5H) ; 7.88 (s, 1H) ; 9.09 (s, 1H).

Example 367. Preparation of compound 544 in Table 18

An analogous reaction to that described in example 363 but starting with 3-anilinoacetonitrile (335 mg, 2.18 mmol) yielded title compound (100 mg, 18 %).

MS ES$^+$: 588.6 $(M+H)^+$

^{1}H NMR ($DMSOd_6$, TFA): 2.29 (t, 2H) ; 2.75 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (m, 4H) ; 3.95 (t, 2H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.42 (s, 1H) ; 7.48 (m, 3H) ; 7.55 (m, 2H) ; 7.87 (s, 1H) ; 9.08 (s, 1H).

Example 368. Preparation of compound 545 in Table 18

An analogous reaction to that described in example 363 but starting with N-(2-tert-butylethyl)-3-chloro-4-fluoroaniline (346 mg, 1.42 mmol) yielded title compound (147 mg, 30 %).

MS ES$^+$: 687.6 $(M+H)^+$

^{1}H NMR ($DMSOd_6$, TFA): 1.08 (s, 9H) ; 2.31 (t, 2H) ; 3.14 (t, 2H) ; 4.3-4.5 (m, 4H) ; 3.55 (d, 2H) ; 3.68 (m, 6H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.29 (t, 2H) ; 7.30 (s, 1H) ; 7.41 (s, 1H) ; 7.51 (m, 2H) ; 7.78 (m, 1H) ; 7.87 (s, 1H) ; 9.06 (s, 1H).

N-(2-hydroxyethyl)-3-chloro-4-fluoroaniline.

ethyl-2-(3-chloro-4-fluoroanilino)acetate (J. Med. Chem. 1965, 405-407) (2 g, 8.6 mmol) in THF (15 ml) ether (10 ml) was treated with Li Al H4 (460 mg, 12.1 mmol) at 40°C for 4 hours. The mixture was then poured onto ice, treated with NaOH (2N, 10 ml), extracted with ethyl acetate, dried, evaporated to give title compound (1.48 g, 90 %).

^{1}H NMR ($CDCl_3$) : 1.67 (s, 1H) ; 3.24 (t, 2H) ; 3.84 (t, 2H) ; 3.92 (s, 1H) ; 6.47 (m, 1H) ; 6.64 (m, 1H) ; 6.95 (t, 1H).

N-(2-tert-butoxyethyl)-3-chloro-4-fluoroaniline

N-2-hydroxyethyl-3-chloro-4-fluoroaniline (1.48 g, 7.81 mmol) in CH_2Cl_2 (20 ml) was reacted with N,N-diisopropyl O-tert-butyl-isourea (6.25 g, 31.2 mmol) at room temperature over night. The product was purified by silicagel chromatography, Eluant, ether / petroleum ether 5/95, 10/90 to give title compound (1.15 g, 60 %).

^{1}H NMR ($CDCl_3$) : 1.20 (s, 9H) ; 3.18 (t, 2H) ; 3.55 (t, 2H) ; 4.00 (s, 1H) ; 6.44 (m, 1H) ; 6.62 (m, 1H) ; 6.93 (t, 1H).

Example 369. Preparation of compound 546 in Table 18

An analogous reaction to that described in example 363 but starting with N-allylaniline (0.3 ml, 2.18 mmol) yielded title compound (252 mg, 50 %).

MS ES$^+$: 575.7 $(M+H)^+$

^{1}H NMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (m, 4H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.28 (m, 4H) ; 5.12 (m, 2H) ; 5.82 (m, 1H) ; 7.30 (s, 1H) ; 7.38 (m, 3H) ; 7.40 (s, 1H) ; 7.51 (m, 2H) ; 7.87 (s, 1H) ; 9.07 (s, 1H).

Example 370. Preparation of compound 547 in Table 18

An analogous reaction to that described in example 363 but starting with N-ethyl-3,4-(methylenedioxy)aniline (320 µl, 2.18 mmol) yielded title compound (351 mg, 66 %).

MS ES$^+$: 607.7 $(M+H)^+$

^{1}H NMR ($DMSOd_6$, TFA): 1.04 (t, 3H) ; 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.34 (t, 2H) ;.3.54 (d, 2H) ; 3.68 (m, 6H) ; 3.97 (s, 3H) ; 4.09 (d, 2H) ; 4.29 (t, 2H) ; 6.12 (s, 2H) ; 6.83 (d, 1H) ; 7.02 (m, 2H) ; 7.30 (s, 1H) ; 7.42 (s, 1H) ; 7.86 (s, 1H) ; 9.06 (s, 1H).

Example 371. Preparation of compound 548 in Table 18

An analogous reaction to that described in example 363 but starting with ethyl-4-(N-butylamino)benzoate (482 mg, 2.18 mmol) yielded title compound (58 mg, 10 %).

MS ES$^+$: 663.7 $(M+H)^+$

^{1}H NMR ($DMSOd_6$, TFA): 0.85 (t, 3H) ; 1.32 (m, 7H) ; 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.70 (m, 6H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 4.35 (s, 2H) ; 7.30 (s, 1H) ; 7.41 (s, 1H) ; 7.54 (d, 2H) ; 7.87 (s, 1H) ; 8.07 (d, 2H) ; 9.07 (s, 1H).

Example 372. Preparation of compound 549 in Table 18

An analogous reaction to that described in example 363 but starting with N-ethyl-m-toluidine (294 mg, 2.18 mmol) yielded title compound (294 mg, 58 %).

MS ES$^+$: 577.7 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 1.05 (t, 9H) ; 2.31 (t, 2H) ; 2.38 (s, 3H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.67 (m, 6H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.18 (m, 2H) ; 7.28 (d, 1H) ; 7.30 (s, 1H) ; 7.39 (s, 1H) ; 7.42 (d, 1H) ; 7.86 (s, 1H) ; 9.07 (s, 1H).

Example 373. Preparation of compound 550 in Table 18

Compound 545 (120 mg) in CH_2Cl_2 (2 ml) was treated with TFA (3 ml) and H_2O (200 µl) at room temperature for 3 hours. The solvent was evaporated to give title compound (45 mg, 41 %).

MS ES$^+$: 631.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA) : 2.29 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.51 (t, 2H) ; 3.54 (d, 2H) ; 3.70 (m, 6H) ; 3.97 (s, 3H) ; 4.03 (d, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.42 (s, 1H) ; 7.54 (m, 2H) ; 7.78 (d, 1H) ; 7.87 (s, 1H) ; 9.06 (s, 1H).

Example 374. Preparation of compound 551 in Table 19

4-((2-amino-4-methyl-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (118 mg, 0.25 mmol) in DMF (1.5 ml) was reacted with aniline (32 mg, 0.35 mmol) in presence of O-(7-azabenzotriazol-1-yl) -N,N,N',N'-tetramethyluronium hexafluorophosphate (142 mg, 0.375 mmol) and DIEA (65 mg, 0.5 mmol) at 65° over night. The mixture was cooled, sodium bicarbonate was added, and the resulting mixture was evaporated. The residue was dissolved in CH_2Cl_2 / MeOH 92/8 and purified by chromatography over alumina, Eluant CH_2Cl_2, CH_2Cl_2 /MeOH 98/2 to 95/5 a second purification over silicagel was performed, Eluant CH_2Cl_2 /MeOH 95/5 to 90/10 to give title compound (86 mg, 62 %).

MS ES$^+$: 549.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.34 (s, 3H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.54 (d, 2H) ; 3.72 (t, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ;(4.03) ; (d, 2H) ; 4.30 (t, 2H) ; 7.08 (t, 2H) ; 7.29 (s, 1H) ; 7.31 (t, 2H) ; 7.62 (d, 2H) ; 7.85 (s, 1H) ; 9.05 (s, 1H).

4-(ethyl(2-amino-4-methyl-1,3-thiazole-5-yl)acetate)-6-methoxy-7-(3-morpholinopropoxy)quinazoline

N'-(2-cyano-4-methoxy-5-(3-morpholinopropoxy)phenyl)-N,N-dimethylimidoformamide (1.38 g, 4 mmol) in acetic acid was reacted with ethyl-2-amino-4-methyl-1,3-thiazole-5-yl)acetate at reflux for 3.5 hours. The mixture was cooled, evaporated, HCl (1N) was added and the mixture extracted with ethylacetate. Sodium bicarbonate was cautiously added to the aqueous phase, which was extracted with ethylacetate. The organic fractions were dried, evaporated, the residue was purified by chromatography over alumina, Eluant CH_2Cl_2, CH_2Cl_2 /AcOEt 1/1, CH_2Cl_2 /AcOEt/MeOH 50/45/5 to give starting material as a yellow solid. (1.12 g, 52 %).

MS ES$^+$: 502.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 1.24 (t, 3H) ; 2.28 (m, 5H) ; 3.15 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.15 (q, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.86 (s, 1H) ; 9.05 (s, 1H).

4-((2-amino-4-methyl-1,3-thiazole-5-yl)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline

4-(ethyl(2-amino-4-methyl-1,3-thiazole-5-yl)acetate)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (1.1 g, 2.2 mmol) in ethanol (11 ml) was treated with NaOH (2N, 5.5 ml, 11 mmol) at room temperature for 1 hour. The mixture was then acidified with HCl (2N) to pH 3. The solution was evaporated, the solid suspended in CH_2Cl_2 (8 ml) MeOH (6 ml), and DIEA was added (852 mg, 6.6 mmol). The mixture was stirred for 10 minutes, filtered. The filtrate was concentrated, ethanol was added and the solid recovered to give title compound (980 mg, 94 %).

MS ES$^+$: 474.5 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.28 (m, 5H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.70 (t, 2H) ; 3.83 (s, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.86 (s, 1H) ; 9.05 (s, 1H).

Example 375. Preparation of compound 552 in Table 19

An analogous reaction to that described in example 374 but starting with 3-chloro-4-fluoroaniline (51 mg, 0.35 mmol) yielded the title compound (60 mg, 40 %).

MS ES$^+$: 601.5 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.30 (t, 2H) ; 2.33 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; (3.55) (d, 2H) ; 3.69 (t, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.28 (s, 1H) ; 7.39 (t, 1H) ; 7.49 (m, 1H) ; 7.86 (s, 1H) ; 7.96 (m, 1H) ; 9.05 (s, 1H).

Example 376. Preparation of compound 553 in Table 19

An analogous reaction to that described in example 374 but starting with 2-aminopyridine (33 mg, 0.35 mmol) yielded the title compound (45 mg, 32 %).

MS ES$^+$: 550.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 2.35 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.98 (s, 3H) ; 4.04 (m, 4H) ; 4.30 (t, 2H) ; 7.30 (m, 2H) ; 7.87 (s, 1H) ; 7.95 (d, 1H) ; 8.05 (m, 1H) ; 8.40 (d, 1H) ; 9.04 (s, 1H).

Example 377. Preparation of compound 554 in Table 19

An analogous reaction to that described in example 374 but starting with 3,4 difluoroaniline (50 mg, 0.39 mmol) yielded the title compound (120 mg, 74 %).

MS ES$^+$: 585.6 $(M+H)^+$

^{1}H NMR (DMSOd_6, TFA) : 2.30 (t, 2H) ; 2.33 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.67 (t, 2H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.05 (d, 2H) ; 4.31 (t, 2H) ; 7.28 (s, 1H) ; 7.32 (m, 1H) ; 7.40 (q, 1H) ; 7.80 (m, 1H) ; 7.86 (s, 1H) ; 9.05 (s, 1H).

Example 378. Preparation of compound 555 in Table 20

N'-(2-cyano-5-((2S)-2-hydroxy-3-piperidinylpropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide (381 mg, 0.96 mmol) in acetic acid (6 ml) was irradiated in a microwave oven in presence of N-(4-fluoro-3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (275 mg, 0.96 mmol) at reflux for 0.5 hour. The solvent was evaporated, and the residue purified by silica gel chromatography, eluant CH_2Cl_2 / MeOH sat. NH_3 95/5 to 93/7 to give title compound (230 mg, 40 %).

MS ES$^+$: 601.5 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.42 (m, 1H) ; 1.6-1.9 (m, 5H) ; 3.02 (m, 2H) ; 3.28 (m, 2H) ; 3.52 (m, 2H) ; 3.99 (s, 5H) ; 4.19 (d, 2H) ; 4.43 (m, 1H) ; 7.35 (s, 1H) ; 7.40 (t, 1H) ; 7.48 (m, 1H) ; 7.64 (s, 1H) ; 7.91 (s, 1H) ; 7.95 (m, 1H) ; 9.08 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-piperidinylpropoxy)-4-methoxyphenyl)-N,N,-dimethylimidoformamide.

(2-tritylamino-1,3-thiazol-5-yl)acetic acid (1.96 g, 4.9 mmol) in DMF (25 ml) was reacted with 3-chloro-4-fluoroaniline (1.07 g, 7.3 mmol) in presence of 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (2.42 g, 6.37 mmol) and DIEA (1.7 ml, 9.8 mmol) at 50°C for 18 hours. DMF was evaporated, the residue taken up in CH_2Cl_2 / EtOAc, washed with a saturated solution of sodium bicarbonate. The solid precipitating in the organic phase was recovered, the organic phase was evaporated, MeOH was added to the residue to give a solid, a second crop of title compound was thus recovered to give together (1.38 g, 53 %).

^{1}HNMR ($DMSOd_6$): 3.56 (s, 2H) ; 6.61 (s, 1H) ; 7.28 (m, 17H) ; 7.88 (m, 1H) ; 8.41 (s, 1H).

N-(4-fluoro-3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide

N-(4-fluoro-3-chlorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide (12.28 g, 23 mmol) was dissolved in TFA (100 ml) and water (10 ml). The mixture was stirred at room temperature for 45 minutes. Water (300 ml) was added to the reaction mixture, a solid was recovered by filtration, washed with water and ether. The solid was dissolved in MeOH, and the solution treated with ammonia (pH 8), MeOH was then partially evaporated, water (300 ml) was added and a precipitate of title compound recovered, dried (5.37 g, 81 %).

^{1}HNMR ($DMSOd_6$): 3.64 (s, 2H) ; 6.76 (m, 3H) ; 7.38 (t, 1H) ; 7.48 (m, 1H) ; 7.92 (m, 1H).

Example 379. Preparation of compound 556 in Table 20

An analogous reaction to that described in example 378 but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-pyrrolidinylpropoxy)-4-methoxyphenyl)-N,N,-dimethylimido-formamide (267 mg, 0.77 mmol) yielded title compound (213 mg, 52 %).

MS ES$^+$: 587.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.68 (m, 4H) ; 2.5 (m, 5H) ; 2.66 (m, 1H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.00 (m, 1H) ; 4.07 (m, 1H) ; 4.20 (m, 1H) ; 4.95 (m, 1H) ; 7.26 (s, 1H) ; 7.36 (s, 1H) ; 7.37 (m, 1H) ; 7.47 (m, 1H) ; 7.95 (m, 1H) ; 8.11 (s, 1H) ; 8.66 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-pyrrolinylpropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide.

An analogous reaction to that described in example 378, but starting with pyrrolidine (1.4 ml, 16 mmol) yielded title compound (2.8 g, 74 %).

MS ES$^+$: 347.6 $(M+H)^+$

^{1}HNMR (DMSOd_6) : 1.67 (m, 4H) ; 1.45 (m, 4H) ; 1.63 (m, 2H) ; 2.95 (s, 3H) ; 3.05 (s, 3H) ; 3.73 (s, 3H) ; 3.95 (m, 2H) ; 4.04 (m, 1H) ; 4.93 (m, 1H) ; 6.73 (s, 1H) ; 7.08 (s, 1H) ; 7.89 (s, 1H).

Example 380. Preparation of compound 557 in Table 20

An analogous reaction to that described in example 378 but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-(4-hydroxypiperidinyl)propoxy)-4-methoxy-phenyl)-N,N-dimethylimidoformamide (195 mg, 0.52 mmol) yielded title compound (88 mg, 30 %).
MS ES$^+$: 617.5, 619.5 $(M+H)^+$
^{1}HNMR (DMSOd_6): 1.40 (m, 2H) ; 1.70 (m, 2H) ; 2.13 (m, 2H) ; 2.43 (m, 2H) ; 2.77 (m, 2H) ; 3.43 (m, 1H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.03 (m, 2H) ; 4.19 (m, 1H) ; 4.52 (d, 1H) ; 4.87 (m, 1H) ; 7.27 (s, 1H) ; 7.39 (m, 2H) ; 7.49 (m, 1H) ; 7.99 (m, 1H) ; 8.67 (s, 1H).
N'-(2-cyano-5-((2S)-2-hydroxy-3-(4-hydroxypiperidinyl)propoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide
An analogous reaction to that described in example 378, but starting with 4-hydroxypiperidine (131 mg, 1.27 mmol) yielded title compound (200 mg, 58 %).
MS ES$^+$: 377.6 $(M+H)^+$
^{1}HNMR (DMSOd_6): 1.39 (m, 2H) ; 1.68 (m, 2H) ; 2.10 (m, 2H) ; 2.40 (m, 2H) ; 2.75 (m, 2H) ; 2.95 (s, 3H) ; 3.05 (s, 3H) ; 3.21 (s, 3H) ; 3.31 (m, 1H) ; 3.95 (m, 2H) ; 4.00 (m, 1H) ; 4.52 (m, 1H) ; 4.82 (m, 1H) ; 6.73 (s, 1H) ; 7.08 (s, 1H) ; 7.88 (s, 1H).

Example 381. Preparation of compound 558 in Table 20

An analogous reaction to that described in example 378, but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-(4-tert-butyloxycarbonylpiperazinyl)propoxy)-4-methoxtphenyl)-N,N-dimethylimidoformamide (355 mg, 0.77 mmol) yielded title compound (70 mg, 17 %).
MS ES$^+$: 602.4 $(M+H)^+$
^{1}HNMR (DMSOd_6) : 2.42 (m, 6H) ; 2.73 (d, 4H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.04 (m, 2H) ; 4.19 (m, 1H) ; 4.90 (m, 1H) ; 7.28 (s, 1H) ; 7.37 (m, 2H) ; 7.47 (m, 1H) ; 7.94 (m, 1H) ; 8.11 (s, 1H) ; 8.66 (s, 1H) .
N'-(2-cyano-5-((2S)-2-hydroxy-3-(4-tert-butyloxycarbonylpiperazinyl)propoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide.

An analogous reaction to that described in example 378, but starting with tert-butyloxycarbonylpiperazine (284 mg, 1.53 mmol) yielded title compound (444 mg, 88 %).

MS ES$^+$: 462.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.39 (s, 9H) ; 2.40 (m, 6H) ; 2.95 (s, 3H) ; 3.04 (s, 3H) ; 3.30 (m, 4H) ; 3.72 (s, 3H) ; 3.95 (m, 2H) ; 4.02 (m, 1H) ; 4.91 (d, 1H) ; 6.74 (s, 1H) ; 7.09 (s, 1H) ; 7.88 (s, 1H).

Example 382. Preparation of compound 559 in Table 20

An analogous reaction to that described in example 378 , but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-cyclopentylaminopropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide (290 mg, 0.77 mmol) yielded title compound (226 mg, 54 %).

MS ES$^+$: 601.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.32 (m, 2H) , 1.48 (m, 2H) ; 1.62 (m, 2H) ; 1.73 (m, 2H) ; 2.63 (m, 1H) ; 2.71 (m, 1H) ; 3.05 (m, 1H) ; 3.89 (s, 2H) ; 3.98 (m, 4H) ; 4.09 (m, 1H) ; 4.17 (m, 1H) ; 5.03 (m, 1H) ; 7.27 (s, 1H) ; 7.40 (m, 2H) ; 7.51 (m, 1H) ; 7.97 (m, 1H) ; 8.12 (s, 1H) ; 8.67 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-cyclopentylaminopropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide.

An analogous reaction to that described in example 378, but starting with cyclopentylamine (2.7 ml, 27 mmol) yielded title compound (1.6 g, 82 %).

MS ES$^+$: 361.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.30 (m, 2H) ; 1.48 (m, 2H) ; 1.60 (m, 2H) ; 1.72 (m, 2H) ; 2.56 (m, 1H) ; 2.67 (m, 1H) ; 2.97 (s, 3H) ; 3.01 (m, 1H) ; 3.07 (s, 3H) ; 3.75 (s, 3H) ; 3.89 (m, 1H) ; 4.00 (m, 2H) ; 5.01 (m, 1H) ; 6.75 (s, 1H) ; 7.10 (s, 1H) ; 7.91 (s, 1H).

Example 383. Preparation of compound 560 in Table 20

An analogous reaction to that described in example 378, but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-((2-hydroxy-1,1-dimethylethyl)amino)propoxy-4-methoxyphenyl)-N,N-dimethylimidoformamide (350 mg, 0.77 mmol) yielded title compound (147 mg, 34 %).

MS ES$^+$: 305.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 0.97 (s, 3H) ; 0.98 (s, 3H) ; 2.63 (m, 2H) ; 3.19 (dd, 2H) ; 3.89 (m, 3H) ; 3.98 (s, 3H) ; 4.10 (m, 1H) ; 4.18 (m, 1H) ; 4.56 (m, 1H) ; 7.29 (s, 1H) ; 7.39 (m, 2H) ; 7.50 (m, 1H) ; 7.97 (m, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-((2-hydroxy-1,1-dimethylethyl)amino)propoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide.

An analogous reaction to that described in example 378, but starting with 2-amino-2-methyl-1-propanol (1.8 ml, 18.2 mmol) yielded title compound (1.25 g, 93 %).

^{1}HNMR ($DMSOd_6$): 0.93 (s, 3H) ; 0.94 (s, 3H) ; 2.58 (m, 2H) ; 3.19 (m, 2H) ; 3.73 (s, 3H) ; 3.80 (m, 1H) ; 3.97 (m, 1H) ; 4.03 (m, 1H) ; 4.50 (m, 1H) ; 4.95 (m, 1H) ; 6.75 (s, 1H) ; 7.10 (s, 1H) ; 7.91 (s, 1H).

Example 384. Preparation of compound 561 in Table 20

An analogous reaction to that described in example 378, but starting with N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) and acetic acid (3 ml) yielded title compound (263 mg, 60 %).

MS ES$^+$: 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.37 (m, 2H) ; 1.50 (m, 4H) ; 2.41 (m, 6H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.03 (m, 2H) ; 4.18 (d, 1H) ; 4.88 (m, 1H) ; 7.28 (s, 1H) ; 7.40 (s, 1H) ; 7.40 (m, 2H) ; 7.80 (m, 1H) ; 8.11 (s, 1H) ; 8.66 (s, 1H).

N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 378, but starting with N-(3,4-difluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide (1,75 g, 3.42 mmol) yielded title compound (642 mg, 70 %).

^{1}HNMR ($DMSOd_6$): 3.62 (s, 2H) ; 6.73 (s, 1H) ; 6.74 (s, 2H) ; 7.28 (m, 1H) ; 7.37 (q, 1H) ; 7.77 (m, 1H).

N-(3,4-difluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 378, but starting with 3,4-difluoroaniline (0.97 ml, 9.75 mmol) yielded title compound (1.75 g, 46 %).

MS ES$^+$: 512.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 3.54 (s, 2H) ; 6.58 (s, 1H) ; 7.25 (m, 17H) ; 7.71 (m, 1H) ; 8.39 (s, 1H).

Example 385. Preparation of compound 562 in Table 20

An analogous reaction to that described in example 379 but starting with N-(3,4-difluorophenyl)-2-(2-a:ino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (226 mg, 53 %).

MS ES$^+$: 571.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.70 (m, 4H) ; 2.52 (m, 5H) ; 2.68 (m, 1H) ; 3.89 (s, 2H) ; 3.98 (s, 3H) ; 4.06 (m, 2H) ; 4.21 (m, 1H) ; 4.95 (m, 1H) ; 7.28 (s, 1H) ; 7.33 (m, 1H) ; 7.39 (s, 1H) ; 7.40 (m, 1H) ; 7.81 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 386. Preparation of compound 563 in Table 20

An analogous reaction to that described in example 380, but starting with N-(3,4-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (220 mg, 49 %).

MS ES$^+$: 601.5$(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H) ; 1.70 (m, 2H) ; 2.12 (m, 2H) ; 2.40 (m, 2H) ; 2.78 (m, 2H) ; 3.43 (m, 1H) ; 3.88 (s, 2H) ; 3.96 (s, 3H) ; 4.03 (m, 2H) ; 4.18 (m, 1H) ; 4.51 (d, 1H) ; 4.87 (m, 1H) ; 7.27 (s, 1H) ; 7.32 (m, 1H) ; 7.38 (s, 1H) ; 7.40 (m, 1H) ; 7.80 (m, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H).

Example 387. Preparation of compound 565 in Table 20

An analogous reaction to that described in example 382, but starting with N-(3,4-difluorophenyl)-2-(2(amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (233 mg, 53 %).

MS ES$^+$: 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.32 (m, 2H) ; 1.47 (m, 2H) ; 1.61 (m, 2H) ; 1.72 (m, 2H) ; 2.63 (m, 1H) ; 2.72 (m, 1H) ; 3.05 (m, 1H) ; 3.89 (s, 2H) ; 3.97 (m, 4H) ; 4.09 (m, 1H) ; 4.16 (m, 1H) ; 5.05 (m, 1H) ; 7.27 (s, 1H) ; 7.34 (m, 1H) ; 7.38 (s, 1H) ; 7.42 (m, 1H) ; 7.82 (m, 1H) ; 8.12 (s, 1H) ; 8.67 (s, 1H).

Example 388. Preparation of compound 566 in Table 20

An analogous reaction to that described in example 379 but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (238 mg, 56 %).

MS ES$^+$: 569.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.70 (s, 1H) ; 2.52 (m, 5H) ; 2.68 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.06 (m, 2H) ; 4.21 (m, 1H) ; 4.97 (m, 1H) ; 7.14 (d, 1H) ; 7.27 (s, 1H) ; 7.37 (m, 2H) ; 7.48 (d, 1H) ; 7.85 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 378, but starting with N-(3-chlorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide (3.62 g, 7.1 mmol) yielded title compound (1.6 g, 84 %).

^{1}HNMR ($DMSOd_6$): 3.63 (s, 2H) ; 6.74 (m, 3H) ; 7.11 (m, 1H) ; 7.33 (t, 1H) ; 7.42 (d, 1H) ; 7.79 (m, 1H).

N-(3-chlrophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 378, but starting with 3-chloroaniline (1.4 ml, 13 mmol) yielded title compound (3.62 g, 71 %).

^{1}HNMR ($DMSOd_6$): 3.55 (s, 2H) ; 6.59 (s, 1H) ; 7.21 (m, 18H) ; 7.76 (m, 1H) ; 8.39 (s, 1H).

Example 389. Preparation of compound 567 in Table 20

An analogous reaction to that described in example 380, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.75 mmol) yielded title compound (156 mg, 35 %).

MS ES$^+$: 599.4, 601.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H) ; 1.70 (m, 2H) ; 2.12 (m, 2H) ; 2.42 (m, 2H) ; 2.77 (m, 2H) ; 3.42 (m, 1H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.02 (m, 2H) ; 4.18 (m, 1H) ; 4.52 (d, 1H) ; 4.89 (m, 1H) ; 7.12 (d, 1H) ; 7.26 (s, 1H) ; 7.35 (t, 1H) ; 7.38 (s, 1H) ; 7.46 (d, 1H) ; 7.84 (m, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H).

Example 390. Preparation of compound 568 in Table 20

An analogous reaction to that described in example 382, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.75 mmol) yielded title compound (255 mg, 58 %).

MS ES$^+$: 583.5, 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.32 (m, 2H) ; 1.48 (m, 2H) ; 1.62 (m, 2H) ; 1.73 (m, 2H) ; 2.63 (m, 1H) ; 2.72 (m, 1H) ; 3.04 (m, 1H) ; 3.90 (s, 2H) ; 3.97 (m, 4H) ; 4.09 (m, 1H) ; 4.16 (m, 1H) ; 5.05 (m, 1H) ; 7.12 (d, 1H) ; 7.27 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 391. Preparation of compound 569 in Table 20

An analogous reaction to that described in example 383, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (130 mg, 30 %).

MS ES$^+$: 587.5, 589.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 0.97 (s, 6H) ; 2.63 (m, 2H) ; 3.19 (m, 2H) ; 3.90 (m, 3H) ; 3.98 (s, 3H) ; 4.10 (m, 1H) ; 4.18 (m, 1H) ; 4.55 (m, 1H) ; 5.03 (m, 1H) ; 7.13 (d, 1H) ; 7.29 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (d, 1H) ; 7.86 (m, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H).

Example 392. Preparation of compound 570 in Table 20

An analogous reaction to that described in example 381, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.75 mmol) yielded title compound (211 mg, 48 %).

MS ES$^+$: 584.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.37 (m, 6H) ; 2.70 (m, 4H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.05 (m, 2H) ; 4.19 (m, 1H) ; 4.90 (m, 1H) ; 7.12 (d, 1H) ; 7.27 (s, 1H) ; 7.35 (t, 1H) ; 7.37 (s, 1H) ; 7.47 (d, 1H) ; 7.84 (m, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H).

Example 393. Preparation of compound 571 in Table 20

An analogous reaction to that described in example 388, but starting with N'-(2-cyano-5-((2S)-2-hydroxy-3-methoxy)propoxy-4-methoxyphenyl)-N,N-dimethyl imidoformamide (252 mg, 0.82 mmol) yielded title compound (200 mg, 50 %).

MS ES^+: 530.4, 532.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 3.22 (s, 3H) ; 3.42 (m, 2H) ; 3.91 (s, 2H) ; 3.98 (s, 2H) ; 4.10 (m, 3H) ; 5.21 (d, 1H) ; 7.13 (d, 1H) ; 7.26 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (d, 1H) ; 7.85 (m, 1H) ; 8.13 (m, 1H) ; 8.69 (s, 1H).

N'-(2-cyano-5-((2S)-2-hydroxy-3-methoxy)propoxy-4-methoxy-phenyl)-N,N-dimethylimidoformamide.

N'-(2-cyano-5-(2S)-oxiranylmethoxy-4-methoxyphenyl)-N,N-dimethylimidoformamide (1 g, 3.6 mmol) in methanol (80 ml) was treated with sodium methoxide (10 g, 218 mmol) at reflux in a microwave oven for 0.5 hour. The solvent was evaporated and the mixture purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH 95/5 to give title compound (896 mg, 80 %).

^{1}HNMR ($DMSOd_6$): 2.97 (s, 1H) ; 3.07 (s, 1H) ; 3.29 (s, 1H) ; 3.38 (m, 2H) ; 3.75 (s, 3H) ; 3.98 (m, 3H) ; 5.16 (d, 1H) ; 6.75 (s, 1H) ; 7.10 (s, 1H) ; 7.93 (s, 1H).

Example 394. Preparation of compound 572 in Table 20

An analogous reaction to that described in example 378, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.75 mmol) yielded title compound (268 mg, 61 %).

MS ES^+: 583.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.38 (m, 2H) ; 1.50 (m, 4H) ; 2.43 (m, 6H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.05 (m, 2H) ; 4.21 (m, 1H) ; 4.88 (m, 1H) ; 7.14 (d, 1H) ; 7.29 (s, 1H) ; 7.37 (t, 1H) ; 7.39 (s, 1H) ; 7.48 (d, 1H) ; 7.85 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 395. Preparation of compound 573 in Table 20

An analogous reaction to that described in example 378, but starting with N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (157 mg, 36 %).

MS ES$^+$: 585.5 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.37 (m, 2H) ; 1.50 (m, 4H) ; 2.40 (m, 6H) ; 3.90 (s, 2H) ; 3.96 (s, 3H) ; 4.05 (m, 2H) ; 4.19 (m, 1H) ; 4.88 (m, 1H) ; 6.92 (m, 1H) ; 7.28 (s, 1H) ; 7.34 (m, 2H) ; 7.38 (s, 1H) ; 8.11 (s, 1H) ; 8.67 (s, 1H).

N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl) acetamide

An analogous reaction to that described in example 378, but starting with N-(3,5-difluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide (11.4 g, 28.5 mmol) yielded title compound (4.75 g, 62 %).

^{1}HNMR (DMSOd_6: 3.64 (s, 2H) ; 6.74 (s, 1H) ; 6.76 (s, 2H) ; 6.89 (m, 1H) ; 7.29 (m, 2H).

N-(3,5-difluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 378, but starting with 3,5-difluoroaniline (1.68 g, 13 mmol) yielded title compound (3.53 g, 69 %).

^{1}HNMR (DMSOd_6: 3.56 (s, 2H) ; 6.59 (s, 1H) ; 6.90 (m, 1H) ; 7.28 (m, 17H) ; 8.40 (s, 1H).

Example 396. Preparation of compound 574 in Table 20

An analogous reaction to that described in example 379 but starting with N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (200 mg, 47 %).

MS ES$^+$: 571.5 $(M+H)^+$

^{1}HNMR (DMSOd_6: 1.65 (m, 4H) ; 2.50 (m, 5H) ; 2.65 (m, 1H) ; 3.91 (s, 1H) ; 3.96 (s, 3H) ; 4.04 (m, 2H) ; 4.20 (m, 1H) ; 4.95 (m, 1H) ; 6.92 (m, 1H) ; 7.26 (s, 1H) ; 7.34 (m, 2H) ; 7.38 (s, 1H) ; 8.11 (s, 1H) ; 8.66 (s, 1H).

Example 397. Preparation of compound 575 in Table 20

An analogous reaction to that described in example 383 but starting with N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (177 mg, 40 %).

MS ES$^+$: 589.4 $(M+H)^+$

^{1}HNMR (DMSOd_6: 0.96 (s, 3H) ; 0.97 (s, 3H) ; 2.64 (m, 2H) ; 3.19 (dd, 2H) ; 3.92 (m, 3H) ; 3.98 (s, 3H) ; 4.09 (m, 1H) ; 4.20 (m, 1H) ; 4.56 (m, 1H) ; 5.05 (m, 1H) ; 6.94 (m, 1H) ; 7.29 (s, 1H) ; 7.35 (m, 2H) ; 7.39 (s, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 398. Preparation of compound 576 in Table 20

An analogous reaction to that described in example 381 but starting with N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (40 mg, 9 %).

MS ES^+ : 628.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$: 2.05 (s, 3H) ; 2.40 (m, 4H) ; 2.57 (m, 2H) ; 2.69 (m, 4H) ; 3.91 (s, 2H) ; 3.97 (s, 3H) ; 4.35 (m, 2H) ; 5.31 (m, 1H) ; 6.93 (m, 1H) ; 7.33 (s, 1H) ; 7.35 (m, 2H) ; 7.39 (s, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H).

Example 399. Preparation of compound 577 in Table 20

An analogous reaction to that described in example 381 but starting with N-(3,5-difluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.74 mmol) yielded title compound (192 mg, 44 %).

MS ES^+ : 586.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$: 2.42 (m, 6H) ; 2.74 (m, 4H) ; 3.92 (s, 2H) ; 3.98 (s, 3H) ; 4.09 (m, 2H) ; 4.20 (m, 1H) ; 4.92 (m, 1H) ; 6.93 (m, 1H) ; 7.29 (s, 1H) ; 7.35 (m, 2H) ; 7.39 (s, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

Example 400. Preparation of compound 578 in Table 20

An analogous reaction to that described in example 379 but starting with N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.8 mmol) yielded title compound (156 mg, 35 %).

MS ES^+ : 553.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$: 1.70 (m, 4H) ; 2.5 (m, 5H) ; 2.67 (m, 1H) ; 3.90 (s, 2H) ; 3.98 (s, 3H) ; 4.06 (m, 2H) ; 4.20 (m, 1H) ; 4.97 (m, 1H) ; 6.92 (m, 1H) ; 7.28 (m, 1H) ; 7.35 (m, 2H) ; 7.39 (s, 1H) ; 7.63 (m, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide

An analogous reaction to that described in example 378 but starting with N-(3-fluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide (14.6 g, 38.4 mmol) yielded title compound (6.21 g, 65 %).

^{1}HNMR ($DMSOd_6$: 3.65 (s, 2H) ; 6.76 (m, 3H) ; 6.89 (t, 1H) ; 7.35 (m, 2H) ; 7.59 (d, 1H).

N-(3-fluorophenyl)-2-(2-tritylamino-1,3-thiazole-5-yl)acetamide.

An analogous reaction to that described in example 378 but starting with 3-fluoroaniline yielded title compound (14.6 g, 79 %).

^{1}HNMR ($DMSOd_6$: 3.56 (s, 2H) ; 6.61 (s, 1H) ; 6.89 (t, 1H) ; 7.25 (m, 17H) ; 7.56 (d, 1H) ; 8.41 (s, 1H).

Example 401. Preparation of compound 579 in Table 20

An analogous reaction to that described in example 378 but starting with N-(3-fluororphenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.8 mmol) yielded title compound (214 mg, 47 %).

MS ES^+ : 567.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.38 (m, 2H) ; 1.52 (m, 4H) ; 2.42 (m, 6H) ; 3.91 (s, 2H) ; 3.98 (s, 3H) ; 4.04 (m, 2H) ; 4.20 (m, 1H) ; 4.89 (m, 1H) ; 6.91 (m, 1H) ; 7.29 (s, 1H) ; 7.37 (m, 2H) ; 7.39 (s, 1H) ; 7.63 (m, 1H) ; 8.13 (s, 1H) ; 8.68 (s, 1H).

Example 402. Preparation of compound 580 in Table 20

An analogous reaction to that described in example 381 but starting with N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.8 mmol) yielded title compound (210 mg, 46 %).

MS ES^+: 568.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$: 2.38 (m, 6H) ; 2.70 (m, 4H) ; 3.89 (s, 2H) ; 3.96 (s, 3H) ; 4.02 (m, 2H) ; 4.19 (m, 1H) ; 4.98 (m, 1H) ; 6.89 (m, 1H) ; 7.27 (s, 1H) ; 7.32 (m, 2H) ; 7.37 (s, 1H) ; 7.61 (m, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H).

Example 403. Preparation of compound 581 in Table 20

An analogous reaction to that described in example 381 but starting with N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.8 mmol) yielded title compound (35 mg, 7 %).

MS ES^+: 610.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$: 2.03 (s, 3H) ; 2.38 (m, 4H) ; 2.57 (m, 2H) ; 2.69 (m, 4H) ; 3.88 (s, 2H) ; 3.95 (s, 3H) ; 4.34 (m, 2H) ; 5.30 (m, 1H) ; 6.89 (m, 1H) ; 7.31 (s, 1H) ; 7.34 (m, 2H) ; 7.37 (s, 1H) ; 7.62 (m, 1H) ; 8.11 (s, 1H) ; 8.66 (s, 1H).

Example 404. Preparation of compound 582 in Table 20

An analogous reaction to that described in example 382 but starting with N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)acetamide (200 mg, 0.8 mmol) yielded title compound (196 mg, 43 %).

MS ES$^+$: 567.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 1.30 (m, 2H) ; 1.47 (m, 2H) ; 1.61 (m, 2H) ; 1.73 (m, 3H) ; 2.62 (m, 1H) ; 2.71 (m,1H) ; 3.0 (m, 1H) ; 3.89 (m, 1H) ; 3.97 (s, 3H) ; 4.07 (m, 1H) ; 4.13 (m, 1H) ; 5.03 (m, 1H) ; 6.90 (m, 1H) ; 7.25 (s, 1H) ; 7.35 (m, 2H) ; 7.37 (s, 1H) ; 7.62 (m, 1H) ; 8.10 (s, 1H) ; 8.66 (s, 1H).

Example 405. Preparation of compound 583 in Table 21

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6,7-dimethoxyquinazoline (173 mg, 0.5 mmol) in NMP (2 ml) was reacted with 3,5-difluoroaniline (98 mg, 0.75 mmol) in the presence of 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (285 mg, 0.75 mmol) and DIEA (130 μl, 0.75 mmol) at 50°C for 20 hours. The mixture was cooled, dimethylamine (2M MeOH, 2 ml) was added, and the resulting solution was stirred at room temperature for 15 hours, MeOH was evaporated, and water (20 ml) added to the mixture, the precipitate was recovered, washed with water, and purified by silicagel chromatography, eluant CH_2Cl_2 / MeOH 50/40/10 to give title compound (22 mg, 10 %).

^{1}HNMR ($DMSOd_6$) : 3.90 (s, 2H) ; 3.95 (s, 6H) ; 6.93 (t, 1H) ; 7.26 (s, 1H) ; 7.34 (d, 2H) ; 7.39 (s, 1H) ; 8.12 (s, 1H) ; 8.68 (s, 1H).

4-((2-amino-1,3-thiazole-5-yl)acetic acid)-6,7-dimethoxyquinazoline

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6,7-dimethoxyquinazoline (3.92 g, 10.9 mmol) in ethanol 50 ml was treated with sodium hydroxyde (2N, 27 ml, 54.5 mmol) for 45 minutes. The solvent was evaporated, the residue dissolved in CH_2Cl_2 / MeOH triethylamine (3 eq.) was added the solid removed by filtration, the filtrate was evaporated and triturated with ethanol to give title compound as a solid (1.88 g, 50 %).

^{1}HNMR ($DMSOd_6$) : 3.83 (s, 2H) ; 3.96 (s, 6H) ; 7.27 (s, 1H) ; 7.35 (s, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H).

4-(methyl(2-amino-1,3-thiazole-5-yl)acetate)-6,7-dimethoxyquinazoline

N'-(2-cyano-4,5-dimethoxyphenyl)-N,N-dimethylimidoformamide (3.5 g, 15 mmol) in acetic acid (35 ml) was reacted with methyl (2-amino-1,3-thiazole-5-yl)acetate (3.22 g, 18.7 mmol)

at reflux for 4 hours. The solvent was evaporated and the residue purified by silicagel chromatography, Eluant CH_2Cl_2 / MeOH 95/5 to give title compound (3.92 g, 73 %).
^{1}HNMR ($DMSOd_6$) : 3.69 (s, 3H) ; 3.95 (s, 2H) ; 3.96 (s, 6H) ; 7.27 (s, 1H) ; 7.38 (s, 1H) ; 8.12 (s, 1H) ; 8.69 (s, 1H).

Example 406. Preparation of compound 584 in Table 21

An analogous reaction to that described in example 405 but starting with 3-chloroaniline (80 µl, 0.75 mmol) yielded title compound (81 mg, 26 %).
MS ES$^+$: 456.4, 458.4 $(M+H)^+$
^{1}HNMR ($DMSOd_6$) : 3.91 (s, 2H) ; 3.96 (s, 6H) ; 7.14 (d, 1H) ; 7.28 (s, 1H) ; 7.37 (t, 1H) ; 7.48 (d, 1H) ; 7.85 (m, 1H) ; 8.13 (s, 1H) ; 8.69 (s, 1H).

Example 407. Preparation of compound 585 in Table 21

An analogous reaction to that described in example 405 but starting 3-chloro-4-fluoroaniline (110 mg, 0.75 mmol) yielded title compound (93.7 mg, 40 %).
MS ES$^+$: 474.4, 476.4 $(M+H)^+$
^{1}HNMR : 3.90 (s, 2H) ; 3.97 (s, 3H) ; 7.28 (s, 1H) ; 7.40 (m, 1H) ; 7.40 (s, 1H) ; 7.50 (m, 1H) ; 7.96 (m, 1H) ; 8.14 (s, 1H) ; 8.70 (s, 1H).

Example 408. Preparation of compound 586 in Table 21

An analogous reaction to that described in example 405 but starting 3,4-difluoroaniline (75 mg, 0.75 mmol) yielded title compound (130 mg, 60 %).
MS ES$^+$: 458.5 $(M+H)^+$
^{1}HNMR : 3.89 (s, 2H) ; 3.97 (s, 6H) ; 7.28 (s, 1H) ; 7.33 (m, 1H) ; 7.40 (s, 1H) ; 7.41 (m, 1H) ; 7.82 (m, 1H) ; 8.14 (s, 1H) ; 8.69 (s, 1H).

Example 409. Preparation of compound 587 in Table 22

4-((2-amino-1,3-thiazole-5-yl)(hydroxy)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (143 mg, 0.3 mmol) in DMF (4 ml) was reacted with aniline (36 mg, 0.39 mmol) 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (63 mg, 0.33 mmol), 2-hydroxypyridine N-oxyde (33 mg, 0.3 mmol) and DIEA (36 mg, 0.3 mmol) at 90°C for 1 hour. The mixture was cooled, diluted with CH_2Cl_2 (8 ml) and purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH 90/10 to 85/15. The combined fractions

containing product were evaporated, the residue was dissolved in MeOH, water was added and the precipitate recovered, dissolved in MeOH / CH_2Cl_2, dried, concentrated to give title compound (145 mg, 88 %).

MS ES$^+$: 551.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.34 (t, 2H) ; 3.55 (d, 2H) ; 3.71 (t, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.31 (t, 2H) ; 5.47 (s, 1H) ; 7.11 (t, 1H) ; 7.31 (s, 1H) ; 7.33 (t, 2H) ; 7.70 (s, 1H) ; 7.73 (d, 2H) ; 7.92 (s, 1H) ; 9.12 (s, 1H).

4-(2-amino-1,3-thiazole-5-yl)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.

N'-(2-cyano-4-methoxy-5-(3-morpholinopropoxy)phenyl)-N,N-dimethylimidoformamide (692 mg, 2 mmol) was reacted with amino-1,3-thiazole (240 mg, 2.4 mmol) in acetic acid (6.9 ml) at reflux for 4 hours. The mixture was concentrated, the residue dissolved in AcOEt, washed with aqueous sodium bicarbonate, the organic phase was dried, concentrated, the residual oil triturated in ether to give a solid (560 mg, 70 %).

MS ES$^+$: 402.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.29 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.31 (t, 2H) ; 7.32 (s, 1H) ; 7.47 (d, 1H) ; 7.75((d, 1H) ; 7.95 (s, 1H) ; 9.11 (s, 1H).

4-((2-amino-1,3-thiazole-5-yl)(hydroxy)acetic acid)-6-methoxy-7-(3-morpholinopropoxy)quinazoline.

4-(2-amino-1,3-thiazole-5-yl)-6-methoxy-7-(3-morpholinopropoxy)quinazoline (1.6 g, 4 mmol) in water (16 ml), MeOH (16 ml), was reacted with glyoxylic acid (740 mg, 8 mmol) at pH 11.5 (NaOH 6N) and 45-50°C for 6 hours. Methanol was evaporated, and the pH of the aqueous phase adjusted to 3 (HCl 6N), and the solution poured on a strong cation exchanger (isolute®) column, washed with water (120 ml), methanol (120 ml) and eluted with CH_2Cl_2/ MeOH, NH_3 (3N) 1/1 200 ml to give title compound (1.58 g, 83 %).

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H) ; 3.15 (t,2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.98 (s, 3H) ; 4.03 (d, 2H) ; 4.30 (t, 2H) ; 5.38 (s, 1H) ; 7.32 (s, 1H) ; 7.68 (s, 1H) ; 7.91 (s, 1H) ; 9.12 (s, 1H).

Example 410. Preparation of compound 588 in Table 22

An analogous reaction to that described in example 409 but starting with 3,4(difluoroaniline (34 mg, 0.26 mmol) yielded title compound (30 mg, 26 %).

amino-1,3-thiazole-5-yl)-2-hydroxyacetamide (82 mg, 0.3 mmol) in acetic acid (260 mg) at 105°C for 40 minutes. The mixture was evaporated and purified by silica gel chromatography, eluant CH_2Cl_2 / MeOH (NH_3 3N) 9/1 to give title compound (42 mg, 26 %).

MS ES$^+$: 567.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.4 (m, 2H) ; 1.51 (m, 4H) ; 1.95 (t, 2H) ; 2.40 (m, 6H) ; 3.95 (s, 3H) ; 4.19 (t, 2H) ; 5.41 (d, 1H) ; 6.78 (d, 1H) ; 6.91 'm, 1H) ; 7.25 (s, 1H) ; 7.35 (q, 1H) ; 7.50 (s, 1H) ; 7.55 (d, 1H) ; 7.71 (m, 1H) ; 8.10 (s, 1H) ; 8.68 (s, 1H).

N'-(2-cyano-4-methoxy-5-(3-piperidinylpropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide.

N'-(2-cyano-4-methoxy-5-(3-chloropropoxy)-4-methoxyphenyl)-N,N-dimethylimidoformamide (3 g, 10 mmol) in acetonitrile (50 ml) was reacted with piperidine (10 ml, 100 mmol) in presence of KI (300 mg, 1.8 mmol) and K_2CO_3 (2.1 g, 0.015 mmol) at 75°C under argon for 3 hours. The solvent was evaporated, and the residue purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH, NH_3 3N 95/5 to give title compound (3.48 g, 100 %).

MS ES$^+$: 345.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.4 (m, 2H) ; 1.50 (m, 4H) ; 1.88 (m, 2H) ; 2.35 (m, 6H) ; 2.95 (s, 3H) ; 3.05 (s, 3H) ; 3.72 (s, 3H) ; 4.05 (t, 2H) ; 6.72 (s, 1H) ; 7.07 (s, 1H) ; 7.89 (s, 1H).

N-(3-fluorophenyl)-2-(2-amino-1,3-thiazole-5-yl)-2-hydroxyacetomide.

An analogous reaction to that described in example 411, but starting with N-(3-fluorobenzyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide (2.55 g, 0.69 mmol) yielded title compound (1.37 g, 75 %).

MS ES$^+$: 268.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 5.16 (d, 1H) ; 6.45 (d, 1H) ; 6.90 (m, 4H) ; 7.34 (q, 1H) ; 7.49 (d, 1H) ; 7.70 (m, 1H).

N-(3-fluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide.

An analogous reaction to that described in example 411, but starting with N-(3-fluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl) (oxo) acetamide (2.92 g, 8 mmol) yielded title compound (2.59 g, 88 %).

^{1}HNMR ($DMSOd_6$): 1.48 (s, 9H) ; 5.34 (d, 1H) ; 6.74 (d, 1H) ; 6.90 (m, 1H) ; 7.33 (m, 2H) ; 7.54 (d, 1H) ; 7.70 (m, 1H).

N-(3-fluorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl) (oxo) acetamide.

An analogous reaction to that described in example 411, but starting with 3-fluoroaniline (1.6 g, 14.4 mmol) yielded title compound (4.06 g, 93 %).

^{1}HNMR ($DMSOd_6$): 1.54 (s, 9H) ; 7.01 (m, 1H) ; 7.42 (m, 1H) ; 7.69 (m, 1H) ; 7.80 (m, 1H) ; 8.6 (s, 1H).

Example 413. Preparation of compound 591 in Table 22

An analogous reaction to that described in example 412, but starting with N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)-2-hydroxyacetamide (99 mg, 0.35 mmol) yielded title compound (47 mg, 23 %).

MS ES^+: 583.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 1.38 (m, 2H) ; 1.51 (m, 4H) ; 1.95 (m, 2H) ; 2.38 (m, 6H) ; 3.95 (s, 3H) ; 4.19 (t, 2H) ; 5.40 (d, 1H) ; 6.79 (d, 1H) ; 7.14 (d, 1H) ; 7.24 (s, 1H) ; 7.35 (t, 1H) ; 7.50 (s, 1H) ; 7.67 (d, 1H) ; 7.95 (s, 1H) ; 8.10 (s, 1H) ; 8.68 (s, 1H).

N-(3-chlorophenyl)-2-(2-amino-1,3-thiazole-5-yl)-2-hydroxyacetamide.

An analogous reaction to that described in example 412, but starting with N-(3-chlorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide (2.13 g, 5.5 mmol) yielded title compound (1.02 g, 65 %).

^{1}HNMR ($DMSOd_6$): 5.15 (d, 1H) ; 6.45 (d, 1H) ; 6.90 (m, 3H) ; 7.12 (dd, 1H) ; 7.33 (t, 1H) ; 7.62 (d, 1H) ; 7.89 (m, 1H).

N-(3-chlorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl)-2-hydroxyacetamide.

An analogous reaction to that described in example 412, but starting with N-(3-chlorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl) (oxo) acetamide (2.5 g, 6.5 mmol) yielded title compound (2.23 g, 89 %).

^{1}HNMR ($DMSOd_6$): 1.48 (s, 9H) ; 5.34 (d, 1H) ; 6.74 (d, 1H) ; 7.14 (m, 1H) ; 7.34 (m, 2H) ; 7.65 (m, 1H) ; 7.92 (m, 1H).

N-(3-chlorophenyl)-2-(2-tert-butoxycarbonylamino-1,3-thiazole-5-yl) (oxo) acetamide.

An analogous reaction to that described in example 412, but starting with 3-chloroaniline (1.84 g, 14 mmol) yielded title compound (3.6 g, 79 %).

^{1}HNMR ($DMSOd_6$): 1.54 (s, 9H) ; 7.24 (d, 1H) ; 7.43 (t, 1H) ; 7.79 (d, 1H) ; 8.03 (s, 1H) ; 8.61 (s, 1H).

of sodium bicarbonate (2 ml) was added and the mixture stirred for 0.5 hour. A solid is recovered by filtration, washed with water, dried to give title compound (15 mg, 16 %).

MS ES^+: 521 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.31 (m, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.32 (t, 2H) ; 7.43 (m, 2H) ; 7.53 (t, 1H) ; 7.94 (d, 1H) ; 8.21 (m, 2H) ; 8.35 (t, 1H) ; 8.49 (d, 1H) ; 9.30 (s, 1H).

Example 416. Preparation of compound 594 in Table 23

An analogous reaction to that described in example 415, but starting with 4-methylaniline (19 mg, 0.18 mmol) yielded title compound (69 mg, 72 %).

MS ES^+: 535 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.34 (s, 3H) ; 2.40 (t, 2H) ; 3.11 (t, 2H) ; 3.38 (t, 2H) ; 3.60 (d, 2H) ; 3.90 (t, 2H) ; 4.03 (d, 2H) ; 4.05 (s, 3H) ; 4.35 (t, 2H) ; 7.15 (d, 2H) ; 7.27 (d, 1H) ; 7.52 (s, 1H) ; 7.62 (d, 2H) ; 7.85 (d, 1H) ; 8.15 (s, 1H) ; 8.87 (s, 1H).

Example 417. Preparation of compound 595 in Table 23

An analogous reaction to that described in example 415, but starting 2-methylaniline (19 mg, 0.18 mmol) yielded title compound (28 mg, 29 %).

MS ES^+: 535 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2/28 (s, 3H) ; 2.32 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.05 (d, 2H) ; 4.07 (s, 3H) ; 7.30 (m, 4H) ; 7.35 (d, 1H) ; 7.41 (s, 1H) ; 7.96 (d, 1H) ; 8.22 (s, 1H) ; 9.26 (s, 1H).

Example 418. Preparation of compound 596 in Table 23

An analogous reaction to that described in example 415, but starting 3-methoxyaniline (22 mg, 0.18 mmol) yielded title compound (14 mg, 14 %).

MS ES^+: 550.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 3.78 (s, 3H) ; 4.04 (d, 2H) ; 4.06 (s, 3H) ; 4.33 (t, 2H) ; 6.7 (d, 1H) ; 7.28 (s, 1H) ; 7.35 (s, 1H) ; 7.36 (d, 1H) ; 7.41 (s, 1H) ; 7.45 (s, 1H) ; 8.01 (d, 1H) ; 8.22 (s, 1H) ; 9.27 (s, 1H).

Example 419. Preparation of compound 597 in Table 23

An analogous reaction to that described in example 415, but starting 2-hydroxymethyl-aniline (22 mg, 0.18 mmol) yielded title compound (7 mg, 7 %).

MS ES$^+$: 550.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.31 (m, 2H) ; 3.18 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.06 (m, 5H) ; 4.32 (t, 2H) ; 4.65 (s, 2H) ; 7.22 (t, 1H) ; 7.32 (t, 1H) ; 7.37 (d, 1H) ; 7.40 (s, 1H) ; 7.46 (d, 1H) ; 7.72 (d, 1H) ; 7.81 (d, 1H) ; 8.22 (s, 1H) ; 9.27 (s, 1H).

Example 420. Preparation of compound 598 in Table 23

An analogous reaction to that described in example 415, but starting 3-nitroaniline (25 mg, 0.18 mmol) yielded title compound (6 mg, 6 %).

MS ES$^+$: 565.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.70 (t, 2H) ; 4.05 (d, 2H) ; 4.07 (s, 3H) ; 4.33 (t, 2H) ; 7.39 (d, 1H) ; 7.42 (s, 1H) ; 7.68 (t, 1H) ; 7.98 (d, 1H) ; 8.08 (d, 1H) ; 8.20 (m, 1H) ; 8.23 (s, 1H) ; 8.77 (s, 1H) ; 9.3 (s, 1H).

Example 421. Preparation of compound 599 in Table 23

An analogous reaction to that described in example 415, but starting 4-trifluoromethylaniline (29 mg, 0.18 mmol) yielded title compound (8 mg, 8 %).

MS ES$^+$: 588.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (m, 2H) ; 3.19 (t, 2H) ; 3.41 (t, 2H) ; 3.61 (d, 2H) ; 3.75 (t, 2H) ; 4.05 (d, 2H) ; 4.08 (s, 1H) ; 4.37 (t, 2H) ; 7.39 (d, 1H) ; 7.43 (s, 1H) ; 7.72 (d, 2H) ; 8.03 (d, 2H) ; 8.10 (d, 1H) ; 8.23 (s, 1H) ; 9.29 (s, 1H).

Example 422. Preparation of compound 600 in Table 23

An analogous reaction to that described in example 415, but starting 3-chloroaniline (23 mg, 0.18 mmol) yielded title compound (21 mg, 21 %).

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (m, 2H) ; 3.19 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 4.03 (d, 2H) ; 4.07 (s, 3H) ; 4.34 (t, 2H) ; 7.17 (d, 1H) ; 7.37 (t, 1H) ; 7.40 (m, 2H) ; 7.70 (d, 1H) ; 7.95 (m, 1H) ; 8.02 (d, 1H) ; 8.22 (s, 1H) ; 9.29 (s, 1H).

Example 423. Preparation of compound 601 in Table 23

An analogous reaction to that described in example 415, but starting 2-methoxyaniline (22 mg, 0.18 mmol) yielded title compound (32 mg, 32 %).

^{1}HNMR ($DMSOd_6$, TFA): 2.35 (t, 2H) ; 3.18 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 3.87 (s, 3H) ; 4.05 (d, 2H) ; 4.06 (s, 3H) ; 4.34 (t, 2H) ; 6.99 (t, 1H) ; 7.11 (d, 1H) ; 7.20 (s, 1H) ; 7.33 (d, 1H) ; 7.40 (s, 1H) ; 7.73 (dd, 1H) ; 7.97 (d, 1H) ; 8.22 (s, 1H) ; 9.27 (s, 1H).

Example 424. Preparation of compound 602 in Table 23

An analogous reaction to that described in example 415, but starting 3-(2-hydroxyethyl) aniline (25 mg, 0.18 mmol) yielded title compound (27 mg, 26 %).

MS ES$^+$: 564.7 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.37 (d, 3H) ; 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.62 (t, 2H) ; 4.06 (d, 2H) ; 4.08 (s, 3H) ; 4.36 (t, 2H) ; 4.76 (q, 1H) ; 7.08 (d, 1H) ; 7.29 (t, 1H) ; 7.35 (d, 1H) ; 7.42 (s, 1H) ; 7.70 (d, 1H) ; 7.76 (s, 1H) ; 8.05 (d, 1H) ; 8.23 (s, 1H) ; 9.28 (s, 1H).

Example 425. Preparation of compound 603 in Table 23

An analogous reaction to that described in example 415, but starting 3-fluoro-4-methoxyaniline (25 mg, 0.18 mmol) yielded title compound (14 mg, 14 %).

MS ES$^+$: 568.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.38 (t, 2H) ; 3.57 (d, 2H) ; 3.72 (t, 2H) ; 3.85 (s, 3H) ; 4.04 (d, 2H) ; 4.07 (s, 3H) ; 4.35 (t, 2H) ; 7.17 (t, 1H) ; 7.36 (d, 1H) ; 7.42 (s, 1H) ; 7.47 (dd, 1H) ; 7.73 (dd, 1H) ; 7.98 (d, 1H) ; 8.24 (s, 1H) ; 9.27 (s, 1H).

Example 426. Preparation of compound 604 in Table 23

An analogous reaction to that described in example 415, but starting 2-methyl-4-fluoroaniline (23 mg, 0.18 mmol) yielded title compound (27 mg, 27 %).

MS ES$^+$: 552.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.28 (s, 3H) ; 2.31 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.57 (d, 2H) ; 3.71 (t, 2H) ; 4.05 (d, 2H) ; 4.07 (s, 3H) ; 7.07 (dt, 1H) ; 7.15 (dd, 1H) ; 7.35 (d, 1H) ; 7.36 (m, 1H) ; 7.41 (s, 1H) ; 7.95 (d, 1H) ; 8.23 (s, 1H) ; 9.26 (s, 1H).

Example 427. Preparation of compound 605 in Table 23

An analogous reaction to that described in example 415, but starting 2-fluoro-5-methylaniline (23 mg, 0.18 mmol) yielded title compound (9 mg, 9 %).

MS ES^+: 552.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.33 (m, 5H) ; 3.19 (t, 2H) ; 3.38 (t, 2H) ; 3.56 (d, 2H) ; 3.71 (t, 2H) ; 4.04 (d, 2H) ; 4.07 (s, 3H) ; 4.35 (t, 2H) ; 7.09 (m, 1H) ; 7.18 (m, 1H) ; 7.35 (d, 1H) ; 7.40 (s, 1H) ; 7.41 (m, 1H) ; 8.0 (d, 1H) ; 8.23 (s, 1H) ; 9.27 (s, 1H).

Example 428. Preparation of compound 606 in Table 23

An analogous reaction to that described in example 415, but starting 3-cyanoaniline (21 mg, 0.18 mmol) yielded title compound (9 mg, 9 %).

MS ES^+: 545.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (t, 2H) ; 3.21 (t, 2H) ; 3.39 (t, 2H) ; 3.60 (d, 2H) ; 3.72 (t, 2H) ; 4.07 (d, 2H) ; 4.10 (s, 3H) ; 4.37 (t, 2H) ; 7.40 (d, 1H) ; 7.44 (s, 1H) ; 7.62 (s, 1H) ; 7.63 (m, 1H) ; 8.06 (m, 1H) ; 8.06 (d, 1H) ; 8.26 (s, 1H) ; 8.30 (s, 1H) ; 9.32 (s, 1H).

Example 429. Preparation of compound 607 in Table 23

An analogous reaction to that described in example 415, but starting isoamylamine (16 mg, 0.18 mmol) yielded title compound (15 mg, 17 %).

MS ES^+: 514.7 $(M+H)^+$

^{1}HNMR ($CDCl_3$) : 0.96 (d, 6H) ; 1.77 (m, 5H) ; 2.11 (m, 2H) ; 2.5 (m, 4H) ; 2.56 (t, 2H) ; 3.73 (m, 4H) ; 4.03 (s, 3H) ; 4.22 (t, 2H) ; 6.05 (t, 1H) ; 6.88 (d, 1H) ; 7.24 (s, 1H) ; 7.39 (d, 1H) ; 7.58 (s, 1H) ; 8.70 (s, 1H).

Example 430. Preparation of compound 608 in Table 23

An analogous reaction to that described in example 415, but starting 2-chloroaniline (23 mg, 0.18 mmol) yielded title compound (5 mg, 5 %).

MS ES^+ : 554.5, 556.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 4.04 (d, 2H) ; 4.07 (s, 3H) ; 4.34 (t, 2H) ; 7.32 (t, 1H) ; 7.36 (d, 1H) ; 7.41 (s, 1H) ; 7.41 (t, 1H) ; 7.57 (d, 1H) ; 7.63 (d, 1H) ; 8.0 (d, 1H) ; 8.23 (s, 1H) ; 9.27 (s, 1H).

Example 431. Preparation of compound 609 in Table 24

An analogous reaction to that described in example 415, but starting with 5-((6-methox-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)thiophene-3-carboxylic acid (80 mg, 0.18 mmol) and aniline (20 µl, 0.22 mmol) yielded title compound (28 mg, 30 %).

MS ES^+: 520 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.56 (d, 2H) ; 3.71 (t, 2H) ; 4.05 (d, 2H) ; 4.06 (s, 3H) ; 4.34 (t, 2H) ; 7.12 (t, 1H) ; 7.37 (t, 2H) ; 7.40 (s, 1H) ; 7.76 (d, 1H) ; 7.79 (d, 2H) ; 8.18 (s, 1H) ; 8.21 (d, 1H) ; 9.17 (s, 1H).

5-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)thiophene-3-carboxylic acid.

Ethyl-5-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino thiophene-3-carboxylate (1.05 g, 2.2 mmol) in methanol (10 ml) was treated with sodium hydroxyde (2N, 10 ml) at 75°C for 1.5 hour. Methanol was evaporated, HCl (2N) was added (pH 3) the solid filtered, redissolved in CH_2Cl_2 / MeOH 1/1, DIEA (1.5 ml, 8.8 mmol) was added the solid removed by filtration, the filtrate was concentrated, and the residue dissolved in ethanol, title material was obtained as a solid (0.7 g, 71 %).

MS ES^+: 445 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.36 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.79 (t, 2H) ; 4.03 (d, 2H) ; 4.08 (s, 3H) ; 4.35 (t, 2H) ; 7.45 (s, 1H) ; 7.81 (s, 1H) ; 8.03 (s, 1H) ; 8.50 (s, 1H) ; 9.15 (s, 1H).

Ethyl-5-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)aminothiophene-3-carboxylate.

4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (1 g, 3 mmol) in isopropanol (25 ml) and isopropanol HCl (0.5 ml) was reacted with ethyl 5-aminothiophene-3-carboxylate (0.6 g, 3.3 mmol) at 110°C for 1 hour. The mixture was cooled, diluted with EtOAc, filtered to give title compound (1.58 g, 99 %).

MS ES^+: 473 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.33 (t, 3H) ; 2.33 (t, 2H) ; 3.17 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.75 (t, 2H) ; 4.03 (d, 2H) ; 4.06 (s, 3H) ; 4.30 (q, 2H) ; 4.33 (t, 2H) ; 7.42 (s, 1H) ; 7.73 (s, 1H) ; 8.09 (s, 1H) ; 8.35 (s, 1H) ; 9.15 (s, 1H).

Example 432. Preparation of compound 610 in Table 24

An analogous reaction to that described in example 431, but starting with 4-fluoroaniline (24 mg, 0.18 mmol) yielded title compound (20 mg, 22 %).

MS ES$^+$: 538.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 3.20 (t, 2H) ; 3.40 (t, 2H) ; 3.60 (d, 2H) ; 3.72 (t, 2H) ; 4.04 (d, 2H) ; 4.07 (s, 3H) ; 4.34 (t, 2H) ; 7.9 (s, 1H) ; 7.20 (m, 2H) ; 7.41 (s, 1H) ; 7.76 (d, 1H) ; 7.82 (m, 1H) ; 8.19 (s, 1H) ; 8.21 (d, 1H) ; 9.17 (s, 1H).

Example 433. Preparation of compound 611 in Table 24

An analogous reaction to that described in example 431, but starting with 3-hydroxyaniline (24 mg, 0.18 mmol) yielded title compound (15 mg, 17 %).

MS ES$^+$: 536.6 $(M+H)^+$

Example 434. Preparation of compound 612 in Table 24

An analogous reaction to that described in example 431, but starting with 3-(methylthio)aniline (30 mg, 0.18 mmol) yielded title compound (23 mg, 24 %).

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (m, 5H) ; 4.33 (t, 2H) ; 7.24 (t, 1H) ; 7.32 (t, 1H) ; 7.41 (s, 1H) ; 7.43 (m, 2H) ; 7.72 (d, 2H) ; 8.16 (m, 2H) ; 9.17 (s, 1H).

Example 435. Preparation of compound 613 in Table 24

An analogous reaction to that described in example 431, but starting with 4-fluoro-3-chloroaniline (32 mg, 0.18 mmol) yielded title compound (21 mg, 21 %).

MS ES$^+$: 577 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H) ; 3.19 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.71 (t, 2H) ; 4.06 (m, 5H) ; 4.34 (t, 2H) ; 7.41 (m, 2H) ; 7.75 (m, 2H) ; 8.11 (m, 1H) ; 8.18 (s, 1H) ; 8.21 B(s, 1H) ; 9.18 (s, 1H).

Example 436. Preparation of compound 614 in Table 24

An analogous reaction to that described in example 431, but starting with 2,4-difluorobenzylamine (31 mg, 0.18 mmol) yielded title compound (22 mg, 22 %).

MS ES$^+$: 570.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.34 (t, 2H) ; 3.19 (t, 2H) ; 3.39 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (t, 2H) ; 4.06 (m, 5H) ; 4.34 (t, 2H) ; 4.51 (s, 2H) ; 7.06 (t, 1H) ; 7.15 (t, 1H) ; 7.40 (s, 1H) ; 7.48 (m, 1H) ; 7.69 (d, 1H) ; 8.03 (d, 1H) ; 8.17 (s, 1H) ; 9.14 (s, 1H).

Example 437. Preparation of compound 615 in Table 24

An analogous reaction to that described in example 431, but starting with 3-fluoroaniline (24 mg, 0.18 mmol) yielded title compound (27 mg, 29 %).

MS ES^+ : 538.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.33 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.58 (d, 2H) ; 3.72 (d, 2H) ; 4.04 (d, 2H) ; 4.07 (s, 3H) ; 4.35 (t, 2H) ; 6.91 (m, 1H) ; 7.42 (m, 2H) ; 7.59 (d, 1H) ; 7.78 (d, 1H) ; 7.79 (m, 1H) ; 8.19 (s, 1H) ; 8.24 (d, 1H) ; 9.18 (s, 1H).

Example 438. Preparation of compound 616 in Table 25

2-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)imidazole-5-carboxylic acid (200 mg, 0.47 mmol) in DMF (3 ml) was reacted with aniline (43 µl, 0.47 mmol) in presence of 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (178 mg, 0.47 mmol) and DIEA (120 µl, 0.7 mmol) at 40°C for 3 hours. A solution of dimethylamine in methanol (2M, 1 ml) was added and stirring was carried on for 3 hours. The solvent was evaporated, and the mixture was purified by silica gel chromatography, Eluant CH_2Cl_2 / MeOH NH_3 (sat.) 95/5 to give title compound (80 mg, 34 %).

MS ES^+ : 504.1 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.29 (t, 2H) ; 3.18 (t, 2H) ; 3.35 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.96 (s, 3H) ; 4.04 (d, 2H) ; 4.27 (t, 2H) ; 7.15 (t, 1H) ; 7.25 (s, 1H) ; 7.40 (t, 2H) ; 7.74 (d, 2H) ; 7.81 (s, 1H) ; 8.09 (s, 1H) ; 8.75 (s, 1H).

Example 439. Preparation of compound 617 in Table 25

An analogous reaction to that described in example 438, but starting with 4-fluoroaniline (60 µl, 0.58 mmol) yielded title compound (120 mg, 39 %).

MS ES+ : 522.1 (M+H)+

^{1}HNMR ($DMSOd_6$, TFA) : 2.29 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 1H) ; 3.69 (t, 2H) ; 3.96 (s, 3H) ; 4.04 (d, 2H) ; 4.27 (t, 2H) ; 7.22 (m, 3H) ; 7.74 (m, 2H) ; 7.82 (s, 1H) ; 8.07 (s, 1H) ; 8.76 (s, 1H).

Example 440. Preparation of compound 618 in Table 25

An analogous reaction to that described in example 438, but starting with allylamine 50 µl, 0.7 mmol) yielded title compound (133 mg, 40 %).

MS ES^+ : 468.1 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.28 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.94 (m, 5H) ; 4.04 (d, 2H) ; 4.26 (t, 2H) ; 5.14 (dd, 1H) ; 5.23 (dd, 1H) ; 5.88 (m, 1H) ; 7.23 (s, 1H) ; 7.77 (s, 1H) ; 7.86 (s, 1H) ; 8.71 (s, 1H).

2 -((6-methoxy-7-(3-morpholinoporpoxy)quinazolin-4-yl)amino)imidazole-5-carboxylic acid.

ethyl-2((4-imino-6-methoxy-7-(3-morpholinopropoxy)quinazolin-3-(4H)-yl)imidazole-5-carboxylate (650 mg, 1.42 mmol) in methanol (14 ml) was treated with sodium hydroxyde (2N, 14 ml) at 80°C for 1.5 hour. Methanol was evaporated, hydrochloric acid (6N) was added (pH 2.5), the precipitate was recovered by filtration, dried to give title compound (650 mg, 100 %).

^{1}HNMR ($DMSOd_6$, TFA) : 2.35 (t, 2H) ; 3.13 (t, 2H) ; 3.32 (t, 2H) ; 3.5 (d, 2H) ; 3.95 (m, 7H) ; 4.28 (t, 2H) ; 7.42 (s, 1H) ; 7.8 (s, 1H) ; 7.86 (s, 1H) ; 8.72 (s, 1H).

Example 441. Preparation of compound 619 in Table 26

4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (265 mg, 0.79 mmol) in 2-propanol (14 ml) was reacted with 4-amino-N-phenylthiophene-3-carboxamide hydrochloride (210 mg, 0.82 mmol) at 100°C for 2 hours. The solvent was evaporated and the residue purified by silica gel chromatography, eluent CH_2Cl_2 / MeOH, NH_3 sat. 95/5 to give title compound (330 mg, 81 %).

MS ES^+ : 520.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.30 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 4.03 (s, 3H) ; 4.04 (d, 2H) ; 4.32 (t, 2H) ; 7.13 (t, 1H) ; 7.35 (t, 2H) ; 7.39 (s, 1H) ; 7.69 (d, 2H) ; 7.79 (s, 1H) ; 8.13 (d, 1H) ; 8.58 (d, 1H) ; 8.95 (s, 1H).

4-(tert-butoxycarbotylamino-N-phenylthiophene-3-carboxamide

4-(tert-butoxycarbonylamino)thiophene-3-carboxylic acid obtained by a literature procedure, Tetrahedron Letters 1997, 2637, (385 mg, 1.58 mmol) in DMF (5 ml) was reacted with aniline (140 µl, 1.58 mmol) in presence of 0-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (602 mg, 1.58 mmol) at 40°C for 7 hours. The solvent was evaporated,

and the residue purified by silica gel chromatography, Eluant petroleum ether / AcOEt : 80/20 to give title compound (348 mg, 70 %).

^{1}HNMR ($CDCl_3$) : 1.50 (s, 9H) ; 7.19 (t, 1H) ; 7.39 (t, 2H) ; 7.54 (d, 2H) ; 7.69 (s, 2H) ; 7.71 (s, 1H) ; 9.45 (s, 1H).

4-amino-N-phenylthiophene-3-carboxamide

4-(tert-butoxycarbonylamino)-N-phenylthiophene-3-carboxamide (300 mg, 0.94 mmol) in CH_2Cl_2 (3 ml) was treated with TFA (0.36 ml, 4.71 mmol) at room temperature for 2.5 hours. The solvent was evaporated, the residue was dissolved in methanol / HCl, ether was added to the solution, the precipitate was recovered to give title compound (210 mg, 87 %) which was used as is in the next step.

Example 442. Preparation of compound 620 in Table 26

An analogous reaction to that described in example 441, but starting with 4-amino-N-allylthiophene-3-carboxamide (218 mg, 1.06 mmol) yielded title compound (366 mg, 75 %).

MS ES$^+$: 484.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.28 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.68 (t, 2H) ; 3.95 (d, 2H) ; 4.03 (m, 5H) ; 4.32 (t, 2H) ; 5.14 (dd, 1H) ; 5.24 (dd, 1H) ; 5.91 (m, 1H) ; 7.41 (s, 1H) ; 7.59 (s, 1H) ; 8.28 (d, 1H) ; 8.51 (d, 1H) ; 9.04 (s, 1H).

4-tert-butoxycarbonylamino)-N-allylthiophene-3-carboxamide

An analogous reaction to that described in example 319, but starting with allylamine (150 µl, 2.06 mmol) yielded title compound (385 mg, 66 %).

^{1}HNMR ($CDCl_3$) : 1.51 (s, 9H) ; 4.04 (m, 2H) ; 5.21 (dd, 1H) ; 5.29 (dd, 1H) ; 5.92 (m, 1H) ; 6.1 (m, 1H) ; 7.54 (d, 1H) ; 7.64 (m, 1H) ; 9.64 (s, 1H).

4-amino-N-allylthiophene-3-carboxamide

An analogous reaction to that described in example 441, but starting with 4-tert-butoxycarboxylamino-N-allyl-thiophene-3-carboxamide (320 mg, 1.13 mmol) yielded title compound (218 mg, 94 %) which was used as is in the next step.

Example 443. Preparation of compound 621 in Table 27

4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinzaoline (100 mg, 0.29 mmol) in isopropanol (5 ml) was reacted with methyl-4-amino-thiophene-4-carboxylate hydrochloride (63.6 mg, 0.33 mmol) at reflux for 1 hour. Ethyl acetate was added to the reaction mixture, the solid was recovered by filtration, dried, to give title compound (140 mg, 89 %).

MS ES$^+$: 459.1 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.39 (t, 2H) ; 3.19 (t, 2H) ; 3.40 (t, 2H) ; 3.58 (d, 2H) ; 3.77 (m, 5H) ; 4.06 (m, 5H) ; 4.37 (t, 2H) ; 7.42 (s, 1H) ; 7.95 (s, 1H) ; 8.01 (d, 1H) ; 8.49 (d, 1H) ; 8.93 (s, 1H).

Example 444. Preparation of compound 622 in Table 28

4-chloro-6-methoxy-7-(3-morpholinopropoxy)quinazoline (110 mg, 0.3 mmol) in 2-pentanol (5 ml) and isopropanol / HCl (55 µl) was reacted with 2-amino-5-isopropylthiophene-3-carboxamide (60 mg, 0.33 mmol) at 100°C for 1 hour, ether and ethylacetate was added to the mixture, the precipitate was filtered to give title compound (155 mg, 93 %).

MS ES$^+$: 486.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) ; 1.38 (d, 6H) ; 2.38 (t, 2H) ; 3.20 (m, 3H) ; 3.38 (t, 2H) ; 3.57 (d, 2H) ; 3.82 (t, 2H) ; 4.05 (d, 2H) ; 4.08 (s, 3H) ; 4.39 (t, 2H) ; 7.40 (s, 1H) ; 7.47 (s, 1H) ; 7.52 (s, 1H) ; 9.23 (s, 1H).

Example 445. Preparation of compound 623 in Table 28

An analogous reaction to that described in example 444 but starting with allyl-5-aminothiophene-2-carboxylate (67 mg, 0.33 mmol) at 100°C for 2 hours yielded title compound (151 mg, 85 %).

MS ES$^+$: 485.6 $(M+H)^+$

^{1}HNMR (DMSOd_6,TFA) : 2.38 (t, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.57 (d, 2H) ; 3.80 (t, 2H) ; 4.06 (d, 2H) ; 4.12 (s, 3H) ; 4.38 (t, 2H) ; 4.84 (d, 2H) ; 5.33 (d, 1H) ; 5.45 (d, 1H) ; 6.10 (m, 1H) ; 7.48 (s, 1H) ; 7.65 (d, 1H) ; 7.84 (d, 1H) ; 8.64 (s, 1H) ; 9.30 (s, 1H).

Example 446. Preparation of compound 624 in Table 28

An analogous reaction to that described in example 444 but starting with 2-aminothiophene-3-carboxamide (46 mg, 0.33 mmol) yielded title commound (154 mg, 99 %).

MS ES$^+$: 444.6 $(M+H)^+$

^{1}HNMR (DMSOd_6,TFA) : 2.34 (t, 2H) ; 3.15 (t, 2H) ; 3.36 (t, 2H) ; 3.54 (d, 2H) ; 3.76 (t, 2H) ; 4.02 (d, 2H) ; 4.05 (s, 3H) ; 4.36 (t, 2H) ; 7.32 (d, 1H) ; 7.41 (s, 1H) ; 7.48 (s, 1H) ; 7.66 (d, 1H) ; 9.23 (s, 1H).

Example 447. Preparation of compound 625 in Table 28

An analogous reaction to that described in example 444 but starting with 2-amino-5-ethylthiophene-3-carboxamide (55 mg, 0.33 mmol) yielded title compound (147 mg, 90 %).

MS ES^+ : 472.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.34 (t, 3H) ; 2.38 (t, 2H) ; 2.86 (q, 2H) ; 3.18 (t, 2H) ; 3.38 (t, 2H) ; 3.57 (d, 2H) ; 3.80 (t, 2H) ; 4.05 (d, 2H) ; 4.07 (s, 3H) ; 4.38 (t, 2H) ; 7.40 (s, 1H) ; 7.43 (s, 1H) ; 7.52 (s, 1H) ; 9.21 (s, 1H).

Example 448. Preparation of compound 626 in Table 29

Methyl-2-cyano-4-methoxy-5-(3-morpholinopropoxy)phenylimidoformate (100 mg ; 0.3 mmol) in DMF (1.5 ml) was reacted with 2-amino-4-phenyl-1,3-thiazole (58 mg ; 0.33 mmol) in presence of sodium hydride (13.2 mg ; 0.33 mmol) at 75°C for 1.5 h. Acetic acid (1.5 eq.) was added and the solvent was evaporated to give 6-methoxy-7-(3-morpholinopropoxy)-3-(4-phenyl-1,3-thiazol-2-yl)quinazolin-4(3H)-imine as an intermediate which was redissolved in DMF (1.5 ml) and ammonium acetate (95 mg ; 0.9 mmol) added. The mixture was stirred at 75°C for 1 h, the solvent was evaporated and the residue purified by silica gel chromatography, CH_2Cl_2/MeOH 95/5 → 90/10 to give title compound (44 mg, 31 %).

^{1}HNMR ($DMSOd_6$, TFA) : 2.30 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.05 (m, 5H) ; 4.33 (t, 2H) ; 7.42 (m, 2H) ; 7.51 (t, 2H) ; 7.90 (s, 1H) ; 8.00 (d, 2H) ; 8.35 (s, 1H) ; 9.27 (s, 1H).

Example 449. Preparation of compound 627 in Table 29

An analogous reaction to that described in example 448 but starting with 2-amino-4-methyl-5-acetyl-1,3-thiazole (103 mg, 0.66 mmol), heating at 75°C for 1 h in the first step, and stirring the intermediate in the above conditions at room temperature for 1 h, gave title compound (71 mg, 52 %).

MS ES^+ : 458 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.32 (t, 2H) ; 2.55 (s, 3H) ; 2.67 (s, 3H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.0 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.37 (s, 1H) ; 7.99 (s, 1H) ; 9.26 (s, 1H).

Example 450. Preparation of compound 628 in Table 29

An analogous reaction to that described in example 448 but starting with ethyl-2-amino-4-trifluoromethyl-1,3-thiazole-5-carboxylate (79 mg, 0.33 mmol) yielded title compound (81 mg, 50 %).

MS ES^+ : 542 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.34 (t, 3H) ; 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.03 (s, 3H) ; 4.04 (d, 2H) ; 4.36 (m, 4H) ; 7.47 (s, 1H) ; 8.41 (s, 1H) ; 9.34 (s, 1H).

Example 451. Preparation of compound 629 in Table 29

An analogous reaction to that described in example 448 but starting with ethyl-2-amino-4-phenyl-1,3-thiazole-5-carboxylate (82 mg, 0.33 mmol) yielded title compound (133 mg, 81 %).

MS ES^+ : 550 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.25 (t, 2H) ; 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.02 (s, 1H) ; 4.04 (d, 2H) ; 4.26 (q, 2H) ; 4.35 (t, 2H) ; 7.45 (s, 1H) ; 7.50 (m, 3H) ; 7.79 (m, 2H) ; 8.33 (s, 1H) ; 9.37 (s, 1H).

Example 452. Preparation of compound 630 in Table 29

An analogous reaction to that described in example 448 but starting with 4,5,6,7-tetrahydro-1,3-benzothiazole-2-amine (51 mg, 0.33 mmol) yielded title compound (97 mg, 71 %).

MS ES^+ : 456 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.83 (m, 4H) ; 2.29 (t, 2H) ; 2.61 (m, 2H) ; 2.67 (m, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.28 (s, 1H) ; 7.84 (s, 1H) ; 9.0 (s, 1H).

Example 453. Preparation of compound 631 in Table 29

An analogous reaction to that described in example 448 but starting with N-(4-(2-amino-1,3-thiazol-4-yl)phenyl)acetamide (77 mg, 0.33 mmol) yielded title compound (58 mg, 36 %).

MS ES^+ : 535 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.09 (s, 3H) ; 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.05 (s, 3H) ; 4.06 (d, 2H) ; 4.35 (t, 2H) ; 7.40 (s, 1H) ; 7.72 (d, 2H) ; 7.77 (s, 1H) ; 7.92 (d, 2H) ; 8.33 (s, 1H) ; 9.25 (s, 1H).

Example 454. Preparation of compound 632 in Table 29

An analogous reaction to that described in example 448 but starting with 5-phenyl-4-(trifluoromethyl)-1,3-thiazole-2-amine (81 mg, 0.33 mmol) yielded title compound (144 mg, 88 %).

MS ES$^+$: 546 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (d, 2H) ; 4.05 (s, 3H) ; 4.36 (t, 2H) ; 7.49 (s, 1H) ; 7.54 (s, 5H) ; 8.46 (s, 1H) ; 9.30 (s, 1H).

Example 455. Preparation of compound 633 in Table 29

An analogous reaction to that described in example 448 but starting with 4-(trifluoromethyl)-1,3-thiazole-2-amine (55 mg, 0.33 mmol) yielded title compound (62 mg, 44 %).

MS ES$^+$: 470 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.04 (s, 3H) ; 4.05 (d, 2H) ; 4.36 (t, 2H) ; 7.49 (s, 1H) ; 8.23 (s, 1H) ; 8.44 (s, 1H) ; 9.34 (s, 1H).

Example 456. Preparation of compound 634 in Table 29

An analogous reaction to that described in example 448 but starting with 4-tert-butyl-1,3-thiazole-2-amine (52 mg, 0.33 mmol) yielded title compound (90 mg, 65 %).

MS ES$^+$: 458 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.46 (s, 9H) ; 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (d, 2H) ; 7.38 (s, 1H) ; 7.95 (s, 1H) ; 9.18 (s, 1H).

Example 457. Preparation of compound 635 in Table 29

An analogous reaction to that described in example 448 but starting with 4,5-dimethyl-1,3-thiazole-2-amine (42 mg, 0.33 mmol) yielded title compound (61 mg, 47 %).

MS ES$^+$: 430 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.25 (s, 3H) ; 2.30 (m, 5H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.96 (s, 3H) ; 4.04 (d, 2H) ; 4.28 (t, 1H) ; 7.28 (s, 1H) ; 7.82 (s, 1H) ; 8.98 (s, 1H).

Example 458. Preparation of compound 636 in Table 29

An analogous reaction to that described in example 448 but starting with 4-methyl-1,3-thiazole-2-amine (38 mg, 0.33 mmol) yielded title compound (40 mg, 32 %).

MS ES$^+$: 415 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (t, 2H) ; 2.34 (s, 3H) ; 3.15 (t, 2H) ; 3.37 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.03 (s, 1H) ; 7.29 (s, 1H) ; 7.87 (s, 1H) ; 9.05 (s, 1H).

Example 459. Preparation of compound 637 in Table 29

1-(2-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)-4-methyl-1,3-thiazole-5-yl)ethanone (50 mg, 0.11 mmol) in ethanol (4 ml) and pyridine (1 ml) was reacted with hydroxylamine hydrochloride (19.5 mg, 0.27 mmol) at reflux for 3 h. The solvent was evaporated, water was added to the residue and a solid was recovered, washed with water to give title compound (14 mg, 27 %)

MS ES$^+$: 473 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.25 (s, 3H) ; 2.30 (t, 2H) ; 2.53 (s, 3H) ; 3.17 (t, 2H) ; 3.38 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.99 (s, 3H) ; 4.05 (d, 2H) ; 4.32 (t, 2H) ; 7.32 (s, 1H) ; 7.88 (s, 1H) ; 9.12 (s, 1H).

Example 460. Preparation of compound 638 in Table 29

2-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino)-1,3-thiazole-5-carboxylic acid (89 mg, 0.2 mmol) in DMF (1.5 ml) was treated with diphenylphosporyl azide (66 mg, 0.24 mmol) and triethylamine (26 mg, 0.26 mmol). The solution was stirred at room temperature for 1 h and at 45°C for 1 h. Tert-butanol (1 ml) was added, and the mixture heated at 90°C for 2 h. The mixture was diluted with ethylacetate, aqueous sodium bicarbonate, the organic phase was recovered, dried over $MgSO_4$, filtered, concentrated and purified by silica gel chromatography, eluent CH_2Cl_2/MeOH 95/5 to 85/15 to give title compound as a yellow solid (25 mg, 24 %).

MS ES$^+$: 517 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.50 (s, 9H) ; 2.31 (t, 2H) ; 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.13 (s, 1H) ; 7.26 (s, 1H) ; 7.94 (s, 1H) ; 9.11 (s, 1H).

Example 461. Preparation of compound 639 in Table 29

An analogous reaction to that described in example 459 but starting with O-methylhydroxylamine hydrochloride (18 mg, 0.22 mmol) and heating at reflux for 72 h yielded title compound (39 mg, 63 %).

MS ES$^+$: 487 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.26 (s, 3H) ; 2.31 (t, 2H) ; 3.53 (s, 3H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.54 (d, 2H) ; 3.76 (s, 2H) ; 3.94 (s, 3H) ; 3.99 (s, 3H) ; 4.02 (d, 2H) ; 4.33 (t, 2H) ; 7.35 (s, 1H) ; 7.89 (s, 1H) ; 9.11 (s, 1H).

Example 462. Preparation of compound 640 in Table 29

An analogous reaction to that described in example 459 but starting with O-phenylhydroxylamine hydrochloride (32 mg, 0.22 mmol) yielded title compound (8 mg, 12 %).

MS ES$^+$: 549 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.28 (t, 2H) ; 3.12 (t, 2H) ; 3.32 (t, 2H) ; 3.52 (d, 2H) ; 3.65 (t, 2H) ; 3.96 (s, 3H) ; 4.0 (d, 2H) ; 4.27 (t, 2H) ; 7.06 (t, 1H) ; 7.20 (d, 2H) ; 7.28 (s, 1H) ; 7.34 (t, 2H) ; 7.91 (s, 1H) ; 9.17 (s, 1H).

Example 463. Preparation of compound 641 in Table 29

An analogous reaction to that described in example 448 but starting with 2-amino-5-(4-methoxyphenyl)-1,3-thiazole, HBr (86 mg, 0.33 mmol) yielded title compound (105 mg, 77 %).

MS ES$^+$: 508.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.33 (t, 2H) ; 3.20 (t, 2H) ; 3.40 (t, 2H) ; 3.60 (d, 2H) ; 3.73 (t, 2H) ; 3.86 (s, 3H) ; 4.08 (s, 3H) ; 4.09 (d, 2H) ; 4.36 (t, 2H) ; 7.10 (d, 2H) ; 7.44 (s, 1H) ; 7.76 (s, 1H) ; 7.96 (d, 2H) ; 8.33 (s, 1H) ; 9.26 (s, 1H).

Example 464. Preparation of compound 642 in Table 29

An analogous reaction to that described in example 448 but starting with 2-amino-5-phenyl)-1,3-thiazole (58 mg, 0.33 mmol) yielded title compound (120 mg, 84 %).

MS ES$^+$: 478.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.01 (s, 3H) ; 4.05 (d, 2H) ; 4.32 (t, 2H) ; 7.34 (s, 1H) ; 7.41 (t, 1H) ; 7.51 (t, 2H) ; 7.72 (d, 2H) ; 7.97 (s, 1H) ; 8.24 (s, 1H) ; 9.16 (s, 1H).

Example 465. Preparation of compound 643 in Table 29

Methyl-2-cyano-4-methoxy-5-(3-morpholinopropoxy)phenyl-imidoformate (300 mg, 0.9 mmol) in DMF (4.5 ml) was reacted with 2-amino-5-ethyl-1,3-thiazole (127 mg, 0.99 mmol) in presence of sodium hydride (39.6 mg, 0.99 mmol) at 75°C for 2 h. Acetic acid (77 µl, 1.35 mmol) was added to the mixture at room temperature, followed by MeOH/Me_2NH (2M) (90 µl, 0.18 mmol) and the mixture was stirred at 75°C for 1 h. The solvent was evaporated and the mixture was purified by silica gel chromatography, eluent CH_2Cl_2/MeOH 95/5 → 90/10 to give title compound (193 mg, 50 %).

MS ES$^+$: 430.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.29 (t, 3H) ; 2.32 (t, 2H) ; 2.81 (q, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 3.98 (s, 3H) ; 4.05 (d, 2H) ; 4.30 (t, 2H) ; 7.30 (s, 1H) ; 7.50 (s, 1H) ; 7.87 (s, 1H) ; 9.04 (s, 1H).

Example 466. Preparation of compound 644 in Table 29

An analogous reaction to that described in example 465 but starting with 2-amino-5-isopropyl)-1,3-thiazole (141 mg, 0.99 mmol) yielded title compound (107 mg, 26 %).

MS ES$^+$: 444.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.33 (d, 6H) ; 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.30 (t, 2H) ; 7.29 (s, 1H) ; 7.49 (s, 1H) ; 7.87 (s, 1H) ; 9.05 (s, 1H).

Example 467. Preparation of compound 645 in Table 29

An analogous reaction to that described in example 465 but starting with 2-amino-5-benzyl)-1,3-thiazole (188 mg, 0.99 mmol) yielded title compound (370 mg, 84 %).

MS ES^+ : 492.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.31 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 3.98 (s, 3H) ; 4.04 (d, 2H) ; 4.18 (s, 2H) ; 4.29 (t, 2H) ; 7.27 (s, 1H) ; 7.28 (m, 1H) ; 7.35 (m, 4H) ; 7.61 (s, 1H) ; 7.88 (s, 1H) ; 9.02 (s, 1H).

Example 468. Preparation of compound 646 in Table 29

An analogous reaction to that described in example 465 but starting with 2-amino-5-methyl)-1,3-thiazole (113 mg, 0.99 mmol) yielded title compound (300 mg, 80 %).

MS ES^+ : 416.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.31 (t, 2H) ; 2.42 (s, 3H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.30 (s, 1H) ; 7.48 (s, 1H) ; 7.86 (s, 1H) ; 9.03 (s, 1H).

Example 469. Preparation of compound 647 in Table 29

An analogous reaction to that described in example 465 but starting with 2-amino-5-butyl)-1,3-thiazole (155 mg, 0.99 mmol) yielded title compound (385 mg, 93 %).

MS ES^+ : 458.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 0.93 (t, 3H) ; 1.36 (m, 2H) ; 1.64 (m, 2H) ; 2.29 (t, 2H) ; 2.79 (t, 2H) ; 3.16 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.97 (s, 3H) ; 4.04 (d, 2H) ; 4.29 (t, 2H) ; 7.29 (s, 1H) ; 7.51 (s, 1H) ; 7.86 (s, 1H) ; 9.03 (s, 1H).

Example 470. Preparation of compound 648 in Table 29

An analogous reaction to that described in example 465 but starting with 2-amino-5-formyl-1,3-thiazole (499.4 mg, 3.9 mmol) yielded title compound (244 mg, 39 %).

MS ES^+ : 430.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.32 (t, 2H) ; 3.17 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 4.03 (s, 3H) ; 4.06 (d, 2H) ; 4.35 (t, 2H) ; 7.45 (s, 1H) ; 8.12 (s, 1H) ; 8.71 (s, 1H) ; 9.32 (s, 1H).

Example 471. Preparation of compound 649 in Table 29

An analogous reaction to that described in example 459 but starting with 2-((6-methoxy-7-(3-morpholinopropoxy)quinazolin-4-yl)amino-1,3-thiazol-5-carbaldehyde (100 mg, 0.23 mmol) and heating at 80°C for 4 h, yielded title compound (21 mg, 20 %).

MS ES$^+$: 445.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 2.31 (t, 2H) ; 3.17 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.70 (t, 2H) ; 4.00 (s, 3H) ; 4.05 (d, 2H) ; 4.32 (t, 2H) ; 7.36 (s, 1H) ; 7.92 (s, 1H) ; 7.98 (s, 1H) ; 8.33 (s, 1H) ; 9.20 (s, 1H).

Example 472. Preparation of compound 650 in Table 30

An analogous reaction to that described in example 448, but starting with 2-amino-5-tert-butyl-1,3,4-thiadiazol (52 mg, 0.33 mmol) yielded title compound (80 mg, 58 %).

MS ES$^+$: 458 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.45 (s, 9H) ; 2.32 (t, 2H) ; 3.16 (t, 2H) ; 3.36 (t, 2H) ; 3.56 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.03 (d, 2H) ; 4.32 (t, 2H) ; 7.38 (s, 1H) ; 7.95 (s, 1H) ; 9.18 (s, 1H).

Example 473. Preparation of compound 651 in Table 30

An analogous reaction to that described in example 448, but starting with 2-amino-5-cyclopropyl-1,3,4-thiadiazol (47 mg, 0.33 mmol) yielded title compound (105 mg, 83 %).

MS ES$^+$: 443 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.08 (m, 2H) ; 1.23 (m, 3H) ; 2.32 (t, 2H); 3.15 (t, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.68 (t, 2H) ; 3.99 (s, 3H) ; 4.04 (d, 2H) ; 4.32 (t, 2H) ; 7.38 (s, 1H) ; 7.93 (s, 1H) ; 9.14 (s, 1H).

Example 474. Preparation of compound 652 in Table 30

An analogous reaction to that described in example 448, but starting with 2-amino-5-ethylthio-1,3,4-thiadiazol (53 mg, 0.33 mmol) yielded title compound (103 mg, 75 %).

MS ES$^+$: 463 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 1.41 (t, 3H) ; 2.31 (t, 2H); 3.15 (t, 2H) ; 3.31 (q, 2H) ; 3.35 (t, 2H) ; 3.55 (d, 2H) ; 3.69 (t, 2H) ; 4.00 (s, 3H) ; 4.04 (d, 2H) ; 4.33 (t, 2H) ; 7.41 (s, 1H) ; 8.08 (s, 1H) ; 9.19 (s, 1H).

Example 475. Preparation of compound 653 in Table 30

An analogous reaction to that described in example 448, but starting with 2-amino-5-phenyl-1,3,4-thiadiazol (91 mg, 0.33 mmol) yielded title compound (110 mg, 76 %).

MS ES$^+$: 479 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H); 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.69 (t, 2H) ; 4.03 (s, 3H) ; 4.05 (d, 2H) ; 4.34 (t, 2H) ; 7.42 (s, 1H) ; 7.61 (m, 3H) ; 7.99 (m, 2H) ; 8.06 (s, 1H) ; 9.25 (s, 1H).

Example 476. Preparation of compound 654 in Table 30

An analogous reaction to that described in example 448, but starting with N-phenyl-4H-1,2,4-triazole-3,5-diamine (58 mg, 0.33 mmol) yielded title compound (70 mg, 49 %).

MS ES$^+$: 477 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA) : 2.32 (t, 2H); 3.16 (t, 2H) ; 3.37 (t, 2H) ; 3.57 (d, 2H) ; 3.70 (t, 2H) ; 4.02 (s, 3H) ; 4.05 (d, 2H) ; 4.34 (t, 2H) ; 6.92 (t, 1H) ; 7.30 (t, 1H) ; 7.42 (s, 1H) ; 7.58 (d, 2H) ; 8.19 (s, 1H) ; 8.95 (s, 1H).

Biological Data

The compounds of the invention inhibit the serine/threonine kinase activity of the aurora2 kinase and thus inhibit the cell cycle and cell proliferation. These properties may be assessed, for example, using one or more of the procedures set out below:

(a) **In Vitro aurora2 kinase inhibition test**

This assay determines the ability of a test compound to inhibit serine/threonine kinase activity. DNA encoding aurora2 may be obtained by total gene synthesis or by cloning. This DNA may then be expressed in a suitable expression system to obtain polypeptide with serine/threonine kinase activity. In the case of aurora2, the coding sequence was isolated from cDNA by polymerase chain reaction (PCR) and cloned into the BamH1 and Not1 restriction endonuclease sites of the baculovirus expression vector pFastBac HTc (GibcoBRL/Life

TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES

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Remitente: ADMINISTRACIÓN ENCARGADA DEL EXAMEN PRELIMINAR INTERNACIONAL

Destinatario:

Global Intellectual Property
AstraZeneca AB
151 85 Södertälje

PCT

NOTIFICACIÓN DEL ENVÍO DEL INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
10 de octubre de 2002
(regla 71.1 PCT)

		Fecha de envío *(día/mes/año)* 08-10-2002
No. de expediente del solicitante o apoderado 100108- WO		COMUNICACIÓN IMPORTANTE
No. de Solicitud Internacional PCT/SE01/01450	Fecha de Presentación Internacional *(día/mes/año)* 21-06-2001	Fecha de Prioridad *(día/mes/año)* 28-06-2000
Solicitante AstraZeneca Aktiebolag y colaboradores		

1. Se comunica al solicitante que la administración encargada del examen preliminar internacional ha establecido el informe de examen preliminar internacional para la solicitud internacional y se lo trasmite como anexo, acompañado, en caso dado, de estos anexos.

2. Una copia del presente informe y, en caso dado, de sus anexos se hace llegar a la Oficina Internacional para su envío posterior a todas las oficinas elegidas.

3. Si cualquiera oficina elegida lo exige, la Oficina Internacional preparará una traducción del informe al inglés (con exclusión de los anexos del mismo) y la remitirá a las oficinas interesadas.

RECORDATORIO

4. Para emprender la fase nacional ante cada oficina elegida el solicitante tiene que cumplir ciertos actos (radicación de la traducción y pago de tarifas nacionales), en el plazo de 30 meses contados a partir de la fecha de prioridad (o después, en lo que concierne a ciertas oficinas) (artículo 39.1) (véase también el recordatorio enviado por la Oficina Internacional en el formulario PCT/IB/301).

Puesto que debe remitirse una traducción de la solicitud internacional a la oficina elegida, dicha solicitud tiene que incluir la traducción de todo anexo del informe del examen preliminar internacional. Es obligación del solicitante elaborar la traducción en cuestión y remitirla directamente a cada oficina elegida interesada.

Para mayores detalles en cuanto a los plazos aplicables y a los requisitos de las oficinas elegidas, véase el volumen II de la guía del solicitante del PCT.

Nombre y dirección postal de la IPEA Patent-och registreringsverket Box 5055 S-102 42 ESTOCOLMO Fax No.: 08-667 72 88 Télex: 17978 PATOREG-S:	Funcionario Autorizado Staffan Rennermalm Tel. No.: 08-782 25 00

Formulario PCT/IPEA/416 (Julio 1992)

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TRATADO DE COOPERACIÓN EN MATERIA DE PATENTES
PCT
INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(artículo 36 y regla 70 PCT)

No. de expediente del solicitante o del apoderado	PROCEDIMIENTO POSTERIOR	Véase comunicación de envío del informe de examen preliminar internacional (formulario PCT/IPEA/416)
100108-1 WO		
No. Solicitud Internacional	**Fecha de Presentación Internacional** *(día/mes/año)*	**Fecha de Prioridad** *(día/mes/año)*
PCT/SE01/01450	21.06.2001	28.06.2000
Clasificación Internacional de Patentes (CIP) o clasificación nacional y CIP		
C07D 403/12, C07D 409/12, C07D 413/15, A61K 31/505, A61P 35/00		
Solicitante		
AstraZeneca AB, y colaboradores		

1. El presente informe de examen preliminar internacional, elaborado por la administración encargada del examen preliminar internacional, se envía al solicitante de conformidad con el artículo 36.

2. Este INFORME comprende un total de ___5____ hojas, incluida la presente portada.

   ☒ Está acompañado de ANEXOS, es decir, de hojas con la descripción, reivindicaciones o dibujos, que se modificaron y que sirven de base al presente informe o de hojas que contienen rectificaciones efectuadas ante la administración encargada del examen preliminar internacional (véase regla 70.16 y la Sección 607 de las instrucciones administrativas del PCT).

   Estos anexos comprenden en total ___233__ hojas

3. Este informe contiene indicaciones con respecto a los siguientes puntos:

   - I ☒ Base del informe
   - II ☐ Prioridad
   - III ☒ Ausencia de formulación de opinión en cuanto a la novedad, actividad inventiva y la posibilidad de aplicación industrial
   - IV ☐ Ausencia de unidad de la invención
   - V ☒ Declaración motivada según el artículo 35(2) en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; citas y explicaciones en apoyo de esta declaración
   - VI ☐ Ciertos documentos citados
   - VII ☐ Irregularidades en la solicitud internacional
   - VIII ☐ Ciertas observaciones relacionadas con la solicitud internacional

Fecha de presentación de la solicitud de examen preliminar internacional	Fecha de terminación del presente informe
19.12.2001	04.10.2002
Nombre y dirección postal de la IPEA Patent-och registreringsverket Box 5055 S-102 42 ESTOCOLMO Fax No.: 08-667 72 88 Télex: 17978 PATOREG-S:	**Funcionario Autorizado** Eva Johannson/BS Tel. No.: 08-782 25 00

Formulario PCT/IPEA/409 (portada) (enero de 1998)

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INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud internacional No.
PCT/SE01/01450

I. **Base del Informe**

1. En lo concerniente a los elementos de la solicitud internacional*

☐ La solicitud internacional como se radicó originalmente

☒ La descripción:

Páginas ver Cuadro Suplementario, como se radicaron originalmente.

Páginas _____, radicadas con la petición.

Páginas ver Cuadro Suplementario, radicadas con la carta del 2002-08-21.

☒ Las reivindicaciones:

Páginas 233-243, como se radicaron originalmente.

Páginas _____, como se modificaron (junto con cualquier declaración) bajo el artículo 19.

Páginas _____, radicadas con la petición.

Páginas _____, radicadas con la carta de _____.

☐ Los dibujos:

Páginas _____, como se radicaron originalmente.

Páginas _____, radicadas con la petición.

Páginas _____, radicadas con la carta de _____.

☐ La secuencia que enumera parte de la descripción:

Páginas _____, como se radicaron originalmente.

Páginas _____, radicadas con la petición.

Páginas _____, radicadas con la carta de _____.

2. En lo concerniente al idioma, todos los elementos indicados más arriba estuvieron a disposición de la administración o le fueron enviados en el idioma en el cual se radicó la solicitud internacional, salvo indicación en contrario consignada bajo este punto.
Estos elementos estuvieron a disposición de la administración o le fueron enviados en el idioma siguiente _____que es:

☐ el idioma de una traducción enviada para efectos de la búsqueda internacional (según la regla 23.1 (b)).

☐ el idioma de publicación de la solicitud internacional (según la regla 48.3 (b)).

☐ el idioma de la traducción enviada para efectos del examen preliminar internacional (según la regla 55.2 o 55.3).

3. En lo que concierne a la secuencia de nucleótidos y/o aminoácidos divulgados en la solicitud internacional, el examen preliminar internacional se llevó a cabo sobre la base del listado de secuencias:

☐ contenido en la solicitud internacional, por escrito.

☐ radicado con la solicitud internacional, en formato de lectura por computador.

☐ remitido posteriormente a la administración, por escrito.

☐ remitido posteriormente a la administración, en formato de lectura por computador.

☐ Se ha prestado la declaración, según la cual el listado de secuencias por escrito y suministrado posteriormente no va más allá de la divulgación hecha en la solicitud tal como se radicó.

☐ Se ha prestado la declaración, según la cual las informaciones registradas en formato de lectura por computador son idénticas a las de los listados de secuencias, presentados por escrito.

4. ☐ Las modificaciones han tenido como resultado la cancelación de:

☐ La descripción, páginas _____

☐ Las reivindicaciones, Nos.: _____

☐ Los dibujos, hoja/figura _____

5. ☐ El presente informe se preparó sin tener en cuenta (algunas de) las modificaciones, que se consideraron que van más allá de la exposición de la invención tal como se radicó según se indica a continuación (regla 70.2 (c)).**

* *(Las hojas intercambiables que se enviaron a la oficina receptora en respuesta a una invitación hecha de acuerdo con el artículo 14, se consideran en el presente informe como "radicadas inicialmente" y no se adjuntan como anexo porque no contienen ningún tipo de modificaciones (reglas 70.16 y 70.17)):*

** *(Toda hoja intercambiable que incluya modificaciones de esta índole debe indicarse en el punto 1 y anexarse al presente informe).*

Formulario PCT/IPEA/409 (Cuadro I) (Enero de 1998)

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INFORME DE EXAMEN PRELIMINAR INTERNACI NAL

Solicitud Internacional No.
PCT/SE01/01450

III. Ausencia de formulación de opinión en cuanto a la novedad, actividad inventiva y la posibilidad de aplicación industrial

1. Las cuestiones sobre si la invención reivindicada parece ser novedosa, suponer una actividad inventiva (ser no obvia), o tener posibilidad de aplicación industrial no se han examinado con respecto a:

☐ Toda la solicitud internacional

☒ Reivindicaciones Nos.: 2, 4, 14 y 16

Porque:

☒ Dicha solicitud internacional, o las reivindicaciones Nos.: 2, 4, 13 y 16, se relacionan con el siguiente asunto que no requier un examen preliminar internacional *(especificar):*

Véase regla PCT 67.1. (iv).: Métodos de tratamiento del organismo humano o animal mediante cirugía o terapia, así como métodos diagnósticos

☐ La descripción, reivindicaciones o dibujos *(indicar elementos particulares más adelante)* o dichas reivindicaciones Nos.: _____ son tan oscuras que no pudo formarse una opinión significativa *(especificar):*

☐ Las reivindicaciones, o dichas reivindicaciones Nos.: _____ están tan inadecuadamente respaldadas por la descripción que no pudo formarse una opinión significativa.

☐ No se ha establecido informe de búsqueda internacional para dichas reivindicaciones Nos.: _____

2. No pudo llevarse a cabo un examen preliminar internacional debido a la falla del listado de la secuencia de nucleótidos y/o aminoácidos en cumplir el estándar contemplado en el Anexo C de las Instrucciones Administrativas:

☐ El formulario escrito no se ha suministrado o no cumple el estándar.

☐ El formato de lectura en computador no se ha suministrado o no cumple el estándar.

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No.
PCT/SE01/01450

V. Declaración motivada según el artículo 35(2) en cuanto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; citas y explicaciones en apoyo de esta declaración

1. Declaración

Novedad (N)	Reivindicaciones	1, 3, 5-12, 14-15	SÍ
	Reivindicaciones		NO
Actividad inventiva (IS)	Reivindicaciones	1, 3, 5-13, 14-15	SÍ
	Reivindicaciones		NO
Posibilidad de Aplicación Industrial (IA)	Reivindicaciones	1, 3, 5-12, 14-15	SÍ
	Reivindicaciones		NO

2. Citas y explicaciones (regla 70.7)

Documentos citados:
D1) WO 9935132 A1
D2) WO 9703069 A1
D3) WO 9515758 A1
D4 WO 9909016 A1

D1, D2 y D3 los documentos más relevantes divulgan derivados de quinazolina donde X en posición 4 es O, S, SO, S(O)2, NH o NR que pueden sustituirse con un anillo heterocíclico de 5 miembros. La sustitución de la parte aromática del sistema de anillo puede variar en la misma forma que para el compuesto reivindicado. Los compuestos conocidos pueden usarse para el tratamiento de enfermedades mediadas por actividad de proteína tirosina cinasa, por ejemplo, cáncer.

La invención reivindicada divulga el uso de derivados de quinazolina en la preparación de un medicamento para uso en la inhibición de aurora 2 cinasa, por ejemplo, cáncer. La invención también divulga nuevos derivados de quinazolina.

Los compuestos conocidos son estructuralmente cercanos a los reivindicados y se utilizan para tratar cáncer.

No hay información en los documentos citados que los compuestos conocidos puedan inhibir el efecto de aurora 2 cinasa. En consecuencia, la actividad en los documentos citados y en esta solicitud son diferentes.

Por lo tanto, las reivindicaciones 1, 3, 5-12, 14 y 15 se consideran que satisfacen el requerimiento de novedad, actividad inventiva y posibilidad de aplicación industrial.

D4) divulga el estado general del arte y no se considera que sea de relevancia particular.

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud internacional No.
PCT/SE01/01450

Cuadro Suplementario
(A emplearse cuando el espacio en cualquiera de los cuadros precedentes no es suficiente)

Continuación de: I Base del informe

Páginas originales 1-17, 21, 24, 26-39, 57-65, 67-82, 85-90, 93, 97-99, 101, 103-105, 107-119, 131-132, 140, 149, 189, 204-205, 208 y 228-232

Páginas radicadas con la carta 2002-08-21
18-20, 22-23, 25, 40-56, 66, 83-84, 91-92, 94-96, 100, 102, 106, 120-129, 130, 133-139, 141-148, 150-188, 190-203, 206-207 y 209-227.

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DERIVADOS DE QUINAZOLINA SUSTITUIDOS Y SU USO COMO INHIBIDORES

La presente invención se refiere a ciertos derivados de quinazolina para uso en el tratamiento de ciertas enfermedades, en particular enfermedad proliferativa tal como cáncer, y en la preparación de medicamentos para empleo en el tratamiento de enfermedad proliferativa; a compuestos novedosos de quinazolina y a un proceso para su preparación, así como a composiciones farmacéuticas que las contienen como ingrediente activo.

El cáncer (y otra enfermedad hiperproliferativa) se caracteriza por proliferación celular incontrolada. Esta pérdida de la regulación normal de la proliferación de las células parece ocurrir con frecuencia como el resultado de lesión genética a series de vías celulares que controlan el progreso a través del ciclo celular.

En eucariotas, el ciclo celular se controla ampliamente por una cascada ordenada de fosforilación de proteínas. Actualmente se han identificado varias familias de proteína cinasas que juegan papeles críticos en esta cascada. La actividad de muchas de estas cinasas se aumenta en los tumores humanos cuando se comparan con tejido normal. Esto ocurre o bien por niveles crecientes de expresión de la proteína (como resultado de amplificación génica, por ejemplo), o bien por cambios en la expresión de co-activadores o proteínas inhibitorias.

Los primeros de estos reguladores de ciclo celular identificados primeramente y muy ampliamente estudiados han sido las cinasas dependientes de ciclina (o CDKs). La actividad de CDKs específicas en momentos específicos es esencial tanto para la iniciación como para el progreso coordinado a través del ciclo celular. Por ejemplo, la proteína CDK4 parece controlar la entrada en el ciclo celular (la transición G0-G1-S) fosforilando el producto génico de retinoblastoma pRb. Esto estimula la liberación del factor de transcripción E2F de pRb, el cual actúa luego para aumentar la transcripción de genes necesarios para la entrada en la fase S.

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La actividad catalítica CDK4 se estimula ligando ciclina D a una proteína compañera. Una de las primeras demostraciones de un vínculo directo entre el cáncer y el ciclo celular se hizo con la observación que el gen de la ciclina D1 se amplificaba y aumentaban los niveles de proteína de la ciclina D (y por consiguiente, se incrementaba la actividad de la CDK4) en muchos tumores humanos (Revisado en Sherr, 1996, Science 274: 1672-1677; Pines, 1995, Seminars in Cancer Biology 6: 63-72). Otros estudios (Loda y colaboradores, 1997, Nature Medicine 3(2): 231-234; Gemma y colaboradores, 1996, International Journal of Cancer 68(5): 605-11; Elledge y colaboradores, 1996, Trends in Cell Biology 6; 388-392) han demostrado que reguladores negativos de la función CDK se regulan con frecuencia en forma descendente o se eliminan en tumores humanos, conduciendo nuevamente a una activación inapropiada de estas cinasas.

Más recientemente, se han identificado proteína cinasas que son estructuralmente distintas de la familia CDK, las cuales juegan papeles críticos en regular el ciclo celular y que, además, parecen ser importantes en la oncogénesis. Éstas incluyen los homólogos humanos recientemente idenficados de las proteínas de la *Drosophila* aurora y *S. cerevisiae* Ipll. *Drosophila* aurora y *S. cerevisiae* Ipll, las cuales son altamente homólogas a nivel de la secuencia de aminoácidos, codifican proteína cinasas de serina/treonina. Las dos, aurora e Ipll, son conocidas por estar implicadas en controlar la transición de la fase G2 del ciclo celular a través de la mitosis, función centrosoma, formación de un huso mitótico y separación/segregación apropiada del cromosoma en células hijas. Los dos homólogos humanos de estos genes, denominados aurora1 y aurora2, codifican proteína cinasas reguladas por el ciclo celular. Éstas muestran un pico de expresión y actividad cinasa en la frontera G2/M (aurora2) y en la mitosis misma (aurora1). Varias observaciones implican la participación de proteínas aurora humanas y, particularmente, aurora2 en el cáncer. El gen de aurora2 se asocia al cromosoma 20q13, una región que se amplifica frecuentemente en tumores humanos incluyendo tumores tanto de mama como de colon. Aurora2 puede ser el principal gen blanco de esta

amplificación, puesto que el ADN de aurora2 se amplifica y el mARN de aurora2 se sobre-expresa en más del 50% de los cánceres colo-rectales humanos primarios. En estos tumores los niveles de proteína aurora2 aparecen enormemente elevados comparados con tejido normal adyacente. Adicionalmente, la transfección de fibroplastos de roedor con aurora2 humano conduce a la transformación, confiriendo la capacidad de crecer en agar suave y forma tumores en ratones desnudos (Bischoff y colaboradores, 1998, The EMBO Journal, 17(11): 3052-3065). Otro trabajo (Zhou y colaboradores, 1998, Nature Genetics, 20(2): 189-93) ha demostrado que la sobre-expresión artificial de aurora2 lleva a un aumento en el número de centrosomas y a un incremento en aneuploidia.

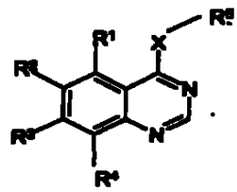
En forma importante, también se ha demostrado que la abrogación de la expresión de aurora2 y la función mediante tratamiento con oligonucleótido antisentido de líneas celulares de tumores humanos (WO 97/22702 y WO 99/37788) lleva a una detención del ciclo celular en la fase G2 del ciclo celular y ejerce un efecto antiproliferativo en estas líneas celulares de tumores. Esto indica que la inhibición de la función de aurora2 tendrá un efecto antiproliferativo que puede ser útil en el tratamiento de tumores humanos y otras enfermedades hiperproliferativas.

Hasta ahora se han propuesto un número de derivados de quinazolina para uso en la inhibición de varias cinasas. Ejemplos de dichas propuestas se incluyen en WO 92/20642 y EP-B-584222 que se relacionan con compuestos bicíclicos que inhiben la cinasa tirosina receptor del factor de crecimiento epidérmico (EGF) y factor de crecimiento derivado de plaquetas (PDGF), WO 95/15758 que describe el uso de sistemas de anillo bis para la inhibición selectiva de actividad de tirosina cinasa CSF-1R, y WO 99/09016, WO 97/03069 y US 570158 que describen el uso de ciertos compuestos de quinazolina como inhibidores de tirosina cinasa en otros contextos.

Los solicitantes han encontrado una serie de compuestos que inhiben el efecto de la aurora2 cinasa y que, por lo tanto, son útiles en el tratamiento de enfermedad proliferativa tal como cáncer, en particular, en aquellas

enfermedades tales como cáncer colo-rectal o de mama, en donde se sabe que es activa la aurora2 cinasa.

La presente invención contempla el uso de un compuesto de fórmula (I)



(I)

o una sal,.éster o amida de la misma;

en donde X es O, o S, S(O), o $S(O)_2$, o NR^6 en donde R^6 es hidrógeno o C_{1-6}alquilo;

R^5 es un anillo heteroaromático de 5 miembros opcionalmente sustituido,

R^1, R^2, R^3, R^4 se seleccionan independientemente de, halo, ciano, nitro, trifluorometilo, C_{1-3}alquilo, $-NR^7R^8$ (en donde R^7 y R^8, que pueden ser los mismos o diferentes, representa cada uno hidrógeno o C_{1-3}alquilo), o $-X^1R^9$ (en donde X^1 representa un enlace directo, -O-,$-CH_2$, -OCO-, carbonilo, -S-, -SO-, $-SO_2$-, $-NR^{10}CO$-, $-CONR^{11}$-, $-SO_2NR^{12}$-, $-NR^{13}SO_2$- o $-NR^{14}$- (en donde R^{10}, R^{11}, R^{12}, R^{13} y R^{14}, cada uno independientemente, representa hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxiC_{2-3}alquilo), y R^9 se selecciona de uno de los siguientes grupos:

1) hidrógeno o C_{1-5}alquilo que pueden ser no sustituidos o que pueden ser sustituidos con uno o más grupos seleccionados de hidroxi, fluoro o amino,

2) C_{1-5}alquilX^2COR^{15} (en donde X^2 representa -O-, o $-NR^{16}$- (en el cual R^{15} representa hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxiC_{2-3}alquilo) y R^{16} representa C_{1-3}alquilo, $-NR^{17}R^{18}$ o $-OR^{19}$ (en donde R^{17}, R^{18} y R^{19}, que pueden ser los mismos o diferentes, representan cada uno hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxi C_{2-3}alquilo));

3) C_{1-5}alquilX^3R^{20} (en donde X^3 representa -O-, -S-, -SO-, $-SO_2$-, -OCO-, $-NR^{21}CO$-, $-CONR^{22}$, $-SO_2NR^{23}$-, $-NR^{24}SO_2$- o $-NR^{25}$- (en donde R^{21}, R^{22},

R^{23}, R^{24} y R^{25}, cada uno independientemente, representa hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxiC_{2-3}alquilo) y R^{20} representa hidrógeno, C_{1-3}alquilo, ciclopentilo, ciclohexilo o un grupo heterocíclico saturado de 5-6 miembros con 1-2 heteroátomos, seleccionados independientemente de O, S, y N, el cual grupo C_{1-3}alquilo puede llevar 1 ó 2 sustituyentes seleccionados de oxo, hidroxi, halógeno y C_{1-4}alcoxi y el cual grupo cíclico puede llevar 1 ó 2 sustituyentes seleccionados de oxo, hidroxi, halógeno, C_{1-4}alquilo, C_{1-4}hidroxialquilo y C_{1-4}alcoxi;

4) C_{1-5}alquilX^4C_{1-5}alquilX^5R^{26} (en donde X^4 y X^5 que pueden ser los mismos o diferentes son cada uno -O-, -S-, -SO-, -SO_2-, -NR^{27}CO-, -$CONR^{28}$-, -SO_2NR^{29}, -$NR^{30}SO_2$-, ó –NR^{31} (en donde R^{27}, R^{28}, R^{29}, R^{30} y R^{31}, cada uno independientemente, representa hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxiC_{2-3}alquilo) y R^{26} representa hidrógeno o C_{1-3}alquilo);

5) R^{32} (en donde R^{32} es un grupo heterocíclico saturado de 5-6 miembros (enlazado mediante carbono o nitrógeno) con 1-2 heteroátomos, seleccionados independientemente de O, S y N, el cual grupo hetrocíclico puede llevar 1 o 2 sustituyentes seleccionados de oxo, hidroxi, halógeno, C_{1-4}alquilo, C_{1-4}hidroxialquilo, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo y C_{1-4}alquilsulfonilC_{1-4}alquilo);

6) C_{1-5}alquilR^{32} (en donde R^{32} es como se define más arriba);

7) C_{2-5}alquenilR^{32} (en donde R^{32} es como se define más arriba);

8) C_{2-5}alquinilR^{32} (en donde R^{32} es como se define más arriba);

9) R^{33} (en donde R^{33} representa un grupo piridona, un grupo fenilo o un grupo heterocíclico aromático de 5-6 miembros (enlazado mediante carbono o nitrógeno) con 1-3 heteroátomos seleccionados de O, N y S, el cual grupo piridona, fenilo o grupo heterocíclico aromático puede llevar hasta 5 sustituyentes en un átomo de carbono disponible; seleccionado de hidroxi, halógeno, amino, C_{1-4}alquilo, C_{1-4}hidroxialquilo, C_{1-4}aminoalquilo, C_{1-4}alquilamino, C_{1-4}hidroxialcoxi, carboxi, trifluorometilo, ciano, -$CONR^{34}R^{35}$ y –$NR^{36}COR^{37}$ (en donde R^{34}, R^{35}, R^{36} y R^{37}, los cuales pueden ser los mismos o diferentes, representa cada uno hidrógeno, C_{1-4}alquilo o C_{1-3}alcoxiC_{2-3}alquilo));

10) C_{1-5}alquilR^{33}, (en donde R^{33} es como se define más arriba);

11) C_{2-5}alquenilR^{33}, (en donde R^{33} es como se define más arriba);

12) C_{2-5}alquinilR^{33}, (en donde R^{33} es como se define más arriba);

13) C_{1-5}alquilX^6R^{33} (en donde X^6 representa -O-, -S-, -SO-, $-SO_2-$, $-NR^{38}CO-$, $-CONR^{39}-$, $-SO_2NR^{40}$, $-NR^{41}SO_2-$, ó $-NR^{42}$ (en donde R^{38}, R^{39}, R^{40}, R^{41} y R^{42}, cada uno independientemente, representa hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxiC_{2-3}alquilo) y R^{33} es como se define más arriba);

14) C_{2-5}alquenilX^7R^{33} (en donde X^7 representa -O-, -S-, -SO-, $-SO_2-$, $-NR^{43}CO-$, $-CONR^{44}-$, $-SO_2NR^{45}$, $-NR^{46}SO_2-$, ó $-NR^{47}$ (en donde R^{43}, R^{44}, R^{45}, R^{46} y R^{47}, cada uno independientemente, representa hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxiC_{2-3}alquilo) y R^{33} es como se define más arriba);

15) C_{2-5}alquinilX^8R^{33} (en donde X^8 representa -O-, -S-, -SO-, $-SO_2-$, $-NR^{48}CO-$, $-CONR^{49}-$, $-SO_2NR^{50}$, $-NR^{51}SO_2-$, ó $-NR^{52}$ (en donde R^{48}, R^{49}, R^{50}, R^{51} y R^{52}, cada uno independientemente, representa hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxiC_{2-3}alquilo) y R^{33} es como se define más arriba);

16) C_{1-3}alquilX^9C_{1-3}alquilR^{33} (en donde X^9 representa -O-, -S-, -SO-, $-SO_2-$, $-NR^{53}CO-$, $-CONR^{54}-$, $-SO_2NR^{55}$, $-NR^{56}SO_2-$, ó $-NR^{57}$ (en donde R^{53}, R^{54}, R^{55}, R^{56} y R^{57}, cada uno independientemente, representa hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxiC_{2-3}alquilo) y R^{33} es como se define más arriba);

17) C_{1-3}alquilX^9C_{1-3}alquilR^{32} (en donde X^9 y R^{28} son como se define más arriba);

en la preparación de un medicamento para uso en la inhibición de aurora2 cinasa. En particular, dichos medicamentos son útiles en el tratamiento de enfermedad proliferativa tal como cáncer y, en particular, cánceres en donde aurora2 es regulada ascendentemente, tales como cánceres del colon o mama.

En esta especificación el término "alquilo", cuando usa solo o como sufijo, incluye estructuras ramificadas, de cadena recta. A menos que se exprese lo contrario, estos grupos pueden contener hasta 10, preferiblemente hasta 6 y, más preferiblemente, hasta 4 átomos de carbono. Análogamente, los términos "alquenilo" y "alquinilo" se refieren a estructuras insaturadas rectas o ramificadas que contienen por ejemplo

desde 2 hasta 10, preferiblemente desde 2 hasta 6 átomos de carbono. Mitades cíclicas tales como cicloalquilo, cicloalquenilo y cicloalquinilo son similares en naturaleza pero tienen por lo menos 3 átomos de carbono. Términos tales como "alcoxi" comprenden grupos alquilo como se entiende en el arte.

El término "halo" incluye fluoro, cloro, bromo y yodo. Referencias a grupos arilo incluyen grupos carboxílicos aromáticos tales como fenilo y naftilo. El término "heterociclilo" incluye anillos aromáticos o no aromáticos, que contienen por ejemplo desde 4 hasta 20, convenientemente desde 5 hasta 8 átomos de anillo, por lo menos uno de los cuales es un heteroátomo tal como oxígeno, azufre o nitrógeno. Ejemplos de dichos grupos incluyen furilo, tienilo, pirroilo, pirrolidinilo, imidazolilo, triazolilo, tiazolilo, tetrazolilo, oxazolilo, isoxazolilo, pirazolilo, piridilo, pirimidinilo, pirazinilo, piridazinilo, triazinilo, quinolinilo, isoquinolinilo, quinoxalinilo, benzotiazolilo, benzoxazolilo, benzotienilo o benzofurilo.

"Heteroarilo" se refiere a aquellos grupos descritos arriba que tienen un carácter aromático.

El término "aralquilo" se refiere a grupos alquilo arilo sustituidos tales como bencilo.

Otras expresiones usadas en la especificación incluyen "hidrocarbilo" el cual se refiere a cualquier estructura que comprenda átomos de carbono e hidrógeno. Por ejemplo, éstos pueden ser alquilo, alquenilo, alquinilo, arilo, heterociclilo, alcoxi, aralquilo, cicloalquilo, cicloalquenilo o cicloalquinilo.

El término "grupo funcional" se refiere a sustituyentes reactivos tales como nitro, ciano, halo, oxo, $=CR^{78}R^{79}$, $C(O)_xR^{77}$, OR^{77}, $S(O)_yR^{77}$, $NR^{78}R^{79}$, $C(O)NR^{78}R^{79}$, $=NOR^{77}$, $-NR^{77}C(O)_xR^{78}$, $-NR^{77}CONR^{78}R^{79}$, $-N=CR^{78}R^{79}$, $S(O)_yNR^{78}R^{79}$ ó $-NR^{77}(O)_yR^{78}$ en donde R^{77}, R^{78} y R^{79} se seleccionan independientemente de hidrógeno o hidrocarbilo opcionalmente sustituido, o R^{78} y R^{79} juntos forman un anillo opcionalmente sustituido el cual, opcionalmente, contiene más heteroátomos tales como $S(O)_y$ oxígeno y nitrógeno, x es un entero de 1 ó 2, y es 0 o un entero de 1-3.

Sustituyentes opcionales apropiados para grupos hidrocarbilo R^{77}, R^{78} y R^{79} incluyen halo, perhaloalquilo tal como trifluorometilo, mercapto, hidroxi, carboxi, alcoxi, arilo, heteroarilo, heteroariloxi, alqueniloxi, alquiniloxi, alcoxialcoxi, ariloxi (en donde el grupo arilo puede sustituirse por halo, nitro, o hidroxi), ciano, nitro, amino, mono- o dialquil amino, oximino o $S(O)_y$ donde y es como se definió arriba.

Preferiblemente R^1 es hidrógeno o un grupo expuesto para R^2 ó R^3 más adelante. Frecuentemente, R^1 es hidrógeno.

En una incorporación preferida, por lo menos un grupo R^1, R^2, o R^3, preferiblemente R^3, comprende una cadena de por lo menos 3 y, preferiblemente, por lo menos 4 átomos de carbono opcionalmente sustituidos o heteroátomos tales como oxígeno, nitrógeno o azufre. Muy preferiblemente, la cadena se sustituye por un grupo polar que contribuye a la solubilidad.

Convenientemente R^3 es un grupo X^1R^9. Preferiblemente en este caso, X^1 es oxígeno y R^9 se selecciona de un grupo de fórmula (1) o (10) más arriba. Grupos particulares R^9 son aquellos en el grupo (1) más arriba, especialmente alquilo tal como metilo o alquilo halo sustituido, o aquellos en el grupo (10) más arriba. En una incorporación preferida, por lo menos uno de R^2 o R^3 es un grupo $-OC_{1-5}alquilR^{33}$ y R^{33} es un anillo hetrocíclico tal como un anillo de morfolina enlazado a N tal como 3-morfolinopropoxi.

Convenientemente R^2 se selecciona de halo, ciano, nitro, trifluorometilo, C_{1-3}alquilo, $-NR^9R^{10}$ (en donde R^9 y R^{10}, los cuales pueden ser los mismos o diferentes, representa cada uno hidrógeno o C_{1-3}alquilo), o un grupo $-X^1R^{11}$. Ejemplos preferidos de $-X^1R^{11}$ para R^2 incluyen aquellos enumerados más arriba en relación con R^3.

Otros ejemplos para R^2 y R^3 incluyen metoxi o 3,3,3-trifluoroetoxi.

Preferiblemente X es NH ó O y, muy preferiblemente, es NH.

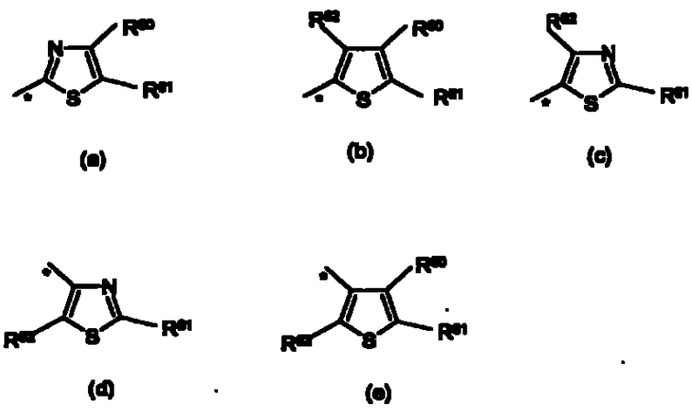
Ejemplos de anillos aromáticos de 5 miembros R^5 incluyen anillos que contienen uno o más heteroátomos seleccionados de azufre, oxígeno y nitrógeno. Dichos anillos incluyen pirrol, pirazol, pirazolona, imidazol, oxazol, furano, tetrazol, triazol, tiazol, tiofeno, o tiadiazol, cualquiera de los

cuales puede ser opcionalmente sustituido. En particular, R^5 incluye por lo menos un nitrógeno o heteroátomos de azufre. Anillos preferidos para R^5 incluyen pirrol, pirazol, imidazol, triazol, tiazol, tiofeno, o tiadiazol.

En una incorporación particular, R^5 es un anillo que contiene azufre. Convenientemente R^5 es tiazol opcionalmente sustituido, tiofeno opcionalmente sustituido o tiadiazol opcionalmente sustituido y, preferiblemente, tiazol opcionalmente sustituido o tiofeno opcionalmente sustituido.

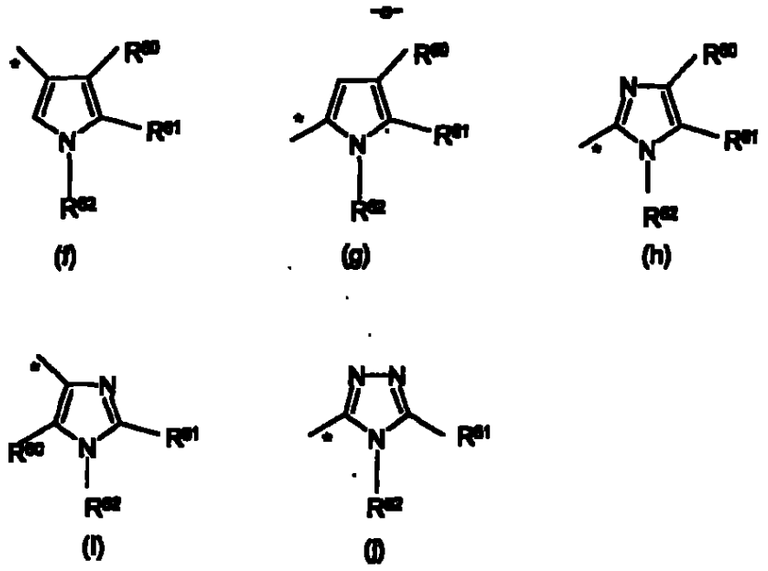
Más preferiblemente, R^5 es un grupo tiazol sustituido o tiofeno sustituido.

En particular, R^5 es un grupo de fórmula (a), (b), (c) o (d) y, preferiblemente, (a) o (b):



en donde R^{60}, R^{61} y R^{62} se seleccionan independientemente de hidrógeno o un grupo sustituyente y * indica el punto de unión al grupo X en fórmula (I). En particular, uno de R^{60}, R^{61} y R^{62} es un grupo sustituyente y los demás son o bien hidrógeno o bien un sustituyente pequeño tal como C_{1-3}alquilo, por ejemplo, metilo. Convenientemente R^{62} es hidrógeno. Preferiblemente R^{61} es distinto de hidrógeno.

Alternativamente, R^5 es un anillo que contiene nitrógeno opcionalmente sustituido tal como un grupo de fórmula (f), (g), (h), (i) o (j):

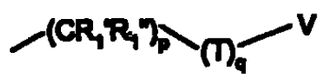


(f) (g) (h)

(l) (j)

Sustituyentes apropiados para grupos R^5 incluyen hidrocarbilo opcionalmente sustituido, heterociclilo opcionalmente sustituido o un grupo funcional como se define más arriba.

En particular, R^{60}, R^{61}, o R^{62} es un grupo de la sub-fórmula (k)



(k)

en donde p y q son independientemente 0 ó 1 y en donde R_1' y R_1'' son independientemente hidrógeno, hidroxi, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, halógeno, ciano, alquinilo opcionalmente sustituido, alquienilo opcionalmente sustituido. El alquilo o alquinilo opcionalmente sustituidos pueden sustituirse con halo, nitro, ciano, hidroxi, trifluorometilo, amino, carboxi, carbamoilo, mercapto, sulfamoilo, C_{1-4}alquilo, C_{2-4}alquenilo, C_{2-4}alquinilo, C_{3-6}cicloalquilo, C_{3-6}cicloalquenilo, C_{1-4}alcoxi, C_{1-4}alcanoilo, C_{1-4}alcanoiloxi, N-(C_{1-4}aquilo), N-(C_{1-4}alquilo)$_2$, C_{1-4}alcanoilamino, (C_{1-4}alcanoil)$_2$amino, N-(C_{1-4}alquil)carbamoilo, N,N-(C_{1-4})carbamoilo, (C_{1-4})S, C_{1-4}S(O), (C_{1-4}

$_4$alquil)S(O)$_2$, (C_{1-4})alcoxicarbonilo, N-(C_{1-4}alquil)sulfamoilo, N,N-C_{1-4}alquil)sulfamoilo, C_{1-4}alquilsulfonilamino, o heterociclilo. R es preferiblemente C_{1-4}alquilo, C_{2-4}alquenilo, o C_{2-4}aquinilo, y R_1' puede formar con R_1" un anillo de 3 a 6 miembros.

T es C=O, SO_n, C(=NOR)CO, C(O)C(O), C=NCN, CV=NO o donde n = 0, 1 ó 2 y V es independientemente R^{63} o $N(R^{63})R^{64}$ en donde R^{63} y R^{64} se seleccionan independientemente de hidrógeno, hidrocarbilo opcionalmente sustituido o heterociclilo opcionalmente sustituido, o R^{63} y R^{64}, junto con el átomo al cual están unidos, forman un anillo heterocíclico opcionalmente sustituido.

Ejemplos de grupos para R^{63} y R^{64} incluyen el grupo $-(CH_2)_qR^{70}$ en donde q y R^{70} son como se define más adelante en relación con fórmula (II). Convenientemente uno de R^{63} o R^{64} es hidrógeno, o metilo, etilo o propilo opcionalmente sustituido con hidroxi y, preferiblemente, uno de R^{63} o R^{64} es hidrógeno. En este caso, el otro es convenientemente un sustituyente mayor, por ejemplo, de por lo menos 4 carbonos o heteroátomos, y es hidrocarbilo opcionalmente sustituido o heterociclilo opcionalmente sustituido. Grupos particulares hidrocarbilo opcionalmente sustituido para R^{63} o R^{64} incluyen alquilo, cicloalquilo, alquenilo, o arilo, cualquiera de los cuales es opcionalmente sustituido con un grupo funcional como se definió más arriba o, en el caso de grupos arilo, con un grupo alquilo y, en el caso de un grupo alquilo, con un grupo arilo o heterocíclico cualquiera de los cuales pueden ser ellos mismos opcionalmente sustituidos con un alquilo o un grupo funcional. Ejemplos de grupos arilo opcionalmente sustituidos R^{63} o R^{64} incluyen fenilo opcionalmente sustituido con uno o más grupos seleccionados del grupo C_{1-6}alquilo tal como metilo o etilo (cualquiera de los cuales puede ser opcionalmente sustituido con un grupo funcional tal como hidroxi), o un grupo funcional como se definió más arriba (tal como halo similar a floro, cloro o bromo, hidroxi, alcoxi tal como metoxi, trifluorometilo, nitro, ciano, trifluorometoxi, $CONH_2$, $C(O)CH_3$, amino, o dimetilamino).

Cuando R^{63} o R^{64} es un grupo alquilo opcionalmente sustituido, es

convenientemente un grupo C_{1-6}alquilo, sustituido opcionalmente con uno o más grupos funcionales (tales como ciano, hidroxi, alcoxi, en particular metoxi, COOalquilo tal como $COOCH_3$), o arilo opcionalmente sustituido con un grupo funcional como se definió más arriba (en particular en relación con R^{63} o R^{64} mismos, o un grupo heterocíclico opcionalmente sustituido tal como un N-metil pirrol.

Cuando R^{63} y R^{64} es cicloalquilo opcionalmente sustituido, es convenientemente ciclohexilo opcionalmente sustituido con un grupo funcional tal como hidroxi.

Cuando R^{63} y R^{64} es alquenilo opcionalmente sustituido, es convenientemente prop-2-enilo.

Cuando R^{63} y R^{64} es heterociclilo opcionalmente sustituido, o R^{63} y R^{64} forman juntos un grupo heterocíclico, entonces éste puede ser aromático o no aromático e incluye, en particular, piperidina, piperazina, morfolino, pirrolidina o piridina, cualquiera de los cuales puede sustituirse opcionalmente con un grupo funcional tal como hidroxi, alcoxi tal como metoxi, o alquilo tal como metilo, el cual puede él mismo sustituirse por ejemplo con un grupo hidroxi.

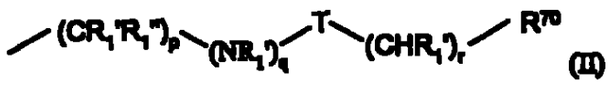
Alternativamente, por lo menos uno de R^{60}, R^{61} o R^{62} es un grupo funcional y, en particular, uno de R^{60}, R^{61} o R^{62} es un grupo funcional de fórmula $(CR_2)_pC(O)_xR^{77}$ en conde R, p, x y R^{77} son como se definen más arriba y, en particular, x es 2 y R^{77} es hidrógeno o alquilo tal como metilo.

Alternativamente, R^5 se sustituye por uno o más grupos seleccionados de nitro, halo, C_{1-6}alquilo, C_{1-6}alcoxi opcionalmente sustituido, C_{1-4}alcoximetilo, di(C_{1-4}alcoxi)metilo, C_{1-6}alcanoilo, trifluorometilo, ciano, amino, C_{2-6}alquenilo, C_{2-6}alquinilo, un grupo fenilo, un grupo bencilo o un grupo heterocíclico de 5-6 miembros con 1-3 heteroátomos, seleccionados independientemente de O, S y N, grupo heterocíclico que puede ser aromático o no aromático y puede ser saturado (enlazado mediante un anillo carbono o átomo de nitrógeno) o insaturado (enlazado mediante un átomo de anillo carbono), y el cual grupo fenilo, bencilo o heterocíclico puede llevar en uno o más átomos de anillo carbono

hasta 5 sustituyentes seleccionados de hidroxi, halógeno, C_{1-3}alquilo, C_{1-3}alcoxi, C_{1-3}alalcanoiloxi, trifluorometilo, ciano, amino, nitro, C_{2-4}alcanoilo, C_{1-4}alcanoilamino, C_{1-4}alcoxicarbonilo, C_{1-4}alquilsulfanilo, C_{1-4}alquilsulfinilo, C_{1-4}alquilsulfonilo, carbamoilo, N-C_{1-4}alquilcarbamoilo, N,N-di(C_{1-4}alquil)carbamoilo, aminosulfonilo, N-C_{1-4}alquilaminosulfonilo, N,N-di(C_{1-4}alquil)aminosulfonilo, C_{1-4}alquilsulfonilamino, y un grupo heterocíclico saturado seleccionado de morfolino, tiomorfolino, pirrolidinilo, piperazinilo, piperidinilo, imidazolidinilo y pirazolidinilo, el cual grupo heterocíclico puede llevar 1 ó 2 sustituyentes seleccionados de oxo, hidroxi, halógeno, C_{1-3}alquilo, C_{1-3}alcoxi, C_{1-3}alcanoiloxi, trifluorometilo, ciano, amino, nitro y C_{1-4}alcoxicarbonilo.

Convenientemente R^5 se sustituye con por lo menos un grupo que tiene por lo menos 4 átomos, los cuales pueden ser carbono o heteroátomos que forman una cadena. Un ejemplo particular de dicho sustituyente es alcoxi opcionalmente sustituido o alcoxi metilo. Sustituyentes apropiados para el grupo alcoxi incluyen aquellos listados más arriba en relación con R^{77}, R^{78} y R^{79}.

Otro grupo sustituyente particular para R^5 es un grupo de sub-fórmula (II)



(II)

en donde p y q son independientemente 0 ó 1, y r es 0, 1, 2, 3 ó 4 y, R1', R1" y T son como se definieron anteriormente más arriba;

R^{70} es hidrógeno, hidroxi (distinto de donde q es 0), C_{1-6}alquilo, C_{1-6}alcoxi, amino, *N*-C_{1-6}alquilamino, *N,N*-(C_{1-6}alquil)$_2$amino, hidroxiC_{2-6}alcoxi, C_{1-6}alcoxiC_{2-6}alcoxi, aminoC_{2-6}alcoxi, *N*-C_{1-6}alquilaminoC_{2-6}alcoxi, *N,N*-(C_{1-6}alquil)$_2$amino C_{2-6}alcoxi o C_{3-7}cicloalquilo,

o R^{70} es de la Fórmula (III):



(III)

en donde J es arilo, heteroarilo o heterociclilo y K es un enlace, oxi, imino, *N*-(C_{1-6}alquil)imino, oxiC_{1-6}alquileno, iminoC_{1-6}alquileno, *N*-(C_{1-6}alquil)iminoC_{1-6} alquileno, -NHC(O)-, -SO_2NH-, -NHSO_2- o -NHC(O)-C_{1-6}alquileno-,

y cualquier grupo arilo, heteroarilo o heterociclilo en un grupo R^{70} puede sustituirse opcionalmente por uno o más grupos seleccionados de hidroxi, halo, trifluorometilo, ciano, mercapto, nitro, amino, carboxi, carbamoilo, formilo, sulfamoilo, C_{1-6}alquilo, C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, -O-(C_{1-3}alquil)-O-, C_{1-6}alquilS(O)$_n$- (en donde n es 0-2), *N*-C_{1-6}alquilamino, *N*,*N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcoxicarbonilo, *N*-C_{1-6}alquilcarbamoilo, *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, C_{2-6}alcanoilo, C_{1-6}alcanoiloxi, C_{1-6}alcanolamino, *N*-C_{1-6}alquilsulfamoilo, *N*,*N*-(C_{1-6}alquilsulfamoilo, C_{1-6}alquilsulfonilamino y C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino, o cualquier grupo arilo, heteroarilo o heterociclilo en un grupo R^{70} puede sustituirse opcionalmente con uno o más grupos de la Fórmula (IV):

$$-B^1-(CH_2)_p-A^1 \qquad \text{(IV)}$$

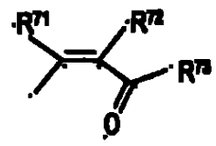
en donde A^1 es halo, hidroxi, C_{1-6}alcoxi, ciano, amino, *N*-C_{1-6}alquilamino, *N*,*N*-(C_{1-6}alquil)$_2$amino, carboxi, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-C_{1-6}alquilcarbamoilo o *N*,*N*-(C_{1-6}alquil)$_2$carbamoilo, p es 1-6, y B^1 es un enlace, oxi, imino, *N*-(C_{1-6}alquil)imino o -NHC(O)-, con la condición que p es 2 o más a menos que B^1 sea un enlace o -NHC(O)-; o cualquier grupo arilo, heteroarilo o heterociclilo en un grupo R^{70} puede sustituirse opcionalmente con uno o más grupos de la Fórmula (V):

$$-B^1-D^1 \qquad \text{(V)}$$

en donde D^1 is arilo, heteroarilo o heterociclilo y E^1 es un enlace, C_{1-6}alquileno, oxiC_{1-6}alquileno, oxi, imino, *N*-(C_{1-6}alquil)imino, iminoC_{1-6}alquileno, *N*-(C_{1-6}alquil)-iminoC_{1-6}alquileno, C_{1-6}alquilen-oxiC_{1-6}alquileno, C_{1-6}alquilen-iminoC_{1-6}alquileno, C_{1-6}alquilen-*N*-(C_{1-6}alquil)-iminoC_{1-6}alquileno, -NHC(O)-, -$NHSO_2$-, -SO_2NH- o -NHC(O)-C_{1-6}alquileno-, y cualquier grupo arilo, heteroarilo o heterociclilo en un sustituyente en D^1 puede sustituirse opcionalmente con uno o más grupos seleccionados de hidroxi, halo, C_{1-6}alquilo, C_{1-6}alcoxi, carboxi, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-C_{1-6}alquilcarbamoilo, *N*-(C_{1-6}alquil)$_2$carbamoilo, C_{2-6}alcanoilo, amino, *N*-C_{1-6}alquilamino y *N* ,*N*-(C_{1-6}alquil)$_2$amino, y cualquier grupo C_{3-7}cicloalquilo o heterociclilo en un grupo R^{70} puede sustituirse opcionalmente con uno o dos sustituyentes oxo o tioxo, y cualquiera de los grupos R^{70} definidos más arriba que comprende un grupo CH_2 que se une a 2 átomos de carbono o un grupo CH_3 que se une a un átomo de carbono puede llevar opcionalmente en cada dicho grupo CH_2 o CH_3 un sustituyente seleccionado de hidroxi, amino, C_{1-6}alcoxi, *N*-C_{1-6}alquilamino, *N*,*N*-(C_{1-6}alquil)$_2$amino y heterociclilo.

Un ejemplo preferido de un sustituyente de fórmula (II) es un grupo en donde q es 0. Un ejemplo particular de un grupo R^{70} en fórmula (II) es fenilo.

Otro grupo sustituyente preferido para R^5 es un grupo de fórmula (VI)



(VI)

donde R^{71} y R^{72} se seleccionan independientemente de hidrógeno o C_{1-4}alquilo, o R^{71} y R^{72} juntos forman un enlace, y R^{73} es un grupo OR^{74}, $NR^{75}R^{76}$ donde R^{74}, R^{75} y R^{76} se seleccionan independientemente de grupos hidrocarbilo opcionalmente sustituido o grupos heterocíclicos opcionalmente sustituidos, y R^{75} y R^{76} pueden, adicionalmente, formar

juntos con el átomo de nitrógeno al cual se unen, un anillo heterocíclico aromático o no aromático que puede contener más heteroátomos.

Sustituyentes opcionales apropiados para grupos hidrocarbilo o heterocíclicos R^{74}, R^{75} y R^{76} incluyen grupos funcionales tal como se definió más arriba. Grupos heterocíclicos R^{74}, R^{75} y R^{76} pueden sustituirse además por grupos hidrocarbilo.

En particular, R^{71} y R^{72} en sub-fórmula (VI) son hidrógeno.

En particular ejemplos de R^{73} son grupos OR^{74} donde R^{74} es C_{1-4}alquilo.

Otros ejemplos de R^{73} son are grupos de fórmula $NR^{75}R^{76}$ donde uno de R^{75} o R^{76} es hidrógeno y el otro es C_{1-6}alquilo opcionalmente sustituido, arilo opcionalmente sustituido o heterociclilo opcionalmente sustituido.

En particular, uno de R^{75} o R^{76} es hidrógeno y el otro es C_{1-6}alquilo opcionalmente sustituido con trifluorometilo, C_{1-3}alcoxi tal como metoxi, ciano, tioC_{1-4}alquilo tal como metiltio, o heterociclilo opcionalmente sustituido con hidrocarbilo, tal como indano, furano opcionalmente sustituido con C_{1-4}alquilo tal como metilo.

En otra incorporación, uno de R^{75} o R^{76} es hidrógeno y el otro es un grupo heterocíclico opcionalmente sustituido tal como piridina, o un grupo fenilo opcionalmente sustituido con, por ejemplo, uno o más grupos seleccionados de halo, nitro, alquilo tal como metilo, o alcoxi tal como metoxi.

Sales farmacéuticamente aceptables de compuestos de Fórmula (I) o Fórmula (IA) incluyen sales de adición de ácido tales como metanosulfonato, fumarato, clorhidrato, bromohidrato, citrato, maleato y sales formadas con ácido fosfórico y sulfúrico. Puede haber más de un catión o anión dependiendo del número de funciones cargadas y la valencia de los cationes o aniones. Donde el compuesto de Fórmula (I) o Fórmula (IA) incluye una funcionalidad ácido, las sales pueden ser sales base tales como una sal de metal alcalino por ejemplo sodio, una sal de metal alcalinotérreo por ejemplo calcio o magnesio, una sal amina orgánica por ejemplo trietilamina, morfolina, *N*-metilpiperidina, *N*-etilpiperidina,

procaína, dibencilamina, *N,N*-dibenciletilamina o aminoácidos por ejemplo lisina. Una sal farmacéuticamente aceptable preferida es una sal de sodio.

Un éster hidrolizable *in vivo* de un compuesto de la Fórmula (I) o Fórmula (IA) que contiene un grupo carboxi o hidroxi es, por ejemplo, un éster farmacéuticamente aceptable que se hidroliza en el organismo humano o animal para producir el ácido precursor o alcohol.

Ésteres farmacéuticamente aceptables apropiados para carboxi incluyen ésteres de C_{1-6}alquilo tales como ésteres de metilo o etilo, ésteres de C_{1-6}alcoximetilo, por ejemplo, metoximetilo, ésteres de C_{1-6}alcanoiloximetilo por ejemplo pivaloiloximetilo, ésteres de ftalidilo, ésteres de C_{3-8}cicloalcoxi-carboniloxiC_{1-6}alquilo por ejemplo 1-ciclohexilcarboniloxietilo; ésteres de 1,3-dioxolen-2-onilmetilo por ejemplo 5-metil-1,3-dioxolen-2-onilmetilo; y ésteres de C_{1-6}alcoxicarboniloxietilo por ejemplo 1-metoxicarboniloxietilo y pueden formarse en cualquier grupo carboxi en los compuestos de esta invención.

Un éster hidrolizable *in vivo* de un compuesto de la Fórmula (I) o Fórmula (IA) que contiene un grupo hidroxi incluyen ésteres inórganicos tales como ésteres de fosfato y éteres de α-aciloxialquilo y compuestos relacionados que, como resultado de la hidrólisis *in vivo* del éster, se descomponen para dar el grupo hidroxi precursor. Ejemplos de éteres de α-aciloxialquilo incluyen acetoximetoxi y 2,2-dimetilpropioniloximetoxi; una selección de éster hidrolizable *in vivo* que forma grupos para hidroxi incluyen alcanoilo, benzoilo, fenilacetilo y benzoilo sustituido y fenilacetilo, alcoxicarbonilo (para dar ésteres de carbonato de alquilo), dialquilcarbamoilo y *N-(*dialquilaminoetil)-N-alquilcarbamoilo (para dar carbamatos), dialquilaminoacetilo y carboxiacetilo.

Amidas apropiadas se derivan de compuestos de Fórmula (I) o Fórmula (IA) que tienen un grupo carboxi, que se deriva en una amida tal como una N-C_{1-6}alquil y N,N-di-(C_{1-6}alquil)amida tal como N-metilo, N-etilo, N-propilo, N,N-dimetilo, N-etil-N-metilo o N,N-dietilamida.

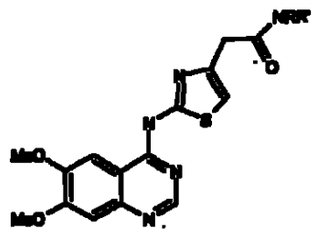
Compuestos prefereridos de Fórmula (I) o Fórmula (IA) son aquellos que son estables en suero de ratón, rata o humano, preferiblemente aquellos

que son estables en suero humano.

Ésteres que no son hidrolizables *in vivo* pueden ser útiles como intermedios en la producción de los compuestos de Fórmula (I) o Fórmula (IA).

Ejemplos particulares de compuestos de Fórmula (I) o Fórmula (IA) se exponen en las siguientes Tablas 1 a 30.

TABLA 1



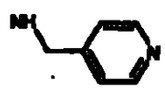
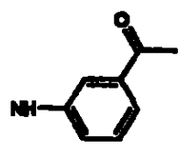
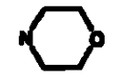
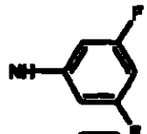
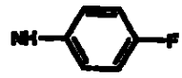
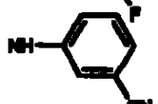
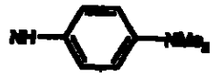
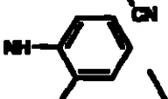
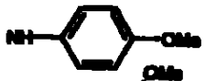
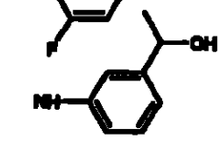
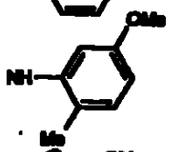
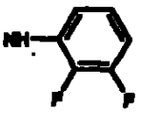
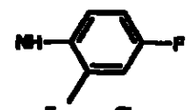
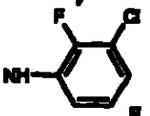
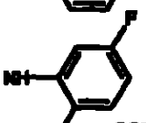
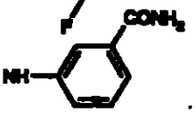
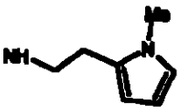
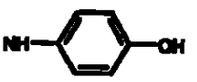
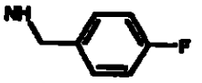
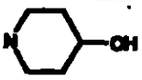
Compuesto No.	NRR'	Compuesto No.	NRR'
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2		16	
3		17	
4		18	
5		19	
6		20	
7		21	
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9		23	
10		24	
11		25	
12			
13			
14			

Tabla 1 (CONTINUACIÓN)

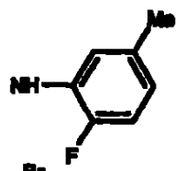
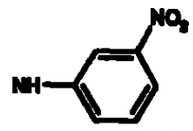
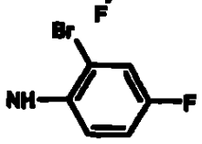
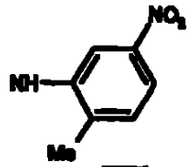
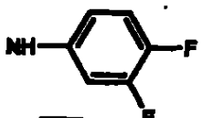
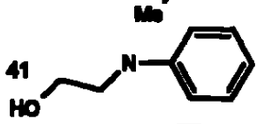
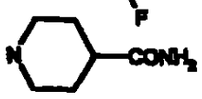
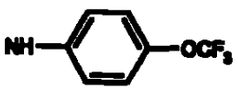
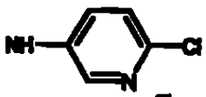
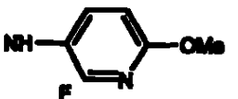
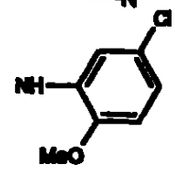
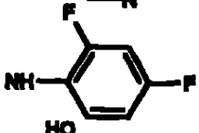
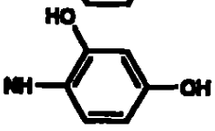
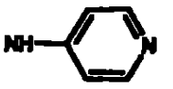
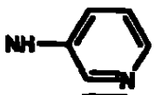
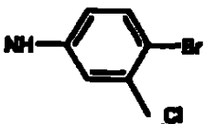
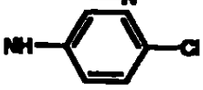
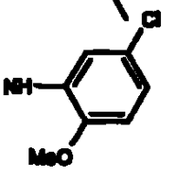
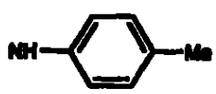
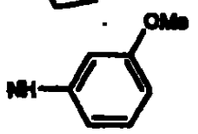
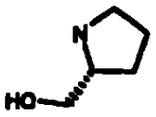
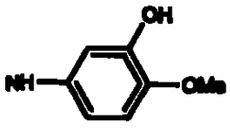
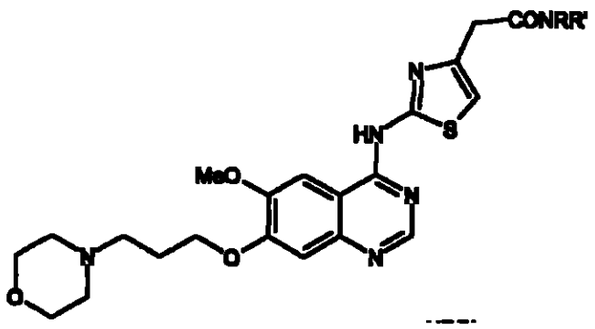
Compuesto No.	NRR'	Compuesto No.	NRR'
26		39	
27		40	
28		41	
29		42	
30		43	
31		44	
32		45	
33		46	
34		47	
35		48	
36		49	
37		50	
38			

Tabla 2



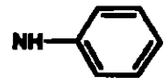
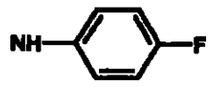
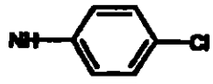
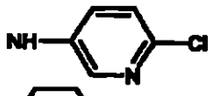
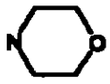
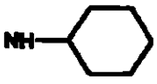
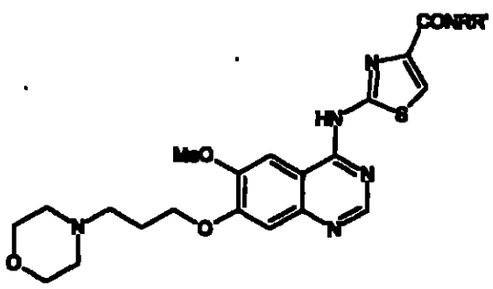
Compuesto No.	NRR'
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53	
54	
55	
56	
57	
58	

Tabla 3



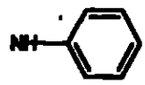
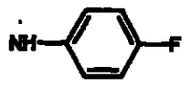
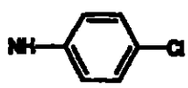
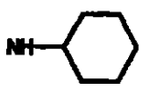
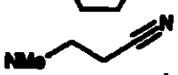
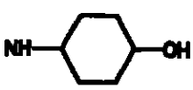
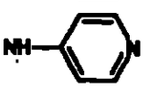
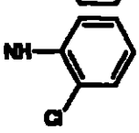
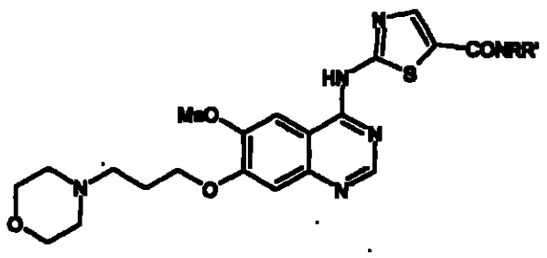
Compuesto No.	NRR'
59	
60	
61	
62	
63	
64	
65	
66	

Tabla 4



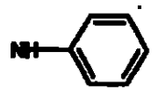
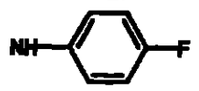
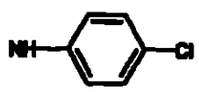
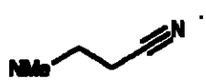
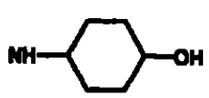
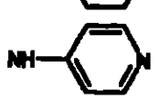
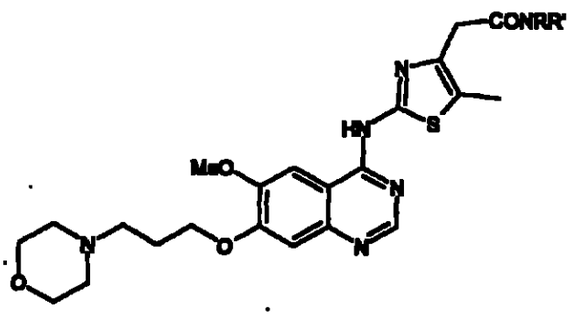
Compuesto No.	NRR'
67	
68	
69	
70	
71	
72	
73	

Tabla 5



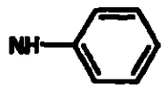
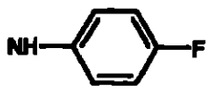
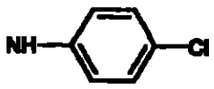
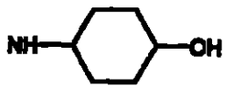
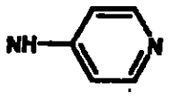
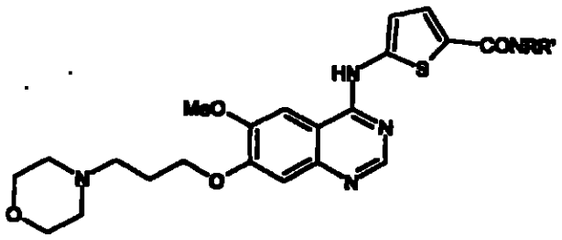
Compuesto No.	NRR'
74	
75	
76	
77	
78	

Tabla 6



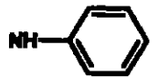
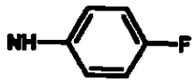
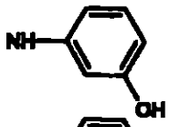
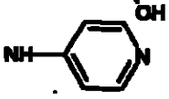
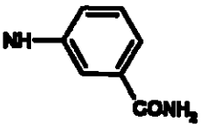
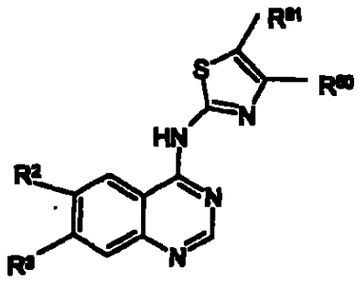
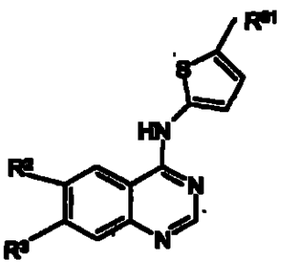
Compuesto No.	NRR'
79	
80	
81	
82	
83	
84	
85	
86	

Tabla 7



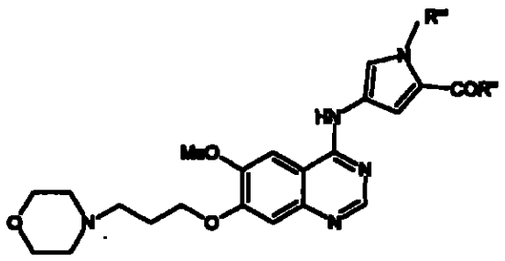
No.	R^2	R^3	R^{60}	R^{61}
200	OCH_3	OCH_3	$CH_2COOCH_2CH_3$	H
201	OCH_3	OCH_3	CH_2COOH	H
202	OCH_3	OCH_3	CH_3	$COOCH_2CH_3$
203	OCH_3	$O(CH_2)_3$-N-morfolino	CH_3	$COOCH_2CH_3$
204	OCH_3	$O(CH_2)_3$-N-morfolino	CH_3	COOCH
205	OCH_3	$O(CH_2)_3$-N-morfolino	$CH_2COOCH_2CH_3$	H
206	OCH_3	$O(CH_2)_3$-N-morfolino	$COOCH_2CH_3$	H
207	OCH_3	$O(CH_2)_3$-N-morfolino	COOH	H
208	OCH_3	$O(CH_2)_3$-N-morfolino	H	$COOCH_2CH_3$
209	OCH_3	$O(CH_2)_3$-N-morfolino	H	COOH
210	OCH_3	$O(CH_2)_3$-N-morfolino	$CH_2COOCH_2CH_3$	CH_3
211	OCH_3	$O(CH_2)_3$-N-morfolino	CH_2COOH	CH_3

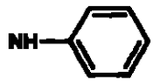
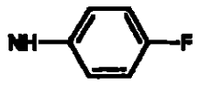
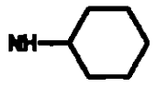
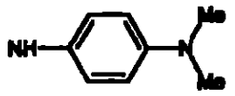
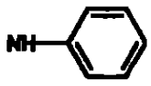
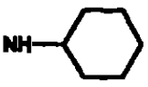
Tabla 8



No.	R^2	R^3	R^{61}
212	OCH_3	$O(CH_2)_3$-N-morfolino	COOH
213	OCH_3	OCH_3	$COOCH_2CH_3$
214	OCH_3	OCH_3	COOH

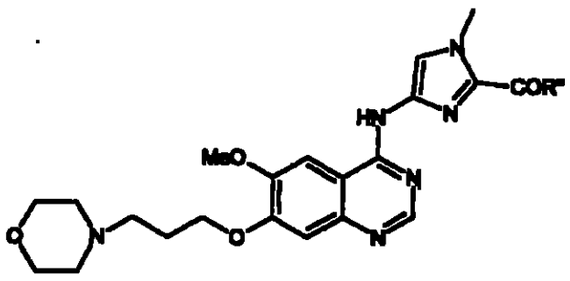
Tabla 9



Compuesto No.	R'''	R''
250	CH_3	OCH_3
251	CH_3	OH
252	CH_3	
253	CH_3	
254	CH_3	
255	CH_3	
256	H	OCH_2CH_3
257	H	OH
258	H	
259	H	

437

Tabla 10



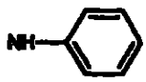
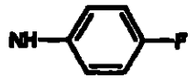
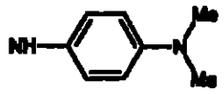
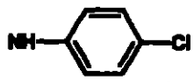
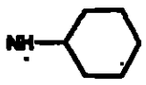
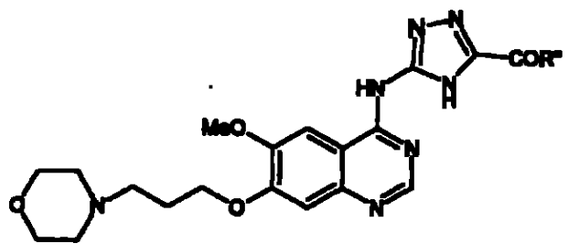
Compuesto No.	R"
280	$COOCH_3$
281	COOH
282	
283	
284	
285	
286	
287	

Tabla 11



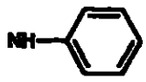
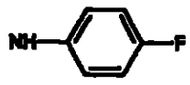
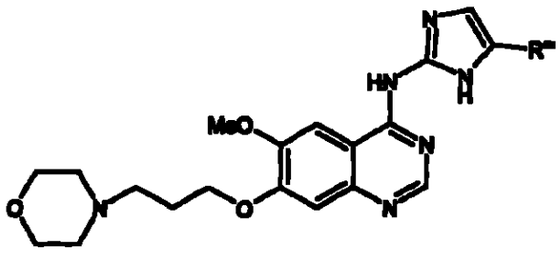
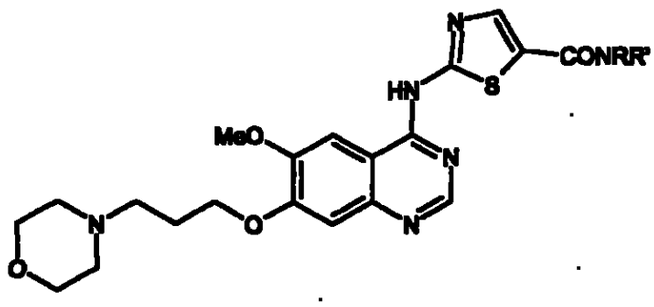
Compuesto No.	R"
269	$COOCH_2CH_3$
269	COOH
270	
271	
272	

Tabla 12



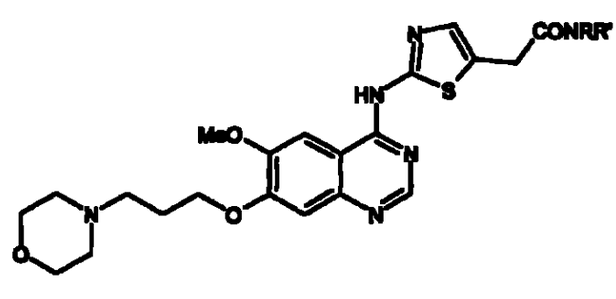
Compuesto No.	R'''
300	H
301	$COOCH_2CH_3$

TABLA 13



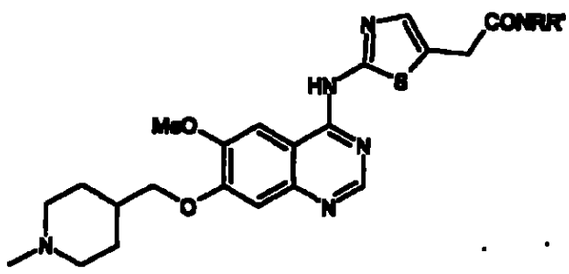
No.	NRR'	No.	NRR'
302	4-metoxianilina	320	2-metil-4-fluoroanilina
303	4-metilanilina	321	2-fluoro-5-metilanilina
304	2-aminopiridina	322	4-fluorobencilamina
305	Alcohol 2-aminobencílico	323	3,4-difluorobencilamina
306	4-metoxibencilamina	324	3-metilanilina
307	3-nitroanilina	325	2-(metiltio)anilina
308	Aminoacetonitrilo	326	5-aminoindol
309	2-metil-5-nitroanilina	327	3-aminobenzonitrilo
310	Ciclopropilamina	328	2,4-difluorobencilamina
311	4-nitrobencilamina	329	3-(2-aminoetil)piridina
312	2-anilinoetanol	330	N-metilisobutilamina
313	Furfurilamina	331	2-aminobencilamina
314	3-cloroanilina	332	3-metilbutilamina
315	2-metoxianilina	333	1-aminometil-1-ciclohexanol
316	tiofen-2-metilamina	334	2-aminometilpirazina
317	Neopentilamina	335	3-metoxianilina
318	2,6-difluorobencilamina	336	4-clorobencilamina
319	2-metilalilamina		

TABLA 14



No.	NRR'	No.	NRR'
337	Anilina	357	2-metoxianilina
338	3-cloro-4-fluoroanilina	358	2-fluoroanilina
339	4-cloroanilina	359	Tiofen-2-metilamina
340	3,4-difluoroanilina	360	2-amino-1-feniletanol
341	3-metoxianilina	361	3-(1-hidroxietil)anilina
342	2-cloroanilina	362	Neopentilamina
343	4-metoxianilina	363	3-fluoro-4-metoxianilina
344	4-metilanilina	364	2-metil-4-fluoroanilina
345	2-metilanilina	365	2,5-difluoroanilina
346	2-aminopiridina	366	2-fluoro-4-cloroanilina
347	2-aminobencilalcohol	367	2-fluoro-4-metilanilina
348	2-amino-3-metil-1-butanol	368	3-metilanilina
349	2-anilino etanol	369	2-(metiltio)anilina
350	3-cloro-4-metilanilina	370	5-aminoindol
351	3-nitroanilina	371	2,4-difluoroanilina
352	aminoacetonitrilo	372	2-fluoro-4-metilanilina
353	2-metil-5-nitroanilina	373	3-cianoanilina
354	2-amino-5-cloropiridina	374	2-metil-5-fluoroanilina
355	4-trifluorometilanilina	375	2-metil-5-cloroanilina
356	3-cloroanilina		

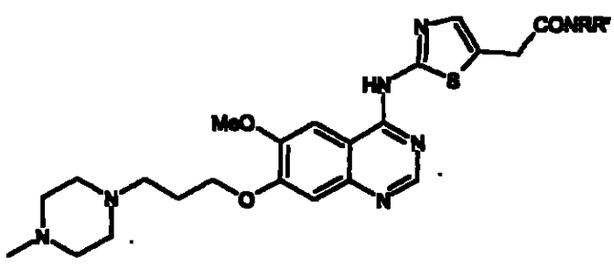
TABLA 15



No.	NRR'	No.	NRR'
376	Anilina	390	3-fluoro-4-metoxianilina
377	3-cloro-4-fluoroanilina	391	2-metil-4-fluoroanilina
378	2-aminopiridina	392	2-amino-4-metilpiridina
379	3,4-difluoroanilina	393	2,5-difluoroanilina

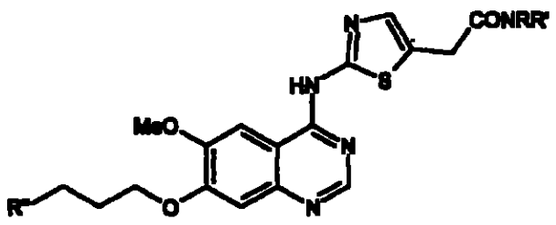
380	2-cloroanilina
381	4-metilanilina
382	2-metilanilina
383	4-cloroanilina
384	4-fluoroanilina
385	2-amino-6-metilpiridina
386	3-metoxianilina
387	2-amino-5-cloropiridina
388	3-cloroanilina
389	2-fluoroanilina
394	2-fluoro-4-cloroanilina
395	2-fluoro-5-metilanilina
396	3-metilanilina
397	2,4-difluoroanilina
398	2-fluoro-4-metilanilina
399	3-cianoanilina
400	2-metil-5-fluoroanilina
401	3,5-difluoroanilina
402	3-fluoroanilina

TABLA 16



No.	NRR'	No.	NRR'
403	Anilina		
404	3,4-difluoroanilina		
405	2-aminopiridina	418	2-fluoro-4-metilanilina
406	3-cloro-4-fluoroanilina	419	3-fluoro-4-metoxianilina
407	2-cloroanilina		
408	4-metilanilina	420	2-metil-4-fluroanilina
409	2-metilanilina	421	2-amino-4-metilpiridina
410	4-cloroanilina	422	2,5-difluoranilina
411	4-fluoroanilina	423	2-fluoro-4-cloroanilina
412	2-amino-6-metilpiridina	424	2-fluoro-5-metilanilina
413	3-metoxianilina	425	3-metilanilina
414	2-amino-5-cloropiridina	426	2,4-difluoroanilina
415	3-cloroanilina	427	2-metil-5-fluoroanilina
416	2-fluoroanilina	428	3,5-difluoroanilina
417	3-cianoanilina	429	3-fuoroanilina

TABLA 17



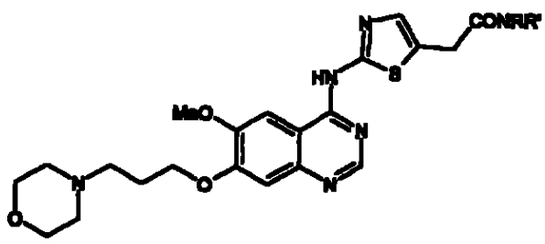
No.	R"	NRR'
430	Pirrolidina	3-cloroanilina
431	Pirrolidina	3,4-difluoroanilina
432	Dimetilamina	3,5-difluoroanilina
433	2-amino-2-metil-1-propanol	3-cloro-4- fluoroanilina
434	2-amino.2-metil-1-propanol	3-fluoroanilina
435	4-hidroxipiperidina	3,4-difluoroanilina
436	N,N-dimetiletilendiamina	3,4-difluoroanilina
437	Piperidina	3,4-difluoroanilina
438	2-metilaminoetanol	3,4-difluoroanilina
439	1,2-diamino-2-metilpropano	3,4-difluoroanilina
440	Ciclohexilamina	3,4-difluoroanilina
441	N,N,N'-trimetiletilendiamina	3,4-difluoroanilina
442	D-prolinol	3,4-difluoroanilina
443	L-prolinol	3,4-difluoroanilina
444	3-pirrolidinol	3,4-difluoroanilina
445	1-(2-aminoetil)pirrolidina	3,4-difluoroanilina
446	1-acetilpiperazina	3,4-difluoroanilina
447	1-(2-morfolinoetil)piperazina	3,4-difluoroanilina
448	2-(2-hidroxietil)piperidina	3,4-difluoroanilina
449	1-(2-hidroxietil)piperazina	3,4-difluoroanilina
450	Ciclopentilamina	3,4-difluoroanilina
451	4-(2-hidroxietil)piperidina	3,4-difluoroanilina
452	L-alamin-tert-butiléster	3,4-difluoroanilina
453	3-hidroxipiperidina	3,4-difluoroanilina
454	4-hidroximetilpiperidina	3,4-difluoroanilina
455	1-amino-2-propanol	3,4-difluoroanilina

456	L-alanin-tert-butiléster	3-cloroanilina
457	2-metilaminoetanol	3-cloroanilina
458	1,2-diamino-2-metilpropano	3-cloroanilina
459	Ciclohexilamina	3-cloroanilina
460	N,N-dimetiletilendiamina	3-cloroanilina
461	N,N,N'-trimetiletilendiamina	3-cloroanilina
462	D-prolinol	3-cloroanilina
463	L-prolinol	3-cloroanilina
464	4-hidroxipiperidina	3-cloroanilina
465	3-pirrolidinol	3-cloroanilina
466	1-(2-aminoetil)pirrolidina	3-cloroanilina
467	4-hidroximetilpiperidina	3-cloroanilina
468	1-(2-hidroxietil)piperazina	3-cloroanilina
469	Ciclopentilamina	3-cloroanilina
470	4-(2-hidroxietil)piperidina	3-cloroanilina
471	3-hidroxipiperidina	3-cloroanilina
472	(S)-1-amino-2-propanol	3-cloroanilina
473	(R)-1-amino-2-propanol	3-cloroanilina
474	Piperazina	3-cloroanilina
475	2-(2-hidroxietil)piperidina	3-cloroanilina
476	2-amino-2-metil-1-propanol	3-cloroanilina
477	1-(2-dimetilaminoetil)piperazina	3-cloroanilina
478	Dimetilamina	3-cloroanilina
479	Aminometilciclopropano	3-cloroanilina
480	Piperidina	3-cloroanilina
481	1-(2-dimetilaminoetil)piperazina	3,5-difluoroanilina
482	(S)-(+)-2-Pirrolidinmetanol	3,5-difluoroanilina
483	4-hidroxipiperidina	3,5-difluoroanilina
484	3-pirrolidinol	3,5-difluoroanilina
485	1-(2-aminoetil)pirrolidina	3,5-difluoroanilina
486	4-hidroximetilpiperidina	3,5-difluoroanilina
487	2-(2-hidroxietil)piperidina	3,5-difluoroanilina
488	1-(2-hidroxietil)piperazina	3,5-difluoroanilina
489	4-(2-hidroxietil)piperidina	3,5-difluoroanilina
490	3-hidroxipiperidina	3,5-difluoroanilina
491	N,N,N'-trimetiletilendiamina	3,5-difluoroanilina
492	Piperidina	3,5-difluoroanilina

493	Pirrolidina	3,5-difluoroanilina
494	2-amino-2-metil-1-propanol	3,5-difluoroanilina
495	2-metilaminoetanol	3,5-difluoroanilina
496	N,N-dimetiletilendiamina	3,5-difluoroanilina
497	(S)-(+)-1-amino-2-propanol	3,5-difluoroanilina
498	(R)-(-)-1-amino-2-propanol	3,5-difluoroanilina
499	Piperazina	3,5-difluoroanilina
500	N-alilpiperazina	3,5-difluoroanilina
501	(R)-(-)-2-pirrolidinmetanol	3,5-difluoroanilina
502	Ciclopentilamina	3,5-difluoroanilina
503	2-metilaminoetanol	3-cloro-4-fluoroanilina
504	N,N,N' -trimetiletilendiamina	3-cloro-4-fluoroanilina
505	N-alilpiperazina	3-cloro-4-fluoroanilina
506	4-hidroxipiperidina	3-cloro-4-fluoroanilina
507	3-pirrolidinol	3-cloro-4-fluoroanilina
508	1-(2-aminoetil)pirrolidina	3-cloro-4-fluoroanilina
509	N-acetilpiperazina	3-cloro-4-fluoroanilina
510	2-(2-hidroxietil)piperidina	3-cloro-4-fluoroanilina
511	1-(2-hidroxietil)piperazina	3-cloro-4-fluoroanilina
512	Ciclopentilamina	3-cloro-4-fluoroanilina
513	4-(2-hidroxietil)piperidina	3-cloro-4-fluoroanilina
514	3-hidroxipiperidina	3-cloro-4-fluoroanilina
515	4-hidroximetilpiperidina	3-cloro-4-fluoroanilina
516	1-amino-2-propanol	3-cloro-4-fluoroanilina
517	Piperazina	3-cloro-4-fluoroanilina
518	1-(2-morfolinoetil)piperazina	3-cloro-4-fluoroanilina
519	Pirrolidina	3-cloro-4-fluoroanilina
520	2-metilaminoetanol	3-fluoroanilina
521	1,2-diamino-2-metilpropano	3-fluoroanilina
522	N,N-dimetiletilendiamina	3-fluoroanilina
523	N,N,N' –trimetiletilendiamina	3-fluoroanilina
524	N-alilpiperazina	3-fluoroanilina
525	4-hidroxipiperidina	3-fluoroanilina
526	3-pirrolidinol	3-fluoroanilina
527	1-(aminoetil)pirrolidina	3-fluoroanilina
528	N-acetilpiperazina	3-fluoroanilina

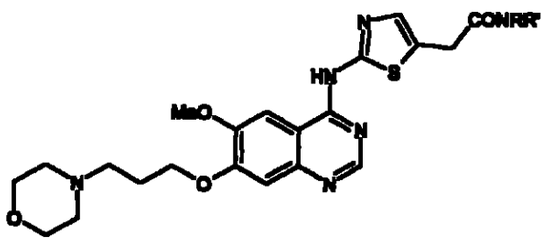
529	1-(2-hidroxietil)piperazina	3-fluoroanilina
530	Ciclopentilamina	3-fluoroanilina
531	4-(2-hidroxietil)piperidina	3-fluoroanilina
532	3-hidroxipiperidina	3-fluoroanilina
533	4-hidroximetilpiperidina	3-fluoroanilina
534	1-amino-2-propanol	3-fluoroanilina
535	(R)-(-)-2-pirrolidinmetanol	3-fluoroanilina
536	(S)-(+)-2-pirrolidinmetanol	3-fluoroanilina
537	Piperazina	3-fluoroanilina
538	1-(2-morfolinoetil)piperazina	3-fluoroanilina

TABLA 18



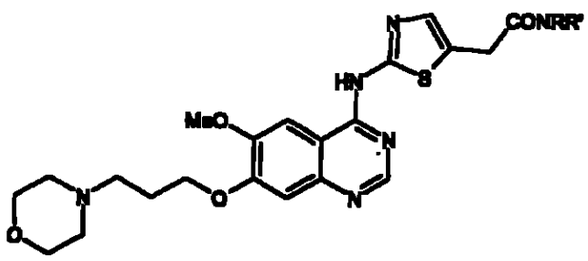
No.	NRR'
539	N-etilanilina
540	3-cloro-4- fluoro-N-metilanilina
541	etil- 2-(3 -cloro-4- fluoroanilino)acetate
542	2-anilinoacetronitrilo
543	3-anilinoproponitrilo
544	N -(2-tert-butoxietil)- 3 -cloro-4- fluoroanilina
545	N-alilanilina
546	N -etil-3,4-(metilmedioxi)anilina
547	etil-4-(N-butilamino)benzato
548	N-etil-M-toluidina
549	N -(2-hidroxietil)- 3-cloro-4-fluoroanilina

TABLA 18



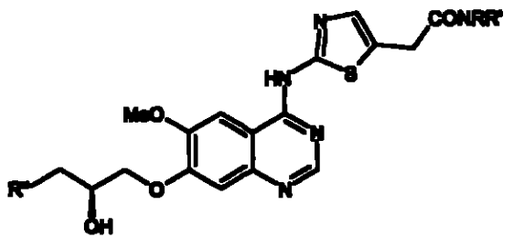
No.	NRR'
550	N-etilanilina
551	3-cloro-4-fluoro-N-metilanilina
552	etil-2-(3-cloro-4-fluoroanilino)acetato
553	2-anilinoacetronitrilo
554	3- anilinoproponitrilo
555	N -(2-tert-butoxietil)-3-cloro-4-fluoroanilina
556	N-alilanilina
557	N-etil-3,4-(metilmedioxi)anilina
558	etilI-4-(N-butilamino)benzoato
559	N-etil-M-toluidina
560	N-(2-hidroxietil)-3-cloro-4- fluoroanilina

TABLA 19



No.	NRR'
561	Anilina
562	3-cloro-4-fluoroanilina
563	2-aminopiridina
564	3,4-difluoroanilina

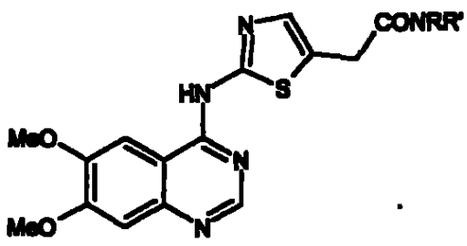
TABLA 20



No.	R''''	NRR'
565	Piperidina	3-cloro-4-fluoroanilina
566	Pirrolidina	3-cloro-4-fluoroanilina
567	4-hidroxipiperidina	3-cloro-4-fluoroanilina
568	Piperazina	3-cloro-4- fluoroanilina
569	Ciclopentilamina	3-cloro-4-fluoroanilina
570	2-amino-2-metil-1-propanol	3-cloro-4-fluoroanilina
571	Piperidina	3,4-difluoroanilina
572	Pirrolidina	3,4-difluoroanilina
573	4-hidroxipiperidina	3,4-difluoroanilina
574	Ciclopentilamina	3,4-difluoroanilina
575	Pirrolidina	3-cloroanilina
576	4-hidroxipiperidina	3-cloroanilina
577	Ciclopentilamina	3-cloroanilina
578	2-amino-2-metil-1-propanol	3-cloroanilina
579	Piperazina	3-cloroanilina
580	Ome	3-cloroanilina
581	Piperidina	3-cloroanilina
582	Piperidina	3,5-difluoroanilina
583	Pirrolidina	3,5-difluoroanilina
584	2-amino-2-metil-1-propanol	3,5-difluoroanilina
585	Piperazina (acetato)	3,5-difluoroanilina
586	Piperazina	3,5-difluoroanilina
587	Pirrolidina	3-fluoroanilina
588	Piperidina	3-fluoroanilina
589	Piperazina	3-fluoroanilina

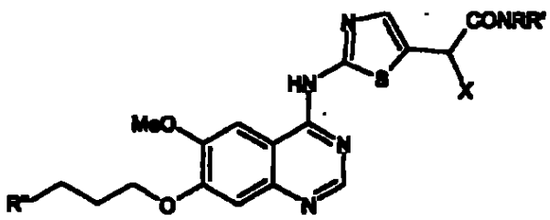
590	Piperazina (acetato)	3-fluoroanilina
591	Ciclopentilamina	3-fluoroanilina

TABLA 21



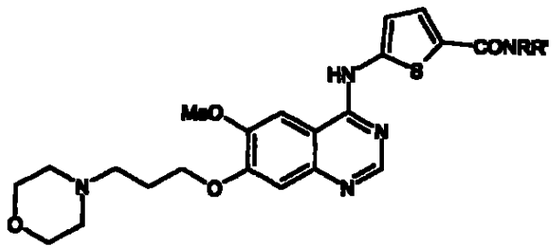
No.	NRR'
592	3,5-difluoroanilina
593	3-cloroanilina
594	3-cloro-4-fluoroanilina
595	3,4-difluoroanilina

TABLA 22



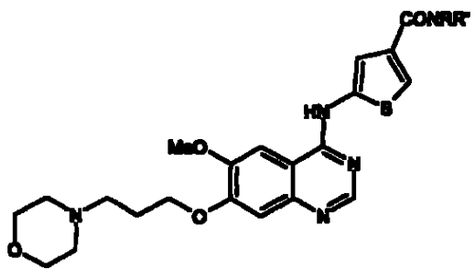
No.	R''''	Y	NRR'
596	Morfolina	OH	Anilina
597	Morfolina	OH	3,4-difluoroanilina
598	N-Me-piperazina	OH	3,4-difluoroanilina
599	Piperidina	OH	3-fluoroanilina
600	Piperidina	OH	3-cloroanilina
601	N-Me-piperazina	=N-OH	3,4-difluoroanilina

TABLA 23



No.	NRR'	No.	NRR'
602	2-aminopiridina	610	2-metoxianilina
603	4-metilanilina	611	3-(2-hidroxietil)anilina
604	2-metilanilina	612	3-fluoro-4-metoxianilina
605	3-metoxianilina	613	2-metil-4-fluoroanilina
606	2-hidroximetilanilina	614	2-fluoro-5-metilanilina
607	3-nitroanilina	615	3-cianoanilina
608	4-trifluorometilanilina	616	Isoamilamina
609	3-cloroanilina	617	2-cloroanilina

TABLA 24



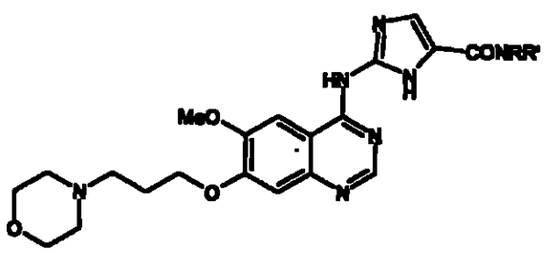
No.	NRR'
618	Anilina
619	4-fluoroanilina
620	3-hidroxianilina
621	3-(metiltio)anilina

622 4-fluoro-3-cloroanilina

623 2,4-difluorobencilamina

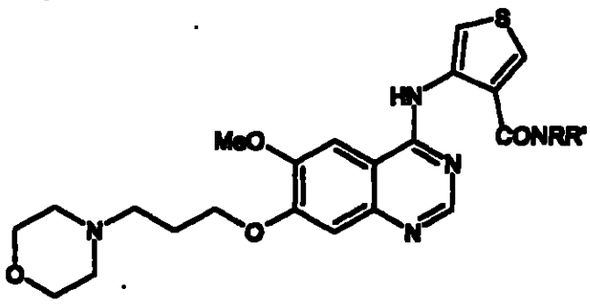
624 3-fluoroanilina

TABLA 25



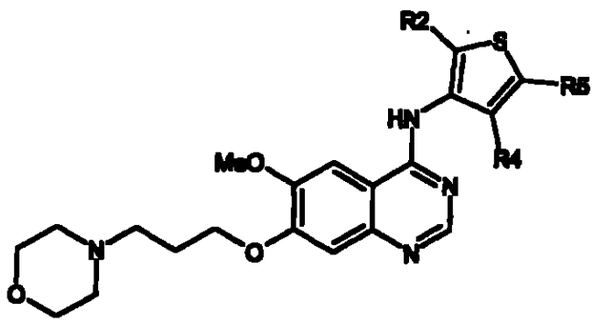
No.	NRR'
625	Anilina
626	4-fluoroanilina
627	Alilamina

TABLA 26



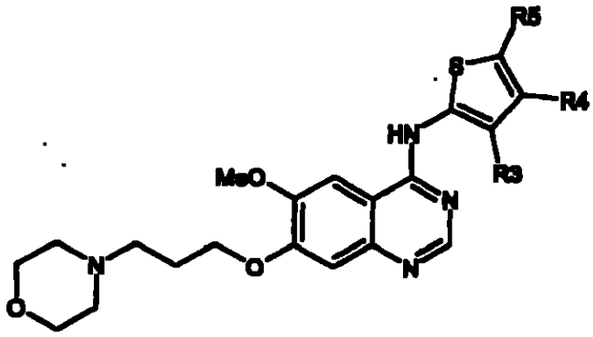
No.	NRR'
628	Anilina
629	Alilamina

TABLA 27



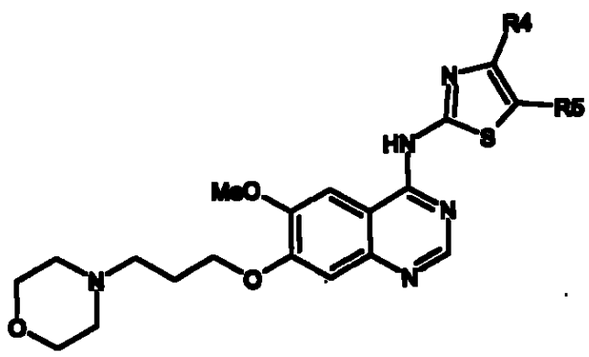
No.	R_2	R_4	R_5
630	COOMe	H	H

TABLA 28



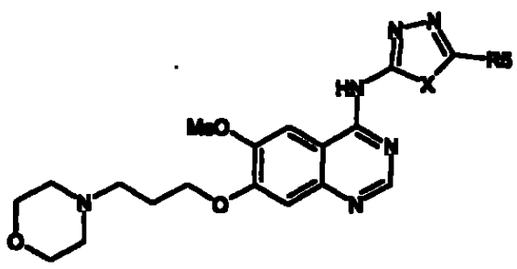
No.	R_2	R_4	R_5
631	CONH2	H	Isopropilo
632	H	H	COO alilo
633	CONH2	H	H
634	CONH2	H	etilo

TABLA 29



	R4	R5
635	Ph	H
636	Me	COCH3
637	CF3	COOEt
638	Ph	
639	-(CH2)4-	
640	4-acetilaminofenilo	H
641	CF3	Ph
642	CF3	H
643	tert-butilo	H
644	Me	Me
645	Me H	H
646	Me -C(=N-OH)-Me	-C(=N-OH)-Me
647	H	-NHCOO-tert-butilo
648	Me	-C(=NOMe)-Me
649	Me	-C(=NOPh)-Me
650	H	4-metoxifenilo
651	H	Ph
652	H	Et
653	H	Isopropilo
654	H	-CH2Ph
655	H	Me
657	H	n-butilo
658	H	CHO
659	H	-CH=N-OH

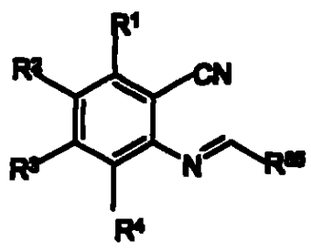
TABLA 30



	X	R5
660	S	tert-butilo
661	S	Ciclopropilo
662	S	-S-CH2-CH3
662	S	-Ph
664	NH	-NH-Ph

Otros compuestos de Fórmula (I) o Fórmula (IA), en particular aquellos en los cuales R^5 lleva un sustituyente de éster carboxi o carboxilo se describen más adelante en los Ejemplos.

Compuestos de la Fórmula (I) o Fórmula (IA) pueden preparase por varios métodos que serán evidentes de la literatura. Por ejemplo, compuestos de fórmula (I) donde X es NH pueden prepararse haciendo reaccionar un compuesto de fórmula (VII).



(VII)

en donde R^1, R^1, R^3 y R^4 son como se definen en relación con la fórmula (I) y R^{85} es un grupo $NR^{86}R^{87}$ en donde R^{86} y R^{87} se seleccionan independientemente de alquilo tal como metilo, con un compuesto de

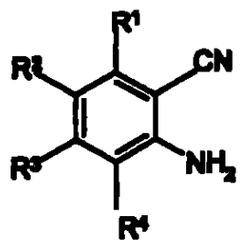
fórmula (VIII).

$$H_2N\text{-}R^{5'} \qquad \text{(VIII)}$$

en donde $R^{5'}$ es un grupo R^5 como se define en relación con la fórmula (I) o un grupo precursor del mismo; y, a partir de entonces, si se desea o es necesario, convirtiendo un grupo precursor $R^{5'}$ en un grupo R^5 y/o modificando sustituyentes en el grupo R^5. La reacción se efectúa apropiadamente en un solvente orgánico tal como un ácido acético a temperatura elevada, convenientemente a la temperatura de reflujo del solvente.

Ejemplos de reacciones en las cuales el grupo precursor $R^{5'}$ se convierte en un grupo R^5 y/o se modifican sustituyentes en el grupo R^5 son reacciones químicas estándar, tales como conversión de ésteres en ácidos y, a partir de entonces, si se requiere, en las amidas preferidas. Ejemplos de dichas reacciones se proporcionan más adelante.

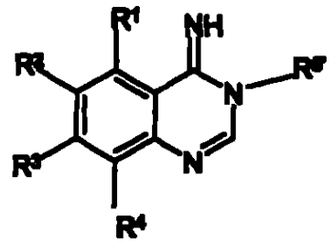
Compuestos de fórmula (VII) se preparan apropiadamente haciendo reaccionar un compuesto de fórmula (IX)



(IX)

con un acetal adecuado tal como dimetil acetal de N,N-dimetilformamida. La reacción se efectúa apropiadamente en un solvente orgánico tal como benceno, a temperatura elevada, convenientemente a la temperatura de reflujo del solvente.

Alternativamente, compuestos de fórmula (I) donde X es NH pueden prepararse re-arreglando un compuesto de fórmula (X).

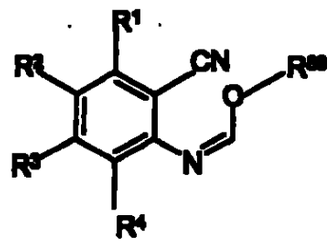


(X)

en donde R^1, R^1, R^3 y R^4 son como se definen en relación con la fórmula (I) y $R^{5'}$ es como se define en relación con fórmula (VIII) más arriba, y a partir de entonces, si se desea o es necesario, convirtiendo un grupo precursor $R^{5'}$ en un grupo R^5 y/o modificando sustituyentes en el grupo R^5, por ejemplo, como se describe generalmente más arriba.

La reacción de re-arreglo se efectúa apropiadamente en un solvente orgánico tal como un alcohol alquílico, en particular, metanol, etanol o ciclohexanol, ácido acético, o dimetilformamida, utilizando una base fuerte tal como hidróxido de sodio, acetato de sodio, metilato de sodio, o dimetilamina. Se emplean temperaturas elevadas, por ejemplo, de desde 20° C – 120° C y, preferiblemente, a alrededor de 75° C.

Compuestos de fórmula (X) se obtienen apropiadamente haciendo reaccionar un compuesto de fórmula (XI)



(XI)

en donde R^1, R^1, R^3 y R^4 son como se definen en relación con la fórmula (I) y R^{86} es un grupo alquilo tal como metilo; con un compuesto de fórmula (XII)

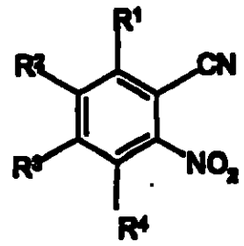
$$H_2N\text{-}R^{5'}$$

(XII)

en donde $R^{5'}$ es como se define en relación con la fórmula (VIII). La reacción se efectúa apropiadamente en un solvente orgánico tal como cloruro de metileno, en la presencia de una sal tal como clorhidrato de piridinio. Se emplean temperaturas moderadas, por ejemplo, de desde 0° - 50° C y, convenientemente, temperatura ambiente.

Compuestos de fórmula (XI) se preparan apropiadamente haciendo reaccionar un compuesto de fórmula (IX), como se define más arriba, con un trialquilortoformato tal como trimetilortoformato. La reacción se efectúa apropiadamente a temperatura elevada, por ejemplo, de desde 50° C hasta 120° C y, preferiblemente, a alrededor de 100° C, en la presencia de una cantidad catalítica de un ácido tal como ácido p-tolueno sulfónico.

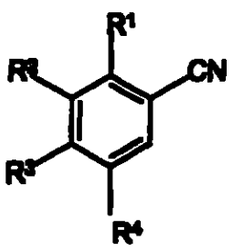
Compuestos de fórmula (IX) son compuestos conocidos o pueden preparase por métodos convencionales. En particular, compuestos de fórmula (IX) pueden prepararse por reducción del correspondiente compuesto nitro de fórmula (XIII)



(XIII)

en donde R^1, R^1, R^3 y R^4 son como se definen en relación con la fórmula (I). Condiciones apropiadas de reacción se ilustran a partir de aquí.

Compuestos de fórmula (XIII) se obtienen apropiadamente por nitración de un compuesto de fórmula (XIV)



(XIV)

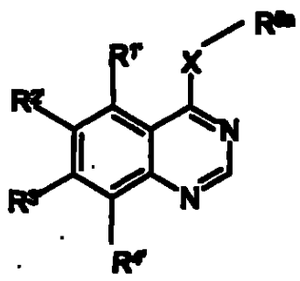
por ejemplo, usando ácido nítrico como agente nitrante. Nuevamente, condiciones de reacción apropiadas se ilustran más adelante.

El nitrilo de fórmula (XIV) se puede derivarse por reacción de la correspondiente formamida con hidroxilamina como se ilustra más adelante.

Compuestos de fórmula (I) y fórmula (IA) son inhibidores de aurora 2 cinasa. Como resultado, estos compuestos pueden usarse para tratar enfermedad mediada por estos agentes, en particular enfermedad proliferativa.

De acuerdo con un aspecto más de la presente invención se provee un método para inhibir la aurora 2 cinasa en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento, el cual comprende administrar a dicho animal una cantidad efectiva de un compuesto de Fórmula (I) o Fórmula (IA), o una sal farmacéuticamente aceptable, o un éster hidrolizable *in vivo* de la misma.

Ciertos compuestos de fórmula (I) son novedosos y éstos forman un aspecto más de la invención. Por consiguiente la invención comprende además un compuesto de fórmula (IA)



(IA)

o una sal, éster o amida de la misma;
donde X es como se define en relación con fórmula (I);
$R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ son equivalentes a R^1, R^2, R^3, R^4 como se definen en relación con fórmula (I) y R^{5a} es un anillo heteroaromático opcionalmente sustituido de 5 miembros, con sujeción a las siguientes condiciones: (i) que donde R^{5a} es un grupo pirazol, lleva un sustituyente de fórmula (k), (II) de

(VI) arriba,

(ii) que donde X es NH y R^{5a} es un grupo tetrazoilo o pirazolana sustituido, por lo menos uno de

$R^{1'}$, $R^{2'}$, $R^{3'}$ y $R^{4'}$ es distinto de hidrógeno;

(iii) que donde X es O y R^{5a} es 1-metil-4-nitro-1H-imidazol-5-ilo, por lo menos uno de $R^{1'}$, $R^{2'}$, $R^{3'}$ y $R^{4'}$ es distinto de hidrógeno.

Preferiblemente por lo menos uno de $R^{1'}$, $R^{2'}$, $R^{3'}$ y $R^{4'}$ es distinto de hidrógeno.

Convenientemente R^{5a} se selecciona de los grupos de las sub-fórmulas (a)-(j) como se expuso más arriba.

Preferiblemente R^{5a} es pirrol, imidazol, triazol, tiazol, tiofeno, o tiadiazol, cualquiera de los cuales puede ser opcionalmente sustituido.

En particular, R^{5a} se sustituye con por lo menos un grupo de fórmula (k), (II) de (VI) arriba.

Otros grupos preferidos o particulares y sustituyentes en fórmula (IA) son como se expone para los grupos equivalentes en fórmula (I) más arriba.

De acuerdo con un aspecto más de la invención se provee un compuesto de la fórmula (IA) como se define aquí, o una sal farmacéuticamente aceptable o un éster hidrolizable *in vivo* de la misma, para uso en un método de tratamiento del organismo humano o animal mediante terapia. En particular, los compuestos se usan en métodos de tratamiento de enfermedad proliferativa tal como cáncer y, en particular, tipos de cáncer tales como cáncer colo-rectal o de mama donde aurora 2 está regulada ascendentemente.

La invención provee además una composición farmacéutica que comprende un compuesto de fórmula (IA) como se define aquí, o una sal farmacéuticamente aceptable, o éster hidrolizable *in vivo* de la misma, en combinación con un portador farmacéuticamente aceptable. Compuestos preferidos o particulares de fórmula (IA) para uso en las composiciones de la invención son como se describen más arriba en relación con compuestos preferidos de fórmula (I).

Las composiciones de la invención pueden estar en una forma apropiada para uso oral (por ejemplo como tabletas, pastillas, cápsulas duras o blandas, suspensiones acuosas u oleosas, emulsiones, polvos con capacidad de dispersión o gránulos, jarabes y elíxires), para uso tópico (por ejemplo como cremas, ungüentos, geles, o soluciones acuosas u oleosas o suspensiones), para administración por inhalación (por ejemplo como un polvo finamente dividido o un aerosol líquido), para administración por insuflación (por ejemplo como un polvo finamente dividido) o para administración parenteral (por ejemplo como una solución acuosa u oleosa estéril para dosificación intravenosa, subcutánea, intramuscular o intramuscular (sic) o como un supositorio para dosificación rectal).

Las composiciones de la invención pueden obtenerse por procedimientos convencionales utilizando excipientes farmacéuticos convencionales, bien conocidos en el arte. Por lo tanto, las composiciones previstas para uso oral pueden contener, por ejemplo, uno o más agentes colorantes, endulzantes, saborizantes y/o preservantes.

Excipientes farmacéuticamente aceptables apropiados para una formulación de tableta incluyen, por ejemplo, diluyentes inertes tales como lactosa, carbonato de sodio, fosfato de calcio o carbonato de calcio, agentes granulantes y desintegrantes tales como almidón de maíz o ácido algénico; agentes aglutinantes tales como almidón; agentes lubricantes tales como estearato de magnesio, ácido esteárico o talco; agentes preservantes tales como etil o propil g-hidroxibenzoato, y anti-oxidantes, tales como ácido ascórbico. Formulaciones de tableta pueden ser recubiertas o no recubiertas bien para modificar su desintegración y la subsiguiente absorción del ingrediente activo en el tracto gastrointestinal, o bien para mejorar su estabilidad y/o apariencia, en cualquiera de los dos casos, usando agentes de recubrimiento convencionales y procedimientos bien conocidos en el arte.

Composiciones para uso oral pueden ser en la forma de cápsulas de gelatina duras en las cuales el ingrediente activo se mezcla con un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolín, o como cápsulas de gelatina blandas en las cuales el ingrediente activo se

mezcla con agua en un aceite tal como aceite de maní, parafina líquida, o aceite de oliva.

Suspensiones acuosas generalmente contienen el ingrediente activo en forma finamente pulverizada junto con uno o más agentes de suspensión, tales como carboximetilcelulosa de sodio, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinil-pirrolidona, goma tragacanto y goma acacia; agente dispersantes o humectantes tales como lecitina o productos de condensación de un óxido de alquileno con ácidos grasos (por ejemplo, estearato de polioxietileno), o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como monooleato de polioxietilen sorbitol, o productos de condensación de óxido de etileno con alcoholes alifáticos de cadena larga, por ejemplo heptadecaetilenoxicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como monooleato de polioxietilen sorbitol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo monooleato de polioxietilen sorbitana. Las suspensiones acuosas pueden contener igualmente uno o más preservantes (tales como g-hidroxibenzoato de etilo o propilo, anti-oxidantes (tales como ácido ascórbico), agentes colorantes, agentes saborizantes, y/o agentes endulzantes (tales como sucrosa, sacarina o aspartame).

Suspensiones oleosas pueden formularse suspendiendo el ingrediente activo en un aceite vegetal (tal como aceite de maní, aceite de oliva, aceite de sésamo o aceite de coco) o en un aceite mineral (tal como parafina líquida). Las suspensiones oleosas pueden contener asimismo un agente espesante tal como cera de abejas, parafina dura o alcohol cetílico. Agentes endulzantes tales como los expuestos más arriba, y agentes saborizantes, pueden agregarse para proporcionar una preparación oral sabrosa. Estas composiciones pueden preservarse mediante la adición de un anti-oxidante

tal como ácido ascórbico.

Polvos con capacidad de dispersión y gránulos apropiados para preparación de una suspensión acuosa mediante la adición de agua contienen generalmente el ingrediente activo junto con un agente dispersante o humectante, agente de suspensión o uno o más preservantes. Agentes dispersantes o humectantes apropiados y agentes de suspensión se ejemplifican por aquellos ya mencionados arriba. También pueden estar presentes excipientes adicionales tales como agentes endulzantes, saborizantes y colorantes.

Las composiciones farmacéuticaas de la invención pueden estar igualmente en la forma de emulsiones aceite-en-agua. La fase oleosa puede ser un aceite vegetal, tal como aceite de oliva o aceite de maní, o un aceite mineral, tal como por ejemplo parafina líquida o una mezcla de cualquiera de éstos. Agentes emulsificantes apropiados pueden ser, por ejemplo, gomas de ocurrencia natural tales como goma acacia o goma tragacanto, fosfátidos de ocurrencia natural tales como soya, lecitina, ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol (por ejempl monooleato de sorbitana) y productos de condensación de los dichos ésteres parciales con óxido de etileno tal como monooleato de polioxietilen sorbitana. Las emulsiones pueden contener asimismo agentes endulzantes, saborizantes y preservantes.

Jarabes y elíxires pueden formularse con agentes endulzantes tales como glicerol, propilen glicol, sorbitol, aspartame o sucrosa, y pueden contener además un agente demulcente, preservante, saborizante y/o colorante.

Las composiciones farmacéuticas pueden estar asimismo en la forma de una suspensión estéril inyectable, acuosa u oleosa, la cual puede formularse de acuerdo con procedimientos conocidos utilizando uno o más de los agentes dispersantes, humectantes o de suspensión apropiados, los cuales ya se han mencionado más arriba. Una preparación estéril inyectable puede ser igualmente una solución estéril inyectable o suspensión en un diluyente o solvente no tóxico parenteralmente aceptable, por ejemplo una

solución en 1,3-butanodiol.

Formulaciones en supositorio pueden prepararse mezclando el ingrediente activo con un excipiente no irritante que sea sólido a temperaturas ordinarias pero líquido a la temperatura rectal y, por lo tanto, se derretirá en el recto para liberar la droga. Excipientes apropiados incluyen, por ejemplo, manteca de cacao y polietilen glicoles.

Formulaciones tópicas, tales como cremas, ungüentos, geles y soluciones acuosas u oleosas o suspensiones, pueden obtenerse generalmente formulando un ingrediente activo con un vehículo o diluyente convencional, tópicamente aceptable, usando un procedimiento convencional bien conocido en el arte.

Composiciones para administración por insuflación pueden estar en la forma de un polvo finamente dividido que contenga partículas de diámetro promedio de, por ejemplo, 30μ o mucho menos, comprendiendo el polvo mismo el ingrediente activo solo o diluido con uno o más portadores fisiológicamente aceptables tales como lactosa. El polvo para insuflación se aloja entonces convenientemente en una cápsula que contenga, por ejemplo, 1 a 50 mg de ingrediente activo para uso con un dispositivo turbo-inhalador, tal como se utiliza para insuflación del conocido agente cromoglicato de sodio.

Composiciones para administración por inhalación pueden estar en la forma de un aerosol convencional presurizado arreglado para dispensar el ingrediente activo o como un aerosol que contenga un sólido finamente dividido o gotitas líquidas. Pueden emplearse propulsores de aerosol convencionales tales como hidrocarburos fluorinados volátiles o hidrocarburos, y el dispositivo aerosol se arregla convenientemente para dispensar una cantidad medida de ingrediente activo.

Para mayor información sobre Formulación se remite al lector al Capítulo 25.2 en el volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

La cantidad de ingrediente activo que se combina con uno o más excipientes para producir una forma de dosis única variará necesariamente

en función del anfitrión tratado y de la ruta particular de administración. Por ejemplo, una formulación prevista para administración oral a humanos contendrá por lo general, por ejemplo, desde 0.5 mg a 2 g agente activo compuesto con una cantidad apropiada y conveniente de excipientes que pueden variar desde alrededor de 5 a alrededor de 98 por ciento en peso de la composición total. Formas unitarias de dosificación contendrán generalmente alrededor de 1 mg a alrededor de 500 mg de un ingrediente activo. Para mayor información sobre Rutas de Administración y Regímenes de Dosificación se remite al lector al Capítulo 25.3 en volumen 5 de Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

El tamaño de la dosis para efectos terapéuticos o profilácticos de un compuesto de la Fórmula I puede variar naturalmente de acuerdo con la índole y severidad de las condiciones, la edad y sexo del animal o paciente y la ruta de administración, de acuerdo con principios de medicina bien conocidos. Como ya se mencionó más arriba, compuestos de la Fórmula I son útiles en tratar enfermedades o condiciones médicas que se deben solas o en parte a los efectos de aurora 2 cinasa.

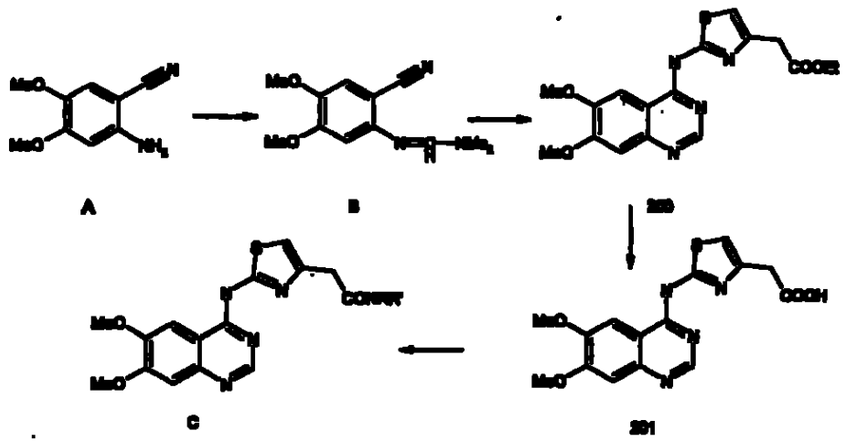
Si se emplea un compuesto de la Fórmula I para efectos terapéuticos o profilácticos se administrará por lo general de modo que se reciba una dosis diaria en el rango de, por ejemplo, 0.5 mg a 75 mg por kg de peso corporal, dada si se requiere en dosis divididas. En general, se administrarán dosis inferiores cuando se emplee una ruta parenteral. Así, por ejemplo, para administración intravenosa, se utilizará generalmente una dosis en el rango, por ejemplo, 0.5 mg a 30 mg por kg de peso corporal. Análogamente, para administración por inhalación, se usará una dosis en el rango, por ejemplo, de 0.5 mg a 25 mg por kg de peso corporal. N obstante, se prefiere la administración oral.

Un aspecto más de la invención comprende un compuesto de fórmula (I) o Fórmula (IA) como se definió más arriba, o una sal farmacéuticamente aceptable o éster hidrolizable *in vivo* de la misma, para uso en la preparación de un medicamento para el tratamiento de enfermedad

proliferativa. Compuestos preferidos de fórmula (I) o Fórmula (IA) para esta finalidad son como descritos más arriba.

Los siguientes Ejemplos ilustran la invención.

Esquema General 1



Compuesto B

El amino nitrilo A (534 mg, 3 mmol) en benceno (15 ml) se hizo reaccionar con dimetil acetal de N,N-dimetilformamida (535 mg, 4.5 mmol) a 90°C, en un matraz equipado Dean Stark. Después de 4.5 horas de reflujo, se concentró la solución, y el aceite residual se trituró con éter para producir el compuesto del título como un sólido (680 mg, 90 %).

^{1}HNMR ($CDCl_3$): 3.08 (s, 6H); 3.86 (s, 3H); 3.91 (s, 3H); 6.48 (s, 1H); 6.94 (s, 1H); 7.58 (s, 1H).

MS ES^+ : 234 $(M^+H)^+$

Compuesto 200

Una mezcla de amidina B (1.4 g, 6 mmol), 2-amimo-4-tiazolacetato de etilo (1.4 g, 7.5 mmol) en ácido acético (14 ml) se calentó a 130°C durante 3 horas. El solvente se retiró bajo vacío, el residuo se trituró en etanol (5 ml) y una solución de $NaHCO_3$ (pH 8) durante 10 minutos. El sólido se recuperó por filtración, se lavó con agua, se disolvió en CH_2Cl_2, y se secó

sobre $MgSO_4$. Se evaporó el CH_2Cl_2, el aceite residual se trató con éter y pet. éter para producir el compuesto del título (1.8 g, 80 %).
^{1}HNMR (DMSO-d_6): 1.2 (t, 3H); 3.74 (s, 2H); 3.95 (s, 6H); 4.1 (q, 2H); 7.02 (s, 1H); 7.26 (s, 1H); 8.14 (s, 1H); 8.68 (s, 1H).

Compuesto 201

Éster 200 (1.8 g, 4.8 mmol) se hizo reaccionar con 2N NaOH (4.8 ml, 9.6 mmol) en etanol (20 ml) a temperatura ambiente durante 2 horas. La mezcla se enfrió a temperatura ambiente, se acidificó con EtOH, HCl (2N) a pH 3. Se realizó agitación durante 15 minutos, y se recuperó por filtración un compuesto amarillo del título (1.7 g, 100 %).
^{1}HNMR (DMSO-d_6): 3.71 (s, 2H); 3.96 (s, 3H); 3.97 (s, 3H); 7.11 (s, 1H); 7.28 (s, 1H); 8.3 (brs, 1H); 8.88 (s, 1H).

Síntesis de amida 5, procedimiento general

El ácido 201 (86.5 mg, 0.25 mmol) en DlvlF (1 ml) se hizo reaccionar con diferentes aminas (2.6 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1il) N,N,N',N',-tetrametiluronio (98 mg, 0.26 mmol), DIEA (33 mg, 0.26 mmol) a temperatura ambiente durante 0.5 hora. A la mezcla se añadió una solución de $NaHCO_3$ (1 ml) y agua (7 ml). La mezcla se dejó de un día para otro, y el sólido precipitaado se recuper+o entonces por filtración, se lavó con agua y se secó bajo vacío en presencia de P_2O_5, para producir compuestos de fórmula C como se enumera más adelante.

Ejemplo 1.

Usando la reacción descrita en el Esquema General 1, comenzando con 4-aminometil piridina (27 mg, 0.25 mmol) se produjo Compuesto No. 1 en Tabla 1 (50 mg, 46 %).
^{1}HNMR (DMSO-d_6): 3.64 (s, 2H); 3.95 (s, 3H); 3.96 (s, 3H); 4.32 (d, 2H); 6.98 (s, 1H); 7.26 (m, 3H); 8.15 (s, 1H); 8.49 (m, 3H); 8.68 (s, 1H).

Ejemplo 2.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con morfolina (23 mg, 0.26 mmol) produjo Compuesto No 2 en Tabla 1 (70 mg, 67 %).

^{1}HNMR (DMSO-d_6, TFA): 3.55 (br m, 8H); 3.88 (s, 2H); 3.97 (s, 3H); 4.0 (s, 3H); 7.15 (s, 1H); 7.27 (s, 1H); 7.92 (s, 1H); 9.07 (s, 1H).

Ejemplo 3

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 4-fluoroanilina (29 mg, 0.26 mmol) produjo el Compuesto No. 3 en Tabla 1 (75 mg, 68 %).

^{1}HNMR (DMSO-d_6): 3.74 (s, 2H); 3.93 (s, 6H); 7.00 (s, 1H); 7.15 (t, 2H); 7.25 (s, 1H); 7.64 (m, 2H); 8.12 (s, 1H); 8.67 (s, 1H); 10.20 (s, 1H).

MS ES$^+$: 440 $(M_+H)^+$

Ejemplo 4.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con N,N-dimetil-1,4-fenilendiamina (35 mg, 0.26 mmol) produjo Compuesto 4 en Tabla 1 (65 mg, 56 %).

^{1}HNMR (DMSO-d_6, TFA): 3.2 (s, 6H); 3.9 (s, 2H); 3.97 (s, 3H); 4.0 (s, 3H); 7.27 (s, 1H); 7.3 (s, 1H); 7.65 (d, 2H); 7.8 (d, 2H); 7.99 (s, 1H).

MS ES$^+$: 465 $(M_+H)^+$

Ejemplo 5.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 4-metoxi-anilina (32 mg, 0.26 mmol) produjo Compuesto 5 en Tabla 1 (80 mg, 71 %).

^{1}HNMR (DMSO-d_6): 3.71 (s, 5H); 3.93 (s, 3H); 3.94 (s, 3R); 6.88 (d, 2H); 6.99 (s, 1H); 7.25 (s, 1H); 7.53 (d, 2H); 8.13 (s, 1H); 8.67 (s, 1H); 9.99 (s, 1H).

MS ES$^+$: 452 $(M_+H)^+$

Ejemplo 6.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con5-metoxi-2-metilanilina (36 mg, 0.26 mmol) produjo Compuesto 6 en Tabla 1 (87 mg, 75 %).

^{1}HNMR (DMSO-d_6): 2.13 (s, 3H); 3.69 (s, 3H); 3.81 (s, 2H); 3.96 (s, 6H); 6.65 (m, 1H); 7.05 (m, 1H); *7.09* (d, 1H); 7.21 (s, 1H); 7.26 (s, 1H); 8.13 (s, 1H); 8.68 (s, 1H); 9.3 (s, 1H).

MS ES$^+$: 466 $(M_+H)^+$

Ejemplo 7.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con dimetil acetal de aminoacetaldehído (27 mg, 0.26 mmol) produjo Compuesto 7 en Tabla 1 (80 mg, 74 %).

^{1}HNMR (DMSO-d_6): 3.2 (t, 2H); 3.29 (s, 3H); 3.31 (s, 3H); 3.55 (s, 2H); 3.94 (s, 6H); 4.37 (t, 1H); 6.92 (s, 1H); 7.26 (s, 1H); 8.02 (t, 1H); 8.14 (s, 1H); 8.67 (s, 1H).

MS ES$^+$: 434 $(M_+H)^+$

Ejemplo 8.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 3-trifluorometilanilina (42 mg, 0.26 mmol) produjo Compuesto 8 en Tabla 1 (72 mg, 59 %).

^{1}HNMR (DMSO-d_6): 3.80 (s, 2H); 3.93 *(s,* 3H); 3.94 (s, 3H); 7.04 (s, 1H); 7.26 (s, 1H); 7.41 (d, 1H); 7.55 (t, 1H); 7.81 (d, 1H); 8.13 (s, 1H); 8.69 (s, 1H); 10.50 (s, 1H).

MS ES$^+$: 490 $(M_+H)^+$

Ejemplo 9.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con N-metilpiperazina (26 mg, 0.26 mmol) produjo Compuesto 9 en Tabla 1 (65 mg, 61 %).

^{1}HNMR (DMSO-d_6): 2.73 y 2.77 (dos t, 4H); 2.86 y 3.10 (dos s, 3H); 3.56

469

y 3.74 (dos t, 4H); 3.79 y 3.84 (dos s, 2H); 3.95 (s, 6H); 6.95 (m, 1H); 7.26 (s, 1H); 8.14 (s, 1H); 8.68 (s, 1H).

MS ES^+: 429 $(M+H)^+$

Ejemplo 10.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 2-metoxietilamina (20 mg, 0.26 mmol) produjo Compuesto 10 en Tabla 1 (68 mg, 67 %).

^{1}HNMR (DMSO-d_6): 3.25 (s, 3H); 3.3 (m, 6H); 3.54 (s, 2H); 3.94 (s, 6B); 6.92 (s, 1H); 7.26 (s, 1H); 8.0 (t, 1H); 8.14 (s, 1H); 8.67 (s, 1H).

MS ES^+: 404 $(M+H)^+$

Ejemplo 11.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 2-(2-aminoetil)-N-metilpirrol (32 mg, 0.26 mmol) produjo Compuesto 11 en Tabla 1 (93 mg, 82 %).

^{1}HNMR (DMSO-d_6): 3.3 (m, 4H); 3.5 (s, 2H); 3.94 (s, 6H); 5.78 (s, 1H); 5.84 (m, 1H); 6.58 (s, 1H); 6.89 (s, 1H); 7.24 (s, 1H); 8.01 (t, 1H); 8.13 (s, 1H); 8.66 (s, 1H).

MS ES^+: 453 $(M+H)^+$

Ejemplo 12.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 3-(metilamino)propionitrilo (22 mg, 0.26 mmol) produjo Compuesto 12 en Tabla 1 (60 mg, 58 %).

^{1}HNMR (DMSO-d_6): 2.15 (s, 3H); 3.45 (m, 4H); 3.77 (s, 2H); 3.96 (s, 6H); 6.91 (s, 1H); 7.25 (s, 1H); 8.14 (s, 1H); 8.67 (s, 1H).

MS ES^+: 413 $(M+H)^+$

Ejemplo 13.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 4-fluorobencilamina (33 mg, 0.26 mmol) produjo Compuesto 13 en

Tabla 1 (81 mg, 81 %).

^{1}HNMR (DMSO-d_6): 3.59 (s, 2H); 3.95 (m, 6H); 4.27 (d, 2H); 6.94 (s, 1H); 7.15 (m, 2H); 7.26 (s, 1H); 7.31 (m, 2H); 7.95 (s, 1H); 8.14 (s, 1H); 8.41 (t, 1H); 8.67 (s, 1H).

MS ES$^+$: 454 $(M_+H)^+$

Ejemplo 14.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 4-hidroxipiperidina (26 mg, 0.26 mmol) produjo Compuesto 14 en Tabla 1 (86 mg, 80 %).

^{1}HNMR (DMSO-d_6): 1.21 (m, 2H); 1.65 (m, 2H); 3.02 (m, 1H); 3.16 (m, 1H); 3.65 (m, 1H); 3.78 (m, 3H); 4.71 (d, 1H); 6.91 (s, 1H); 7.26 (s, 1H); 8.14 (s, 1H); 9.67 (s, 1H).

MS ES$^+$: 430 $(M_+H)^+$

Ejemplo 15

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 3-aminoacetofenona (35 mg, 0.26 mmol) produjo Compuesto 15 en Tabla 1 (92 mg, 79 %).

^{1}HNMR (DMSO-d_6): 2.59 (s, 3H); 3.78 (s, 2H); 3.90 (s, 3H); 3.93 (s, 3H); 7.02 (s, 1H); 7.26 (s, 1H); 7.47 (t, 1H); 7.67 (d, 1H); 7.89 (d, 1H); 8.12 (s, 1H); 8.2 (s, 1H); 8.68 (s, 1H) ; 10.36 (s, 1H).

MS ES$^+$: 464 $(M_+H)^+$

Ejemplo 16.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 3,5-difluoroanilina (34 mg, 0.26 mmol) produjo Compuesto 16 en Tabla 1 (71 mg, 64 %).

^{1}HNMR (DMSO-d_6), TFA): 3.90 (s, 2H); 3.93 (s, 3H); 3.97 (s, 3H); 6.89 (m, 1H); 7.27 (s, 1H); 7.29 (s, 1H); 7.35 (m, 2H); 7.96 (m, 1H); 9.10 (s, 1H).

MS ES$^+$: 458 $(M_+H)^+$

Ejemplo 17.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 3-cianoanilina (31 mg, 0.26 mmol) produjo Compuesto 17 en Tabla 1 (90 mg, 84 %).

MS ES^+: 447 $(M_+H)^+$

Ejemplo 18

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 2-fluoroanilina (29 mg, 0.26 mmol) produjo Compuesto 18 en Tabla 1 (86 mg, 82 %).

MS ES^+: 440 $(M_+H)^+$

Ejemplo 19.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 3-(1-hydroxietil)anilina (36 mg, 0.26 mmol) produjo Compuesto 19 en Tabla 1 (92 mg, 82 %).

MS ES^+: 466 $(M_+H)^+$

Ejemplo 20.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 2,3-difluoroanilina (34 mg, 0.26 mmol) produjo Compuesto 20 en Tabla 1 (51 mg, 47 %).

^{1}HNMR (DMSO-d_6), TFA): 3.98 (s, 3H); 4.01 (s, 3H); 4.03 (s, 2H); 7.19 (m, 2H); 7.27 (s, 1H); 7.29 (s, 1H); 7.73 (m, 1H); 7.99 (s, 1H); 9.11 (s, 1H).

MS ES^+: 458 $(M_+H)^+$

Ejemplo 21.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 2-metil-4-fluoroanilina (33 mg, 0.26 mmol) produjo Compuesto 21 en Tabla 1 (94 mg, 86 %).

MS ES^+: 454 $(M_+H)^+$

Ejemplo 22.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 2-fluoro-3-cloroanilina (38 mg, 0.26 mmol) produjo Compuesto 22 en Tabla 1 (60 mg, 53 %).

^{1}HNMR (DMSO-d_6), TFA): 3.95 (s, 3H); 3.98 (s, 3H); 4.01 (s, 2H); 7.20 (m, 1H); 7.24 (s, 1H); 7.26 (s, 1H); 7.31 (m, 1H); 7.88 (m, 1H); 7.96 (s, 1H); 9.08 (s, 1H).

MS ES$^+$: 474 $(M+H)^+$

Ejemplo 23.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 2,5-difluoroanilina (34 mg, 0.26 mmol) produjo Compuesto 23 en Tabla 1 (52 mg, 48 %).

^{1}HNMR (DMSO-d_6), TFA): 3.97 (s, 3H); 4.00 (s, 2H); 4.01 (s, 3H); 6.97 (m, 1H); 7.26 (s, 1H); 7.29 (s, 1H); 7.33 (m, 1H); 7.94 (m, 1H); 7.98 (s, 1H); 9.11 (s, 1H). MS ES$^+$: 458 $(M+H)^+$

Ejemplo 24.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 3-aminobenzamida (36 mg, 0.26 mmol) produjo Compuesto 24 en Tabla 1 (94 mg, 4 %).

MS ES$^+$: 465 $(M+H)^+$

Ejemplo 25.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 4-aminofenol (29 mg, 0.26 mmol) produjo Compuesto 25 en Tabla 1 (89 mg, 84 %).

^{1}HNMR (DMSO-d_6), TFA): 3.81 (s, 2H); 3.97 (s, 3H); 4.00 (s, 3H); 6.71 (d, 2H); 7.23 (s, 1H); 7.27 (s, 1H); 7.40 (d, 2H); 7.95 (s, 1H); 9.09 (s, 1H).

MS ES$^+$: 438 $(M+H)^+$

Ejemplo 26.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 2-fluoro-5-metilanilina (33 mg, 0.26 mmol) produjo Compuesto 26 en Tabla 1 (88 mg, 81 %).

MS ES^+: 454 $(M+H)^+$

Ejemplo 27.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 2-bromo-4-fluoroanilina (50 mg, 0.26 mmol) produjo Compuesto 27 en Tabla 1 (68 mg, 55 %).

^{1}HNMR (DMSO-d_6, TFA): 3.89 (s, 2H); 3.94 (s, 3H); 3.97 (s, 3H); 7.21 (m, 1H); 7.25 (s, 1H); 7.6 (s, 1H); 7.61 (m, 1H); 7.92 (m, 1H); 7.95 (s, 1H); 9.07 (s, 1H).

MS ES^+: 518, 520 $(M+H)^+$

Ejemplo 28.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 3,4-difluoroanilina (34 mg, 0.26 mmol) produjo Compuesto 28 en Tabla 1 (81 mg, 74 %).

MS ES^+: 458 $(M+H)^+$

Ejemplo 29.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con isonipecotamida (34 mg, 0.26 mmol) produjo Compuesto 29 en Tabla 1 (96 mg, 88 %).

MS ES^+: 457 $(M+H)^+$

Ejemplo 30.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 4-trifluorometoxianilina (47 mg, 0.26 mmol) produjo Compuesto 30 en Tabla 1 (105 mg, 87 %).

MS ES^+: 506 $(M+H)^+$

Ejemplo 31.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 5-amino-2-metoxipiridina (33 mg, 0.26 mmol) produjo Compuesto 31 en Tabla 1 (86 mg, 79 %).

MS ES^+: 453 $(M_+ H)^+$

Ejemplo 32.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 2,4-difluoroanilina (34 mg, 0.26 mmol) produjo Compuesto 32 en Tabla 1 (81 mg, 74 %).

MS ES^+: 458 $(M_+H)^+$

Ejemplo 33.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con clorhidrato de 4-aminoresorcinol (43 mg, 0.26 mmol) produjo Compuesto 33 en Tabla 1 (84 mg, 77 %).

MS ES^+: 454 $(M_+H)^+$

Ejemplo 34.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 3-aminopiridina (25 mg, 0.26 mmol) produjo Compuesto 34 en Tabla 1 (101 mg, 100 %).

MS ES^+: 423 $(M_+H)^+$

Ejemplo 35.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 4-cloroanilina (34 mg, 0.26 mmol) produjo Compuesto 35 en Tabla 1 (109 mg, 100 %).

MS ES+: 423 (M+H)+.

Ejemplo 36.

Una reacción análoga a la descrita en el Esquema General 1, comenzando

con pirrolidina (19 mg, 0.26 mmol) produjo Compuesto 36 en Tabla 1 (33 mg, 35 %).

MS ES^+: 400 $(M_+H)^+$

Ejemplo 37.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 3-metoxianilina (33 mg, 0.26 mmol) produjo Compuesto 36 en Tabla 1 (94 mg, 87 %).

^{1}HNMR (DMSO-d_6, TFA): 3.72 (s, 3H); 3.87 (s, 2H); 3.96 (s, 3H); 4.0 (s, 3R); 6.64 (m, 1H); 7.14 (d, 1H); 7.21 (d, 1H); 7.22 (s, 1H); 7.24 (s, 1H); 7.27 (s, 1H); 7.95 (s, 1H); 9.09 (s, 1H).

MS ES^+: 452 $(M_+H)^+$

Ejemplo 38.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 3-hidroxi-4-metoxianilina (37 mg, 0.26 mmol) produjo Compuesto 38 en Tabla 1 (95 mg, 85 %).

MS ES^+: 468 $(M_+H)^+$

Ejemplo 39.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 3-nitroanilina (36 20 mg, 0.26 mmol) produjo Compuesto 39 en Tabla 1 (87 mg, 78 %).

MS ES^+: 467 $(M_+H)^+$

Ejemplo 40.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 1-metil-3-nitroanilina (40 mg, 0.26 mmol) produjo Compuesto 40 en Tabla 1 (50 mg, 44 %).

MS ES^+: 481 $(M_+H)^+$

Ejemplo 41.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 2-anilinoetanol (36 mg, 0.26 mmol) produjo Compuesto 41 en Tabla 1 (45 mg, 41 %).

MS ES^+: 466 $(M_+H)^+$

Ejemplo 42.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 4-trifluorometilanilina (43 mg, 0.26 mmol) produjo Compuesto 42 en Tabla 1 (86 mg, 73 %).

MS ES^+: 490 $(M_+H)^+$

Ejemplo 43.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 3-amino-6-cloropiridina (33 mg, 0.26 mmol) produjo Compuesto 43 en Tabla 1 (90 mg, 82 %).

^{1}HNMR (DMSO-d_6, TFA): 3.92 (s, 2H); 3.96 (s, 3H); 4.0 (s, 3H); 7.27 (s, 1H); 7.28 (s, 1H); 7.46 (d, 1H); 7.98 (s, 1H); 8.1 (d, 1H); 8.65 (d, 1H); 9.1 (s, 1H).

MS ES^+: 457, 459 $(M_+H)^+$

Ejemplo 44.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 2-metoxi-5-cloroanilina (42 mg, 0.26 mmol) produjo Compuesto 44 en Tabla 1 (90 mg, 77 %).

MS ES^+: 486, 488 $(M_+H)^+$

Ejemplo 45.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 2-metilaminoetanol (20 mg, 0.26 mmol) produjo Compuesto 45 en Tabla 1 (83 mg, 86 %).

MS ES^+: 404 $(M_+H)^+$

Ejemplo 46.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 4-aminopiridina (25 mg, 0.26 mmol) produjo Compuesto 46 en Tabla 1(101 mg, 100 %).

MS ES^+: 423 $(M_+H)^+$

Ejemplo 47:

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 3-metil-4-bromoanilina (49 mg, 0.26 mmol) produjo Compuesto 47 en Tabla 1 (120 mg, 97 %).

MS ES^+: 516, 517 $(M_+H)^+$

Ejemplo 48:

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 2-cloro-5-metoxianilina (42 mg, 0.26 mmol) produjo Compuesto 48 en Tabla 1 (65 mg, 56 %).

^{1}HNMR (DMSO-d_6, TFA): 3.73 (s, 2H); 3.98 (m, 9H); 6.78 (m, 1H); 7.28 (s, 2H); 7.39 (d, 1H); 7.50 (d, 1H); 7.98 (s, 1H); 9.10 (s, 1H).

MS ES^+: 486,488 $(M_+H)^+$

Ejemplo 49.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con 4-aminotolueno (28 mg, 0.26 mmol) produjo Compuesto 49 en Tabla 1 (89 mg, 85 %).

MS ES^+: 436 $(M_+H)^+$

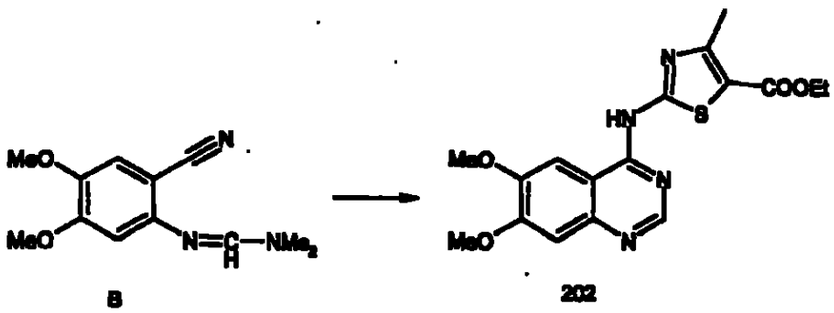
Ejemplo 50.

Una reacción análoga a la descrita en el Esquema General 1, comenzando con R(-)-2-pirrolidinmetanol (27 mg, 0.26 mmol) produjo Compuesto 50 en Tabla 1 (81 mg, 78 %).

MS ES^+: 430 $(M_+H)^+$

Ejemplo 50A.

Preparación del Compuesto 202



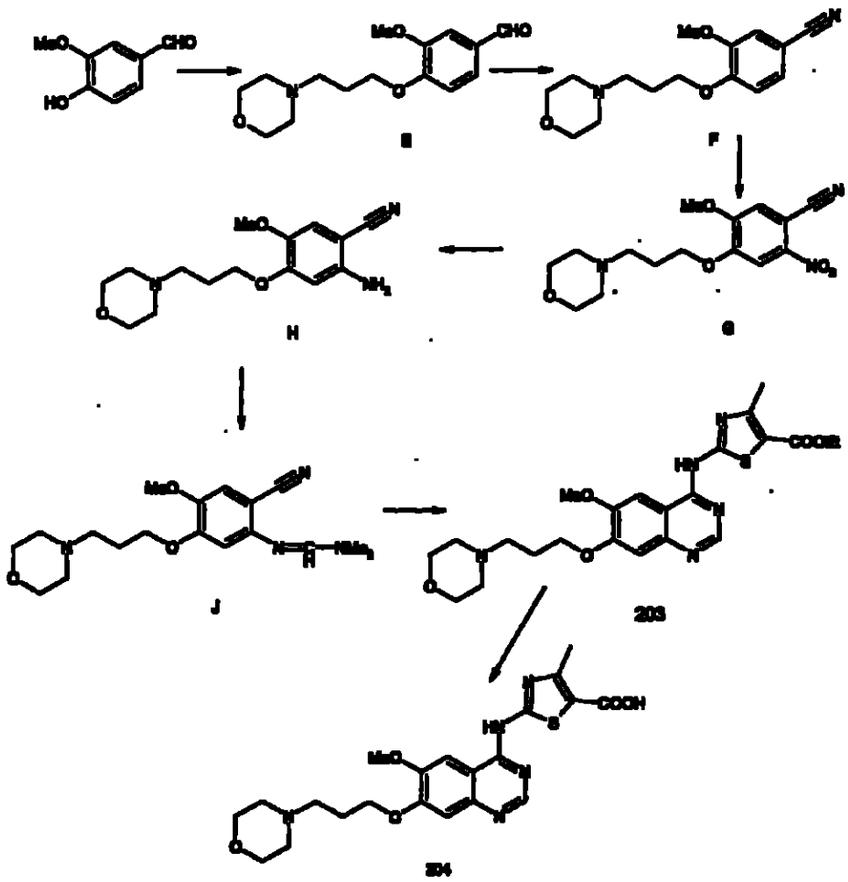
B 202

Amidina B (117 mg, 0.5 mmol) en ácido acético (12 ml) se hizo reaccionar con etil-2-amino-4-metiltiazol-5-carboxilato (112 mg, 0.6 mmol) a 130°C durante 3 horas. El solvente se evaporó, el residuo se recogió en etanol, y se agitó durante 10 minutos con una solución de $NaHCO_3$. El sólido se recuperó por filtración, se lavó con agua, éter y se secó bajo vacío, para producir el compuesto del título como un sólido amarillo (157 mg, 84 %).

^{1}HNMR (DMSO-d_6: 1.31 (t, 3H); 2.6 (s, 3H); 3.96 (s, 6H); 4.27 (q, 2H); 7.28 (s, 1H); 8.11 (s, 1H); 8.77 (s, 1H).

MS ES^+: 375 $(M+H)^+$

Esquema General 2



Compuesto E

Vanillina (30.4 g, 0.2 mol) se solubilizó en DMF (200 ml) en presencia de K_2CO_3 a 50°C. N-(3-cloropropil)morfolina se agregó lentamente durante 30 minutos a esta mezcla375, la cual se calentó de un día para otro a 80°C. El KCl formado se retiró por filtración, se evaporó el solvente, y el aceite residual de color anaranjado se disolvió en AcOEt, se lavó con agua 2 veces, se secó sobre $MgSO_4$, se filtró y concentró. El aceite residual cristaliza para producir el compuesto del título como un sólido blanco (45.6 g, 82 %).

^{1}HNMR (DMSO-d_6, TFA): 2.22 (m, 2H); 3.13 (t, 2H); 3.32 (t, 2H); 3.52 (d, 2H); 3.67 (t, 2H); 3.84 (s, 3H); 4.02 (d, 2H); 4.18 (t, 2H); 7.20 (d, 1H); 7.43 (d, 1H); 7.58 (d, 1H); 9.90 (s, 1H).

MS ES$^+$: 280 $(M_+H)^+$

480

Compuesto F

El aldehído E (5.6 g, 20 mmol) se añadió a una solución de acetato de sodio (3.3 g, 40 mmol) e clorhidrato de hidroxilamina (2.8 g, 40 mmol) en ácido acético (25 ml). La mezcla se hizo refluir durante 18 horas, se enfrió, se diluyó con agua y se extrajo con cloruro de metileno, se secó sobre $MgSO_4$, se filtró, se concentró, para producir el compuesto del título (5.1 g, 93 %).

^{1}HNMR (DMSO-d_6, TFA): 2.19 (m, 2H); 3.12 (t, 2H); 3.29 (t, 2H); 3.50 (d, 2H); 3.67 (t, 2H); 3.81 (s, 3H); 4.01 (d, 2H); 4.15 (t, 2H); 7.12 (d, 1H); 7.39 (s, 1H); 7.41 (d, 1H).

MS ES^+: 277 $(M_+H)^+$

Compuesto G

El nitrilo F (37.2 g, 135 mmol) en ácido acético(100 ml) se agregó a una solución de ácido nítrico (d = 1.42) 180 ml, a una velocidad tal para mantener la temperatura por debajo de 30°C. La mezcla se agitó a temperatura ambiente de un día para otro. A continuación se agregó lentamente una solución de hidróxido de potasio (10N, 370 ml) a la solución a 0° llevando a un pH final de 11-12. La reacción se extrajo con CH_2Cl_2, se secaron las fases orgánicas sobre $MgSO_4$, se filtró, se evaporó para producir un sólido amarillo que se lavó con éter, se secó para producir el compuesto del título (22 g, 50 %).

^{1}HNMR (DMSO-d_6, TFA): 2.2 (m, 2H); 3.13 (t, 2H); 3.3 (t, 2H); 3.53 (d, 2H); 3.67 (t, 2H); 3.99 (s, 3H); 4.01 (d, 2H); 4.31 (t, 2H); 7.74 (s, 1H); 7.90 (s, 1H).

Compuesto H

Compuesto G (21 g, 65 mmol) en solución en CH_2Cl_2 (250 ml) se hizo reaccionar con hidrosulfito de sodio (92 g, 458 mmol) en solución en agua (250 ml) en presencia de cloruro de tetrabutil amonio (12.7 g, 45.8 mmol) a temperatura ambiente, de un día para otro. Seguidamente se agregó hidróxido de sodio (2N), y la mezcla de la reacción se extrajo con CH_2Cl_2,

la fase orgánica se lavó con agua, se secó sobre $MgSO_4$, se filtró, se evaporó. El residuo se purificó por cromatografía de gel de sílice, eluyente: AcOEt / CH_2Cl_2: 50/50 seguido por MeOH / AcOEt / CH_2Cl_2 5/45/50 a 20/30/50 para producir el compuesto del título (12.5 g, 66 %).

^{1}HNMR (DMSO-d_6, TFA): 2.2 (m, 2H); 3.13 (t, 2H); 3.31 (t, 2H); 3.53 (d, 2H); 3.68 (t, 2H); 3.71 (s, 3H); 4.05 (m,4H); 6.56 (s, 1H); 7.02 (s, 1H).

MS ES$^+$: 292 $(M+H)^+$

Compuesto J

El amino nitrilo H (2.91 g, 10 mmol) en solución en tolueno (50 ml) se hizo reaccionar dimetil acetal de N,N-dimethiloformamida (1.79 g, 15 mmol), a 105°C durante 5 horas, en un matraz equipado Dean Stark. El solvente se evaporó, el residuo triturado con éter para producir el compuesto del título (3.4 g, 98 %).

^{1}HNMR (DMSO-d_6): 1.87 (m, 2H); 2.36 (m, 6H); 2.95 (s, 3H); 3.04 (s, 3H); 3.56 (t, 4H); 3.72 (s, 3H); 4.06 (t, 2H); 6.72 (s, 1H); 7.07 (s, 1H); 7.89 (s, 1H).

MS ES$^+$: 347 $(M+H)^+$

Compuesto 203

Amidina J (173 mg, 0.5 mmol) se disolvió en AcOH (1.7 ml) en presencia de etil-2-amino-4-metil tiazol-5-carboxilato (112 mg, 0.6 mmol) y de calentó a 130°C durante 3 horas. El solvente se retiró por evaporación, y el sólido residual se agitó en etanol y una solución diluida de $NaHCO_3$ durante 10 minutos. El sólido se lavó con agua, se secó sobre P_2O_5 bajo vacío, para producir un polvo amarillo del compuesto del título (170 mg, 70 %).

^{1}HNMR (DMSO-d_6, TFA): 1.32 (t, 3H); 2.30 (m, 2H); 2.68 (s, 3H); 3.16 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.99 (s, 3H); 4.03 (d, 2H); 4.32 (m, 4H); 7.38 (s, 1H); 8.01 (s, 1H); 9.26 (s, 1H).

MS ES$^+$: 488 $(M+H)^+$

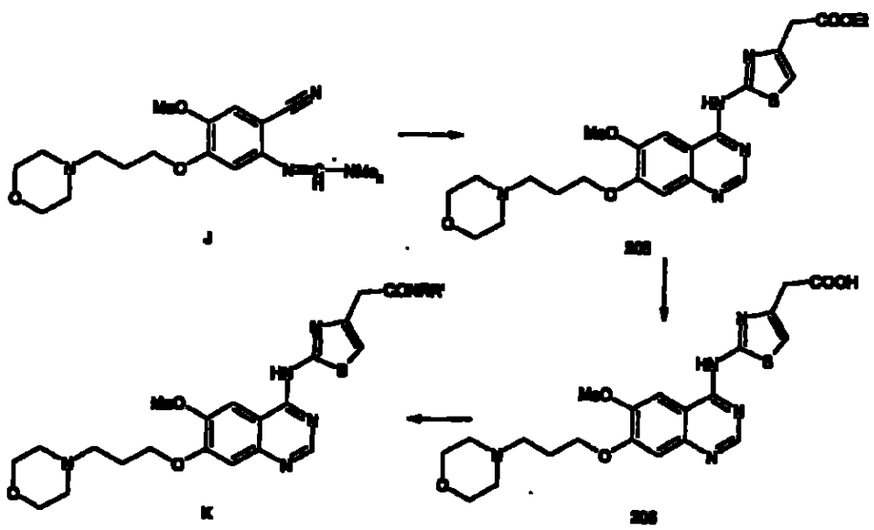
Compuesto 204

El éster **203** (122 mg, 0.25 mmol) se suspendió en etanol (5 ml) y se hizo reaccionar con hidróxido de sodio (10N, 0.5 ml) a 80°C durante 1 hora. La mezcla de la reacción se enfrió, se acidificó (pH 3.5), se filtró el precipitado amarillo, se lavó con agua, se secó bajo vacío, para producir el compuesto del título (100 mg, 87 %).

^{1}HNMR (DMSO-d_6, TFA): 2.32 (m, 2H); 2.62 (s, 3H); 3.16 (t, 2H); 3.36 (t, 2H); 3.57 (d, 2H); 3.71 (t, 2H); 3.99 (s, 3H); 4.03 (d,.2H); 4.33 (t, 2H); 7.35 (s, 1H); 7.98 (s, 1H); 9.23 (s, 1H).

MS ES$^+$: 460 $(M_+H)^+$

Esquema General 3



Compuesto 205

Amidina **J** (2.08 g, 6 mmol) se hizo reaccionar 2-amino-4-tiazolacetato de etilo (1.34 g, 7.2 mmol) en ácido acético (2 ml) a 130°C durante 4 horas, bajo argón. El solvente se evaporó, el aceite residual se trituró en éter / petr. éter, y el sólido se filtró. Este sólido se suspendió en agua a pH 9 ($NaHCO_3$) y se extrajo con CH_2Cl_2, se secó, se evaporó para producir el compuesto del título (2 g, 68 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 3.87 (s, 2H); 4.0 (s, 3H); 4.04 (d, 2H); 4.15 (q, 2H); 4.31

(t, 2H); 7.28 (s, 1H); 7.34 (s, 1H); 8.06 (s, 1H); 9.15 (s, 1H).
MS ES^+: 488 $(M+H)^+$

Compuesto 206

Éster **205** (2 g, 4.1 mmol) se suspendió en etanol (20 ml). 2N de hidróxido de sodio (4.1 ml, 8.2 mmol) se añadieron a la suspensión la cual se agitó durante 3 horas a temperatura ambiente. 2N de HCl se agregaron a la solución, el precipitado amarillo se filtró, se lavó con agua, etanol, éter y se secó bajo vacío, para producir el compuesto del título (1.98 g, 99 %).
^{1}HNMR (DMSO-d_6, TFA): 2.31 (m, 2H); 3.16 (t, 2H); 3.55 (d, 2H); 3.71 (t, 2H); 3.79 (s, 2H); 4.0 (s, 3H); 4.03 (d, 2H); 4.31 (t, 2H); 7.25 (s, 1H); 7.34 (s, 1H); 8.01 (s, 1H); 9.12 (s, 1H).
MS ES^+: 460 $(M+H)^+$

Síntesis de amidas K, procedimiento general

El ácido **206** (83 mg, 0.17 mmol) en DMF (0.8 ml) se hizo reaccionar con amina (0.17 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il) N,N,N',N'-tetrametiluronio (78 mg, 0.204 mmol), DIEA (52 mg, 0.4 mmol), durante 6 horas a temperatura ambiente. La mezcla de la reacción se trató entonces con una solución de $NaHC0_3$ (6 ml) con agitación durante 2 horas, se lavó con agua, se enfrió a 5°C, y el sólido se filtró, trituró con éter, se secó bajo vacío sobre P_2O_5 para producir compuestos del título.

Ejemplo 51.

Una reacción análoga a la descrita en Esquema General 3, comenzando con anilina (19 mg, 0.2 mmol) produjo Compuesto 51 en Tabla 2 (73 mg, 81 %).
^{1}HNMR (DMSO-d_6, TFA): 2.29 (m, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.88 (s, 2H); 3.98 (s, 3H); 4.03 (d, 2H); 4.3 (t, 2H); 7.09 (t, 1H); 7.27 (s, 1H); 7.33 (m, 3H); 7.63 (d, 2H); 7.99 (s, 1H); 9.12 (s, 1H).

MS ES^+: 535 $(M+H)^+$

Ejemplo 52.

Una reacción análoga a la descrita en Esquema General 3, comenzando con 4-fluoroanilina (23 mg, 0.2 mmol) produjo Compuesto 52 en Tabla 2 (79 mg, 84 %).

^{1}HNMR (DMSO-d_6, TFA): 2.29 (m, 2H); 3.15 (t, 2H); 3.34 (t, 2H); 3.54 (d, 2H); 3.67 (t, 2H); 3.87 (s, 2H); 3.98 (s, 3H); 4.02 (d, 2H); 4.3 (t, 2H); 7.17 (t, 2H); 7.27 (s, 1H); 7.3,2 (s, 1H); 7.63 (m, 2H); 7.99 (s, 1H); 9.11 (s, 1H).
MS ES^+: 553 $(M+H)^+$

Ejemplo 53.

A una reacción análoga a la descrita en Esquema General 3, comenzando con 4-dimetilaminoanilina (28 mg, 0.2 mmol) produjo Compuesto 53 en Tabla 2 (52 mg, 53 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.19 (s, 6H); 3.34 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.91 (s,2H); 3.98 (s, 3H); 4.03 (d, 2H); 4.30 (t, 2H); 7.28 (s, 1H); 7.33 (s, 1H); 7.64 (d, 1H); 7.77 (d, 1H); 8.01 (s, 1H); 9.12 (s, 1H). MS ES^+: 578 $(M+H)^+$

Ejemplo 54.

A una reacción análoga a la descrita en Esquema General 3, comenzando con 4-cloroanilina (26 mg, 0.2 mmol) produjo Compuesto 54 en Tabla 2 (72 mg, 75 %).

^{1}HNMR (DMSO-d_6, TFA): 2.31 (m, 2H); 3.14 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.89 (s, 2H); 3.98 (s, 3H); 4.03 (d, 2H); 4.3 (t, 2H); 7.27 (s, 1H); 7.32 (s, 1H); 7.38 (d, 1H); 7.65 (d, 1H); 8.0 (s, 1H); 9.12 (s, 1H).
MS ES^+: 567, 569 $(M+H)^+$

Ejemplo 55.

Una reacción análoga a la descrita en Esquema General 3, comenzando con 3-amino-6-cloropiridina (26 mg, 0.2 mmol) produjo Compuesto 55 en

Tabla 2 (80 mg, 83 %).

^{1}HNMR (DMSO-d_6, TFA): 2.28 (m, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.93 (s, 2H); 3.98 (s, 3H; 4.04 (d, 2H); 4.3 (t, 2H); 7.29 (s, 1H); 7.33 (s, 1H); 7.49 (d, 1H); 8.01 (s, 1H); 8.09 (d, 1H); 8.66 (d, 1H); 9.13 (s, 1H).

MS ES^+ :570, 572 $(M+H)^+$

Ejemplo 56.

Una reacción análoga a la descrita en Esquema General 3, comenzando con morfolina (18 mg, 0.2 mmol) produjo Compuesto 56 en Tabla 2 (14 mg, 16 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.6 (m, 12H); 3.9 (s, 2H); 3.99 (s, 3H); 4.03 (d, 2H); 4.3 (t,2H); 7.17 (s, 1H); 7.3 (s, 1H); 7.95 (s, 1H); 9.09 (s, 1H).

MS ES^+: 529 $(M+H)^+$

Ejemplo 57.

Una reacción análoga a la descrita en Esquema General 3, comenzando con pirrolidina (14 mg, 0.2 mmol) produjo Compuesto 57 en Tabla 2 (73 mg, 84 %).

^{1}HNMR (DMSO-d_6, TFA): 1.82 (m, 2H); 1.93 (m, 2H); 2.28 (m, 2H); 3.16 (t, 2H); 3.36 (m, 4H); 3.55 (m, 4H); 3.68 (t, 2H); 3.71 (s, 2H); 3.99 (s, 3H); 4.04 (d, 2H); 4.3 (t, 2H); 7.17 (s, 1H); 7.3 (s, 1H); 7.94 (s, 1H); 9.08 (s, 1H).

MS ES^+: 513 $(M+H)^+$

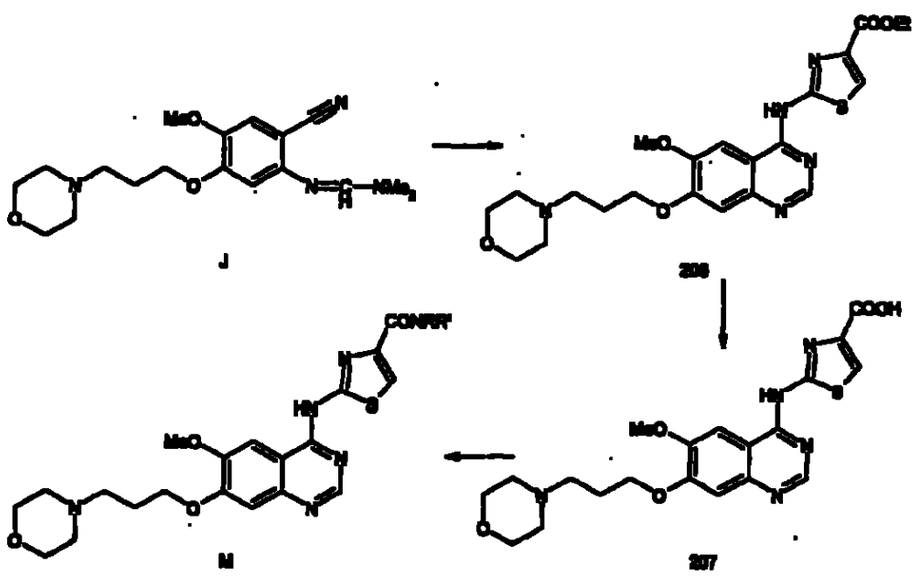
Ejemplo 58.

Una reacción análoga a la descrita en Esquema General 3, comenzando con ciclohexilamina (20 mg, 0.2 mmol) produjo Compuesto 58 en Tabla 2 (80 mg, 87 %).

^{1}HNMR (DMSO-d_6, TFA): 1.25 (m, 4H); 1.75 {m, 4H); 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.56 (d, 2H); 3.6 (s, 2H); 3.69 (t, 2H); 3.99 (s, 3H); 4.04 (d, 2H); 4.3 (t, 2H); 7.15 (s, 1H); 7.97 (s, 1H); 9.09 (s, 1H).

MS ES^+: 541 $(M+H)^+$

Esquema General 4



Compuesto 206

La amidina J (1.38 g, 4 mmol) en ácido acético(14 ml) se hizo reaccionar con etil 2-amino-4-tiazolcarboxilato (0.72 g, 4.2 mmol) a 130°C durante 6 horas. El solvente se evaporó, el residuo se disolvió en etanol, y se agitó con una solución saturada de $NaHCO_3$. La mezcla se extrajo con CH_2Cl_2, se secó, y se purificó mediante cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH 98/2 → 90/10, para producir el compuesto del título(0.738 g, 52 %).

^{1}HNMR (DMSO-d_6, TFA): 1.34 (t, 3H); 2.28 (m, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 4.03 (s, 3H); 4.04 (d, 2H); 4.34 (m, 4H); 7.45 (s, 1H); 8.33 (s, 1H); 8.44 (s, 1H); 9.26 (s, 1H).

MS ES^+: 474 $(M+H)^+$

Compuesto 207

Éster **206** (946 mg, 2 mmol) en suspensión en etanol (20 ml) se trató con hidróxido de sodio (6N, 4 ml) a 75°C durante 45 minutos. A continuación

la mezcla de la reacción se enfrió a temperatura ambiente, se acidificó (pH 3) con 6N HCl. El precipitado se filtró, se lavó con etanol, se trituró con éter, se secó bajo vacío, para producir el compuesto del título (795 mg, 80 %).

^{1}HNMR (DMSO-d_6, TFA): 2.34 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.76 (t, 2H); 4.03 (m, 5H); 4.35 (t, 2H); 7.48 (s, 1H); 8.26 (s, 1H); 8.41 (s, 1H); 9.29 (s, 1H).

Síntesis de amidas de estructura general M, procedimiento general

El ácido **207** (79 mg, 0.16 mmol) en DMF (1 ml) se hizo reaccionar con amina (0.19 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il) N,N,N',N'-tetrametiluronio (73 mg, 0.19 mmol), DIEA (52 mg, 0.4 mmol), durante 1 hora a temperatura ambiente. La mezcla de la reacción se trató luego con una solución de $NaHC0_3$ (5 ml) agitando durante 0.5 hora, y el sólido se filtró, se secó bajo vacío sobre P_2O_5. Para los compuestos que no se precipitaron, la solución se concentró a sequedad, los residuos se lavaron con cloruro de metileno / metanol, se filtraron. Se añadió alúmina a la solución de cloruro de metileno / metanol y el solvente se evaporó. La purificación de los compuestos se llevó a cabo mediante cromatografía sobre alúmina, eluyente CH_2Cl_2; CH_2Cl_2 / MeOH: 95/5, para producir los compuestos del título.

Ejemplo 59.

Una reacción análoga a la descrita en Esquema General 4, comenzando con anilina (18 mg, 0.19 mmol) produjo Compuesto 59 en Tabla 3 (50 mg, 60%).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.03 (d, 2H); 4.05 (s, 3H); 4.34 (t, 2H); 7.14 (t, 1H); 7.39 (t, 2H); 7.45 (s, 1H); 7.8 (d, 2H); 8.29 (s, 1H); 8.41 (s, 1H); 9.29 (s, 1H).

MS ES^+: 521 $(M_+H)^+$

Ejemplo 60.

Una reacción análoga a la descrita en Esquema General 4, comenzando con 4-fluoroanilina (21 mg, 0.19 mmol) produjo Compuesto 60 en Tabla 3 (70 mg, 82 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m,2H); 3.16 (t, 2H); 3.33 (t, 2H); 3.56 (d, 2H); 3.68 (t, 2H); 4.03 (d, 2H); 4.04 (s, 3H); 4.35 (t,2H); 7.22 (t, 2H); 7.45 (s, 1H); 7.83 (m, 2H); 8.28 (s, 1H); 8.4 (s, 1H); 9.27 (s, 1H).

MS ES$^+$: 539 $(M_+H)^+$

Ejemplo 61.

Una reacción análoga a la descrita en Esquema General 4, comenzando con 4-cloroanilina (24 mg, 0.19 mmol) produjo Compuesto 61 en Tabla 3 (70 mg, 79 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.68 (t, 2H); 4.04 (m, 5H); 4.35 (t, 2H); 7.45 (m, 3H); 7.84 (d, 2H); 8.29 (s, 1H); 8.4 (s, 1H); 9.27 (s, 1H).

MS ES$^+$: 555, 557 $(M_+H)^+$

Ejemplo 62.

Una reacción análoga a la descrita en Esquema General 4, comenzando con 4-ciclohexilamina 20 (19 mg, 0.19 mmol) produjo Compuesto 62 en Tabla 3 (60 mg, 72 %).

^{1}HNMR (DMSO-d_6, TFA): 1.32 (m, 5H); 1.62 (m, 1H); 1.73 (m, 2H); 1.87 (m, 2H); 2.33 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.75 (m, 1H); 4.03 (s, 3H); 4.05 (d, 2H); 4.33 (t, 2H); 7.42 (s, 1H); 8.07 (s, 1H); 8.32 (s, 1H); 9.24 (s, 1H).

MS ES$^+$: 527 $(M_+H)^+$

Ejemplo 63.

Una reacción análoga a la descrita en Esquema General 4, comenzando con 3-(metilamino)-propionitrilo (16 mg, 0.19 mmol) produjo Compuesto 63 en Tabla 3 (40 mg, 49 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 2.88 (5m, 3H); 3.14 (m, 4H); 3.35 (t, 2H); 3.54 (d, 2H); 3.71 (t, 2H); 3.75 (m, 2H); 4.02 (s, 3H); 4.04 (d, 2H); 4.33 (t, 2H); 7.44 (s, 1H); 7.85 (s, 1H); 8.37 (s, 1H); 9.27 (s, 1H).
MS ES$^+$: 512 $(M_+H)^+$

Ejemplo 64.

Una reacción análoga a la descrita en Esquema General 4, comenzando con 4- hidroxipiperidina (19 mg, 0.19 mmol) produjo Compuesto 64 en Tabla 3 (45 mg, 54 M).
^{1}HNMR (DMSO-d_6, TFA): 1.36 (m, 2H); 1.78 (m,2H); 2.3 (m, 2H); 3.15 (t, 2H); 3.29 (m, 2H); 3.37 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.77 (m, 2H); 3.84 (m, 1H); 4.02 (s, 3H); 4.04 (d, 2H); 4.33 (t, 2H); 7.42 (s, 1H); 7.75 (s, 1H); 8.35 (s, 1H); 9.27 (s, 1H).
MS ES$^+$: 529 $(M_+H)^+$

Ejemplo 65.

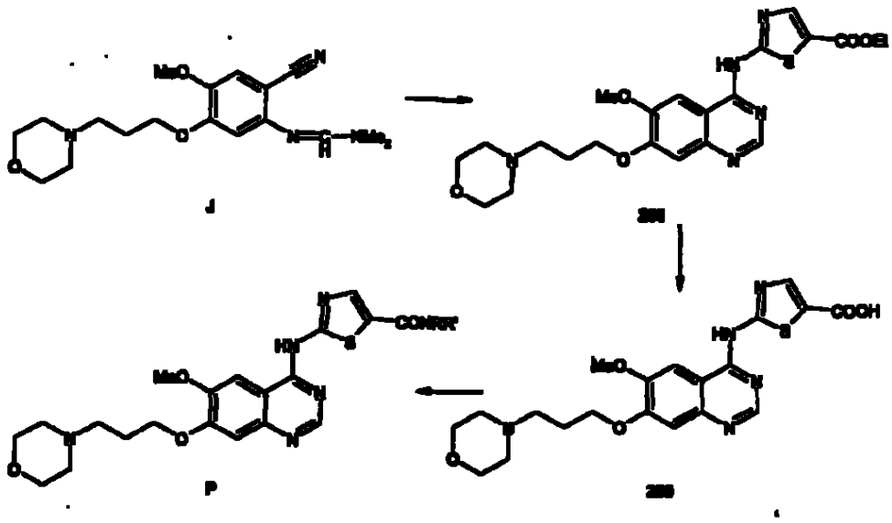
Una reacción análoga a la descrita en Esquema General 4, comenzando con 4-aminopiridina (18 mg, 0.19 mmol) produjo Compuesto 65 en Tabla 3 (35 mg, 42 %).
^{1}HNMR (DMSO-d_6, TFA): 2.29 (m, 2H); 3.15 (t, 2H); 3.34 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 4.03 (m, 5H); 4.34 (t, 2H); 7.48 (s, 1H); 8.41 (d, 2H); 8.43 (s, 1H); 8.52 (s, 1H); 8.81 (d, 2H); 9.24 (s, 1H).
MS ES$^+$: 522 $(M_+H)^+$

Ejemplo 66.

Una reacción análoga a la descrita en Esquema General 4, comenzando con 2-cloroanilina (24 mg, 0.19 mmol) produjo Compuesto 66 en Tabla 3 (25 mg, 28 %).
^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.04 (d, 2H); 4.05 (s, 3H); 4.35 (t, 2H); 7.24 (t, 1H); 7.42 (t, 1H); 7.47 (s, 1H); 7.6 (d, 1H) $(M_+H)^+$

490

Esquema General 5



Compuesto 208

La amidina **J** (1.52 g, 4.4 mmol) in AcOH (15 ml) se hizo reaccionar con 2-amino-5-tiazolcarboxilato de etilo (757 mg, 4.4 mmol) a 130°C bajo argón duranter 3 horas. Se evaporó el solvente, el aceite residual se disolvió en cloruro de metileno y se purificó mediante cromatografía de gel de sílice, eluyente CH_2Cl_2, CH_2Cl_2 / MeOH: 95/5 para producir el compuesto del título como un sólido amarillo (1.44 g, 70%).

^{1}HNMR (DMSO-d_6, TFA): 1.33 (t, 3H); 2.3 (m, 2H); 3.15 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 4.01 (s, 3H); 4.03 (d, 2H); 4.35 (m, 4H); 7.41 (s, 1H); 8.14 (s, 1H); 8.44 (s, 1H) ; 9.3 (s, 1H)

MS ES$^+$: 474 $(M_+H)^+$

Compuesto 209

Éster **208** (1.6 g, 3.4 mmol) en suspensión de etanol 32 ml) se hizo reaccionar con hidróxido de sodio (6N, 6 ml) a 75° C durante 1 hora. La solución enfriada se acidificó con HCl (6N) a pH 4. El sólido se filtró, se lavó con EtOH, éter, se secó, para producir un sólido amarillo (1 .65 g, 86%)

^{1}HNMR (DMSO-d_6, TFA): 2.28 (m, 2H); 3.12 (t, 2H); 3.32 (t, 2H); 3.51 (d,

091

2H); 3.66 (t, 2H); 3.97 (s, 3H); 3.99 (d, 2H); 4.31 (t, 2H); 7.37 (s, 1H); 8.06 (s, 1H); 8.32 (s, 1H); 9.24 (s, 1H)

MS ES^+: 446 $(M+H)^+$

Síntesis de amidas de estructura general P, procedimiento general

El ácido **209** (95 mg, 0.17 mmol) en DMIF, 1 ml se hizo reaccionar con amina (0.2 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il) N,N,N',N'-tetrametiluronio (91 mg, 0.24 mmol), DIEA (110 mg, 0.85 mmol) durante 14 horas a temperatura ambiente y 5 horas a 50°C. La mezcla de la reacción se trató luego con una solución de $NaHC0_3$ (1 ml) con agitación durante 0.5 hora, y se concentró. El residuo se lavó con cloruro de metileno/metanol (1/1,25 ml). Se agregó alúmina a la fase orgánica, la cual seguidamente se evaporó. La purificación del compuesto se llevó a cabo mediante cromatografía sobre alúmina, eluyente CH_2Cl_2, CH_2Cl_2 / MeOH / 95/5, para producir los compuestos del título.

Ejemplo 67.

Una reacción análoga a la descrita en Esquema General 5, comenzando con anilina (19 mg, 0.2 mmol) produjo Compuesto 67 en Tabla 4 (30 mg, 34 %).

^{1}HNMR (DMSO-d_6, TFA): 2.31 (m, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.02 (s, 3H); 4.04 (d, 2H); 4.33 (t, 2H); 7.14 (t, 1H); 7.39 (m, 3H); 7.73 (d, 2H); 8.05 (s, 1H); 8.61 (s, 1H); 9.28 (s, 1H).

MS ES^+: 521 $(M+H)^+$

Ejemplo 68.

Una reacción análoga a la descrita en Esquema General 5, comenzando con 4-fluoroanilina (23 20 mg, 0.2 mmol) produjo Compuesto 68 en Tabla 4 (58 mg, 64 %).

^{1}HNMR (DMSO-d_6, TFA): 2.31 (m, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.01 (s, 3H); 4.03 (d, 2H); 4.32 (t, 2H); 7.20 (t, 1H); 7.38 (s, 1H); 7.73 (m, 1H); 8.05 (s, 1H); 8.57 (s, 1H); 9.28 (s, 1H).

MS ES^+: 539 $(M+H)^+$

Ejemplo 69.

Una reacción análoga a la descrita en Esquema General 5, comenzando con 4-cloroanilina (26 rng, 0.2 mmol) produjo Compuesto 69 en Tabla 4 (32 mg, 34 %).

^{1}HNMR (DMSO-d_6, TFA): 2.32 (m, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.01 (s, 3H); 4.03 (d, 2H); 4.33 (t, 2H); 7.39 (s, 1H); 7.44 (d, 2H); 7.76 (d, 2H). 8.06 30 (s, 1H); 8.6 (s, 1H); 9.29 (s, 1H).

MS ES^+: 555, 557 $(M+H)^+$

Ejemplo 70.

Una reacción análoga a la descrita en Esquema General 5, comenzando con alilamina (12 mg, 0.2 mmol) produjo Compuesto 70 en Tabla 4 (32 mg, 39 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m,2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.7 (t, 2H); 3.92 (d, 2H); 4.0 (s, 3H); 4.03 (d, 2H); 4.33 (t, 2H); 5.16 (d, 1lH); 5.25 (d, 1H); 5.9 (m, 1H); 7.38 (s, 1H); 8.02 (s, 1H); 8.36 (s, 1H); 9.24 (s, 1H).

MS ES^+: 485 $(M+H)^+$

Ejemplo 71.

Una reacción análoga a la descrita en Esquema General 5, comenzando con 3-(metilamino)-propionitrilo (17 mg, 0.2 mmol) produjo Compuesto 71 en Tabla 4 (32 mg, 39 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m,2H); 2.89 (m, 3H); 3.15 (t, 2H); 3.34 (m, 4H); 3.55 (d, 2H); 3.69 (t, 2H); 3.8 (m, 2H); 4.01 (s, 3H); 4.03 (d, 2H); 4.33 (t, 2H); 7.38 (s, 1IH); 8.07 15 (s, 1H); 8.22 (s, 1H); 9.25 (s, 1H).

MS ES^+: 512 $(M+H)^+$

Ejemplo 72.

Una reacción análoga a la descrita en Esquema General 5, comenzando con

4-hidroxipiperidina (20 mg, 0.2 mmol) produjo Compuesto 72 en Tabla 4 (12 mg, 13 %).

^{1}HNMR (DMSO-d_6, TFA): 1.45 (m, 2H); 1.82 (m, 2H); 2.31 (m, 2H); 3.15 (m, 4H); 3.35 (t, 2H); 3.4 (m, 2H); 3.54 (d, 2H); 3.7 (t, 2H); 3.79 (m, 1H); 4.01 (s, 3H); 4.03 (d, 2H); 4.32 (t, 2H); 7.38 (s, 1H); 8.06 (s, 1H); 8.09 (s, 1H); 9.23 (s, 1H).

MS ES$^+$: 529 $(M_+H)^+$

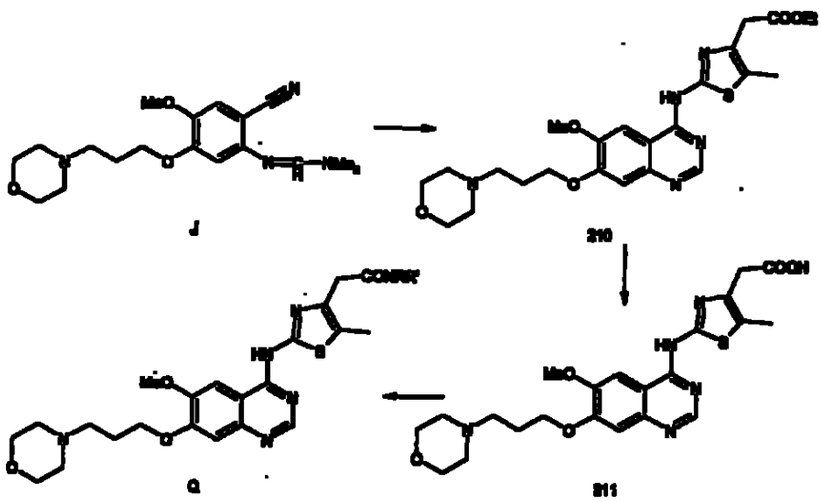
Ejemplo 73.

Una reacción análoga a la descrita en Esquema General 5, comenzando con 4-aminopiridina (19 mg, 0.2 mmol) produjo Compuesto 73 en Tabla 4 (50 mg, 57 %).

^{1}HNMR (DMSO-d_6, TFA): 2.29 (m, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.7 (t, 2H); 4.02 (s, 3H); 4.03 (d, 2H); 4.34 (t, 2H); 7.46 (s, 1H); 8.15 (s, 1H); 8.27 (d, 2H); 8.78 (s, 1H); 8.8 (d, 2H); 9.31 (s, 1H).

MS ES$^+$: 522 $(M_+H)^+$

Esquema General 6



Compuesto 210

Amidina J (450 mg, 1.3 mmol) se hizo reaccionar con 2-amino-5-metil-4-tiazolacetato de metil (242 mg, 1.3 mmol) en ácido acético (5 ml) a 130°C

durante 3 horas, bajo argón. El solvente se evaporó, se adicionó acetato de etilo y agua al aceite residual, el pH se adjustó a 9 con una solución saturada de bicarbonato de sodio y la mezcla se extrajo con acetato de etilo. La fase orgánica se lavó con una solución saturada de cloruro de sodio, se secó sobre sulfato de magnesio, se filtró, se concentró. El aceite residual se purificó mediante cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH: 98/2 a 95/5 para producir el compuesto del título (380 mg, 60 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 2.35 (s, 3H); 3.15 (t, 2H); 3.34 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.68 (s, 3H); 3.83 (s, 2H); 3.98 (s, 3H); 4.03 (d, 2H); 4.29 (t,2H); 7.31 (s, 1H); 7.96 (s, 1H); 9.06 (s, 1H).

MS ES$^+$: 488 $(M_+H)^+$

Compuesto 211

Éster **210** (360 mg, 0.74 mmol) en etanol (10 ml) se hizo reaccionar con hidróxido de sodio (6N, 1 ml) a temperatura ambiente durante 1 hora. HCl (6N) se añadió luego a la solución enfriada a O°C, y el pH se ajustó a 3-4. Se recuperó el sólido por filtración, se lavó con etanol, éter, se secó bajo vacío, para producir el compuesto del título como un diclorhidrato (550 mg, 83 %).

^{1}HNMR (DMSO-d_6, TFA): 2.34 (m, 5H); 3.13 (t, 2H); 3.32 (t, 2H); 3.52 (d, 2H); 3.74 (s, 2H); 3.78 (t, 2H); 3.98 (s, 3H); 4.01 (d, 2H); 4.31 (t, 2H); 7.37 (s, 1H); 7.91 (s, 1H); 9.03 (s, 1H).

MS ES$^+$: 474 $(M_+H)^+$

Síntesis de amidas de estructura general Q, procedimiento general

El ácido **211** (87 mg, 0.13 mmol) en DMF (1 ml) se hizo reaccionar con amina (0.169 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il) N,N,N',N'-tetrametiluronio (69 mg, 0.182 mmol), diisopropiletilamina (84 mg, 0.65 mmol) de un día para otro, a temperatura ambiente. La mezcla de la reacción se diluyó con agua (5 ml) y una solución concentrada de bicarbonato de sodio (1 ml). El sólido se filtró, se lavó con agua, etanol, éter, y se secó bajo vacío, para producir los

compuestos del título. Para los compuestos que no precipitaron, la solución se concentró a sequedad, los residuos se lavaron con cloruro de metileno, metanol, se filtró. Se añadió alúmina a la solución de cloruro de metileno / metanol, y el solvente se evaporó. La purificación de los compuestos se llevó a cabo mediante cromatografía sobre alúmina, eluyente CH_2Cl_2 / MeOH: 98/2 a 95/5, para producir los compuestos del título.

Ejemplo 74.

Una reacción análoga a la descrita en Esquema General 6, comenzando con anilina (16 mg, 0.17 mmol) produjo Compuesto 74 en Tabla 17 (50 mg, 70 %).

^{1}HNMR (DMSO-d_6, TFA): 2.28 (m, 2H); 2.37 (s, 3H); 3.15 (t, 2H); 3.34 (t, 2H); 3.56 (d, 2H); 3.68 (t, 2H); 3.84 (s, 2H); 3.96 (s, 3H); 4.03 (d, 2H); 4.28 (t, 2H); 7.07 (t, 1H); 7.29 (s, 1H); 7.3 (t, 2H); 7.61 (d, 2H); 7.89 (s, 1H); 9.02 (s, 1H).

MS ES^+: 549 $(M+H)^+$

Ejemplo 75.

Una reacción análoga a la descrita en Esquema General 6, comenzando con 4-fluoroanilinA (19 mg, 0.17 mmol) produjo Compuesto 75 en Tabla 17 (50 mg, 67 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 2.38 (s, 3H); 3.16 (t, 2H); 3.34 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.84 (s, 2H); 3.97 (s, 3H); 4.03 (d, 2H); 4.29 (t, 2H); 7.16 (t, 2H); 7.29 (s, 1H); 7.64 (m, 2H); 7.9 (s, 1H); 9.03 (s, 1H).

MS ES^+: 567 $(M+H)^+$

Ejemplo 76.

Una reacción análoga a la descrita en Esquema General 6, comenzando con 4-cloroanilina (22 mg, 0.17 mmol) produjo Compuesto 76 en Tabla 17 (45 mg, 59 %).

^{1}HNMR (DMSO-d_6, TFA): 2.28 (m, 2H); 2.37 (s, 3H); 3.15 (t, 2H); 3.34 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.85 (s, 2H); 3.97 (s, 3H); 4.03 (d, 2H); 4.29

496

(t, 2H); 7.29 (s, 1H); 7.37 (d, 2H); 7.65 (d, 2H); 7.9 (s, 1H); 9.03 (s, 1H).
MS ES^+: 583 $(M_+H)^+$

Ejemplo 77.

Una reacción análoga a la descrita en Esquema General 6, comenzando con 4- hidroxipiperidina (17 mg, 0.17 mmol) produjo Compuesto 77 en Tabla 17 (45 mg, 62 %).

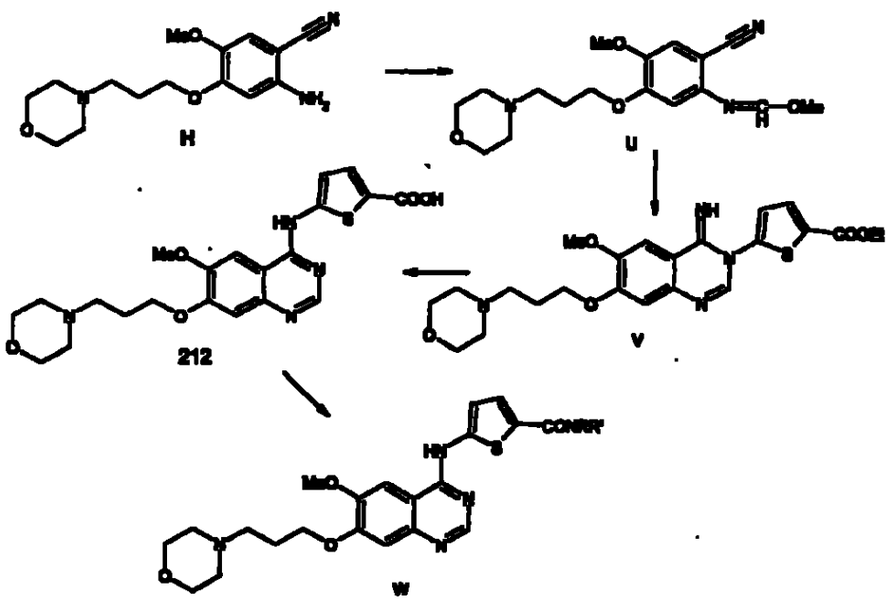
^{1}HNMR (DMSO-d_6, TFA): 1.42 (m, 2H); 1.82 (m, 2H); 2.31 (m, 5H); 3.08 (m, 1H); 3.16 (t, 2H); 3.27 (m, 1H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.78 (m, 2H); 3.83 (s, 2H); 3.92 (m, 1H); 3.97 (s, 3H); 4.03 (d, 2H); 4.29 (t, 2H); 7.28 (s, 1H); 7.85 (s, 1H); 9.0 (s, 1H).
MS ES^+: 557 $(M_+H)^+$

Ejemplo 78.

Una reacción análoga a la descrita en Esquema General 6, comenzando con 4-aminopiridina (16 mg, 0.17 mmol) produjo Compuesto 78 en Tabla 17 (35 mg, 49 %).

^{1}HNMR (DMSO-d_6, TFA): 2.29 (m, 2H); 2.39 (s, 3H); 3.15 (t, 2H); 3.34 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.96 (s, 3H); 4.02 (d, 2H); 4.04 (s, 2H); 4.29 (t, 2H); 7.33 (s, 1H); 7.92 (s, 1H); 8.1 (d, 2H); 8.76 (d, 2H); 9.06 (s, 1H).
MS ES^+: 550 $(M_+H)^+$

Esquema General 7



Compuesto U

El amino nitrilo H (2.91 g, 10 mmol) se hizo reaccionar con trimetilortoformato (10 ml) en presencia de ácido p-tolueno-sulfónico (38 mg, 2 mmol) a 80°C durante 6 horas. El solvente se evaporó, el residuo cristalizó a partir de éter para producir el compuesto del título (3.01 g, 90.4 %).

^{1}HNMR (DMSO-d_6): 1.9 (t, 2H); 2.4 (m, 6H); 3.58 (t, 4H); 3.78 (s, 3H); 3.85 (s; 3H); 4.08 (t, 2H); 6.88 (s, 1H); 7.28 (s, 1H); 8.2 (s, 1H).

MS ES$^+$: 334 $(M+H)^+$

Compuesto V

Imidato U (0.25 g, 0.75 mmol) in CH_2Cl_2 (5 ml) se hizo reaccionar con 2-amino-5-tiofencarboxilato de etilo (0.13 g, 0.79 mmol) en presencia de clorhidrato de piridinio (0.09 g, 0.75 mmol), a temperatura ambiente de un día para otro. A continuación de agregó acetato de etilo, y el sólido se recuperó por filtración, se lavó con acetato de etilo, se secó bajo vacío, para producir el producto (0.23 g, 65 %).

^{1}HNMR (DMSO-d_6, TFA): 1.33 (t, 3H); 2.28 (m, 2H); 3.12 (t, 2H); 3.32 (t, 2H); 3.53 (d, 2H); 3.73 (t, 2H); 3.96 (s, 3H); 4.02 (d, 2H); 4.37 (m, 4H); 7.45 (s, 1H); 7.67 (d, 1H); 7.95 (d, 1H); 8.12 (s, 1H); 8.52 (s, 1H).

MS ES$^+$: 473 $(M+H)^+$

Compuesto 212

Éster V (1.1 g, 2.3 mmol) in metanol (20 ml) se trató con hidróxido de sodio (2N, 20 ml) a 75°C durante 4 horas, y a temperatura ambiente de un día para otro. Metanol se evaporó, y la solución acuosa restante se guardó durante 24 horas a 5°C. El sólido se filtró, se lavó con agua, MeOH / CH_2Cl_2: 1/1, se secó bajo vacío para producir el compuesto del título (0.9 g, 87 %).

^{1}HNMR (DMSO-d_6, TFA): 2.31 (m, 2H); 3.14 (t, 2H); 3.33 (t, 2H); 3.53 (d, 2H); 3.76 (t, 2H); 4.01 (d, 2H); 4.07 (s, 3H); 4.33 (t, 2H); 7.44 (s, 1H); 7.54 (d, 1H); 7.68 (d, 1H); 8.54 (s, 1H); 9.22 (s, 1H).

MS ES^+: 445 $(M+H)^+$

Síntesis de amidas de estructura general W, procedimiento general

Ácido **212** (80 mg, 0.18 mmol) in DMF (1.5 ml) se hizo reaccionar con amina (0.216 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il) N,N,N',N'-tetrametilfuronio (80 mg, 0.21 mmol), DIEA (80µl, 0.46 mmol), durante 3 horas a temperatura ambiente. La mezcla de la reacción se trató entonces con una solución of $NaHCO_3$ (2 ml) agitando durante 0.5 hora, el sólido de filtró, se lavó con agua, éter, se secó bajo vacío sobre P_2O_5, para producir el compuesto del título.

Ejemplo 79.

Una reacción análoga a la descrita en Esquema General 7, comenzando con anilina (17 µl, 0.186 mmol) produjo Compuesto 79 en Tabla 18 (80 mg, 86 %).

^{1}HNMR (DMSO-d_6, TFA): 2.32 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.53 (d, 2H); 3.69 (t, 2H); 4.01 (d, 2H); 4.03 (s, 3H); 4.3 (t, 2H); 7.7 (t, 1H); 7.32 (m, 4H); 7.73 (d, 2H); 7.98 (d, 1H); 8.18 (s, 1H); 9.22 (s, 1H).

MS ES^+: 520 $(M+H)^+$

Ejemplo 80.

Una reacción análoga a la descrita en Esquema General 7, comenzando con 4-fluoroanilinA (24 mg, 0.216 mmol) produjo Compuesto 80 en Tabla 18 (62 mg, 64 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 4.05 (m, 5H); 4.33 (t, 2H); 7.21 (t, 2H); 7.33 (d, 1H); 7.4 (s, 1H); 7.77 (m, 2H); 7.98 (d, 1H); 8.2 (s, 1H); 9.25 (s, 1H).

MS ES^+: 538 $(M+H)^+$

Ejemplo 81.

Una reacción análoga a la descrita en Esquema General 7, comenzando con 3-aminofenol (24 mg, 0.216 mmol) produjo Compuesto 81 en Tabla 18 (60

mg, 66 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.7 (t, 2H); 4.04 (d, 2H); 4.06 (s, 3H); 4.33 (t, 2H); 6.53 (m, 1H); 7.13 (m, 2H); 7.3 (d, 1H); 7.36 (d, 1H); 7.4 (s, 1H); 7.96 (s, 1H); 8.0 (d, 1H); 8.26 (s, 1H); 9.25 (s, 1H).

MS ES$^+$: 536 $(M_+H)^+$

Ejemplo 82.

Una reacción análoga a la descrita en Esquema General 7, comenzando con 4-aminoplridinA (20 mg, 0.216 mmol) produjo Compuesto 82 en Tabla 18 (16 mg, 19 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 4.03 (d, 2H); 4.05 (s, 3H); 4.32 (t, 2H); 7.01 (d, 1H); 7.03 (s, 1H); 8.18 (d, 1H); 8.22 (s, 1H); 8.3 (d, 2H); 8.76 (d, 2H); 9.3 (s, 1IH).

MS ES$^+$: 521 $(M_+H)^+$

Ejemplo 83.

Una reacción análoga a la descrita en Esquema General 7, comenzando con 4-amino-1-butanol (19 mg, 0.216 mmol) produjo Compuesto 83 en Tabla 18 (22 mg, 28 %).

^{1}HNMR (DMSO-d_6, TFA): 1.46 (m, 2H); 1.58 (m, 2H); 2.3 (m, 2H); 3.16 (t, 2H); 3.26 (t, 2H); 3.36 (t, 2H); 3.44 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.04 (m, 5H); 4.32 (t, 2H); 7.26 30 (d, 1H); 7.39 (s, 1H); 7.7 (d, 1H); 8.19 (s, 1H); 9.21 (s, 1H). MS ES$^+$: 516 $(M_+H)^+$

Ejemplo 84.

Una reacción análoga a la descrita en Esquema General 7, comenzando con 3- aminobenzamida (29 mg, 0.216 mmol) produjo Compuesto 84 en Tabla 18 (60 mg, 77 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.67 (t, 2H); 4.03 (d, 2H); 4.05 (s, 3H); 4.32 (t, 2H>); 7.34 (d, 1H); 7.39 (s, 1H); 7.42 (t, 1H); 7.62 (d, 1H); 7.96 (d, 1H); 8.05 (d, 1H); 8.21 (m,

2H); 9.27 (s, 1H). MS ES^+: 563 $(M+H)^+$

Ejemplo 85:

Una reacción análoga a la descrita en Esquema General 7, comenzando con alilamina (12 mg, 0.216 mmol) produjo el Compuesto 85 del título en Tabla 18 (20 mg, 43 %).

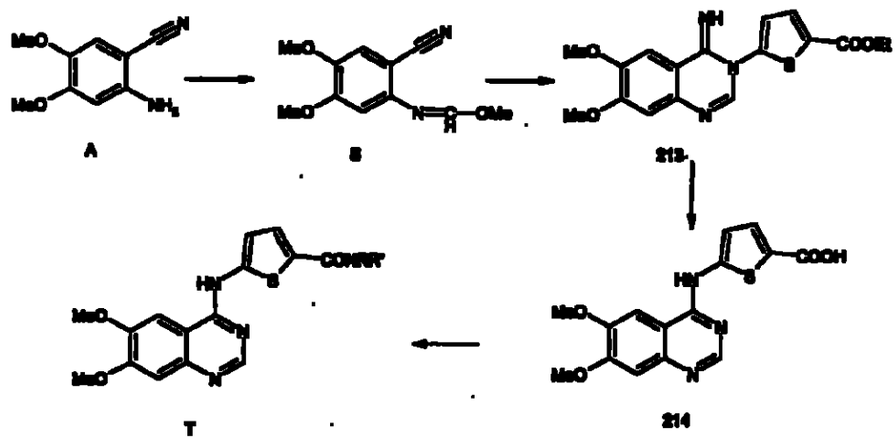
^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.91 (d, 2H); 4.04 (m, 5H); 4.32 (t, 2H); 5.12 (d, 1H); 5.2 (d, 1H); 5.91 (m, 1H); 7.26 (d, 1H); 7.38 (s, 1H); 7.75 (d, 1H); 8.19 (s, 1H); 9.22 (s, 1H). MS ES^+: 484 $(M+H)^+$

Ejemplo 86.

Una reacción análoga a la descrita en Esquema General 7, comenzando con metil-4-aminobutirato (25.mg, 0.216 mmol) produjo Compuesto 86 en Tabla 18 (18 mg, 23 %).

^{1}HNMR: 1.8 (t, 2H); 2.3 (m, 2H); 2.39 (t, 2H); 3.16 (t, 2H); 3.28 (t, 2H); 3.35 (t, 2H); 3.56 (d, 2H); 3.6 (s, 3H); 3.67 (t, 2H); 4.04 (m, 5H); 4.32 (t, 2H); 7.26 (d, 1H); 7.38 (s, 1H); 7.69 (d, 1H); 8.19 (s, 1H); 9.22 (s, 1H).
MS ES^+: 544 $(M+H)^+$

Esquema General 8



Compuesto S

Aminonitrilo N (1.78 g, 10 mmol) se trató con trimetilortoformato (10 ml) y una cantidad catalítica de ácido p-toluen sulfónico a 100°C durante 1 hora. La mezcla se enfrió a temperatura ambiente, se adicionó acetato de etilo, y el sólido insoluble se retiró por filtración, luego se evaporó el solvente, el residuo se trituró con éter para producir el compuesto del título como un sólido amarillo (1.56 g, 71 %).

^{1}HNMR (DMSO-d_6): 3.77 (s, 3H); 3.83 (s, 3H); 3.84 (s, 3H); 6.87 (s, 1H); 7.26 (s, 1H); 8.19 (s, 1H).

MS ES$^+$: 221 $(M_+H)^+$

Compuesto 213

Imidato S (0.165 g, 0.75 mmol) se hizo reaccionar con 12-amino-5-tiofencarboxilato de etilo (0.13 g, 0.79 mmol) en cloruro de metileno (4 ml) en presencia de clorhidrato de piridinio (88 mg, 0.75 mmol) a temperatura ambiente durante 4 horas. El solvente se evaporó, y el residuo se purificó mediante cromatografía de gel de sílice, eluyente: AcOEt / CH_2Cl_2, 1/1 ; seguido por MeOR / AcOEt / CH_2Cl_2, 1/4/5, para producir el compuesto del título (0.135 g, 50 %).

^{1}HNMR (DMSO-d_6, TFA): 1.33 (t, 3H); 3.95 (s, 3H); 4.03 (s, 3H); 4.38 (q, 2H); 7.43 (s, 1H); 7.67 (d, 1H); 7.95 (d, 1H); 8.05 (s, 1H); 8.52 (s, 1H).

MS ES$^+$: 360 $(M_+H)^+$

Compuesto 214

El éster **213** (72 mg, 0.2 mmol) en metanol (2 ml) se trató con hidróxido de sodio (2N, 2 ml) a 75°C durante 1.5 hora. La mezcla de la reacción se enfrió a temperatura ambiente, y se ajustó el pH a 3 por adición de HCl 2N. El sólido se recuperó por filtración, se lavó con agua, se secó bajo vacío en presencia de P_2O_5, para producir el compuesto del título (83 mg, 100 %).

^{1}HNMR (DMSO-d_6, TFA): 4.02 (s, 3H); 4.04 (s, 3H); 7.38 (s, 1H); 7.42 (d, 1H); 7.68 (d, 1H); 8.35 (s, 1H); 9.21 (s, 1H).

MS ES$^+$: 332 $(M_+H)^+$

Ejemplo 87.

Síntesis de compuesto de fórmula general T donde NRR' = NHPh (Compuesto 87)

Quinazolina **214** (45 mg, 0.108 mmol) en DMF (1 ml) se hizo reaccionar con anilina (12µl, 0.13 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il) N,N,N',N'-tetrametiluronio (50 mg, 0.13 mmol), DIEA (75 µl, 0.43 mmol) durante 1.5 hora a temperatura ambiente. Se adicionó una solución saturada de bicarbonato de sodio (2 ml) a la mezcla la cual se agitó durante 0.5 hora. El sólido se filtró, se lavó con agua, y se purificó mediante cromatografía sobre alúmina, eluyente AcOEt / CH_2Cl_2; 1/1 a MeOH / AcOEt / CH_2Cl_2; 1/4/5, para producir el compuesto del título (15 mg, 34 %).

^{1}HNMR (DMSO-d_6): 3.97 (s, 3H); 4.01 (s, 3H); 7.05 (d, 1H); 7.09 (t, 1H); 7.29 (s, 1H); 7.36 (t, 2H); 7.74 (d, 2H); 7.91 (d, 1H); 7.92 (s, 1H); 8.72 (s, 1H).

MS ES$^+$: 406 $(M+H)^+$

Ejemplo 88.

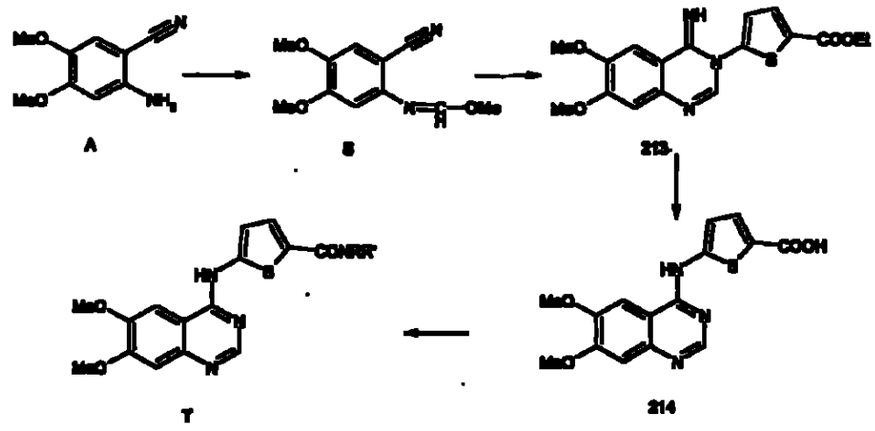
Síntesis de Compuesto 88 de fórmula general T donde NRR' es NHPh(4-F)

Una reacción análoga a la descrita en el Ejemplo 87, pero comenzando con quinazolina 213 (60 mg, 0.14 mmol), 4-fluoroanilina (17 µl, 0.17 mmol) produjo el compuesto del título (15 mg, 24 %).

^{1}HNMR (DMSO-d_6, TFA): 4.04 (s, 3H); 4.06 (s, 3H); 7.18 (t, 2H); 7.32 (d, 1H); 7.35 (s, 1H); 7.75 (t, 2H); 7.98 (d, 1H); 8.17 (s, 1H); 9.23 (s, 1H).

MS ES$^+$: 425 $(M+H)^+$

Esquema General 9



Ejemplo 89. Preparación de Compuesto 250 en Tabla 9

Amidine **J** (1.04 g, 3 mmol) en ácido acético(10 ml) se hizo reaccionar con clorhidrato de 4-amino-1-metil-2-pirrolcarboxilato (686 mg, 3.6 mmol) y dimetilamina en metanol (1.25 M 2.9 ml, 3.6 mmol) a 130°C durante 5.5 horas. El solvente se evaporó, se adicionaron agua y una solución acuosa de bicarbonato de sodio al residuo, se filtró el precipitado, se secó bajo vacío sobre $P2O_5$. El sólido volvió a disolverse en un gran volumen de tetrahidrofurano, cloruro de metileno, metanol, la solución se concentró, el sólido se filtró, se lavó con éter, se secó, para producir el compuesto del título (1.18 g, 86 %).

^{1}HNMR (DMSO-d_6, TFA): 2.31 (m, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3.8 (s, 3H); 3.95 (s, 3H); 4.01 (s, 3H); 4.03 (d, 2H); 4.29 (t, 2H); 7.26 (d, 1H); 7.32 (s, 1H); 7.69 (d, 1H); 8.06 (s, 1H); 8.94 (s, 1H).

MS ES^+: 456 $(M_+H)^+$

Ejemplo 90. Preparación de Compuesto 251 en Tabla 9

Éster **250** (1.34 g, 3 mmol) se trató con hidróxido de sodio (6N, 3 ml) en etanol (25 ml) at75° durante 2 horas. La solución se enfrió luego a temperatura ambiente, se acidificó a pH 3 con 20 HCl (6N), el precipitado se recuperó por filtración, se lavó con etanol, éter, se secó bajo vacío para

producir el compuesto del título (636 mg, 42 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.34 (t, 2H); 3.54 (d, 2H); 3.72 (t, 2H); 4.02 (m, 5H); 4.3 (t, 2H); 7.19 (s, 1H); 7.32 (s, 1H); 7.62 (s, 1H); 8.17 (s, 1H); 8.93 (s, 1H).

MS ES^+: 428 $(M_+H)^+$

Ejemplo 91. Síntesis de amidas N, procedimiento general

Ácido **251** (79 mg, 0.15 mmol) en DMF (1 ml) se hizo reaccionar con hexafluorofosfato de O-(benzotriazol-1-il)-N,N,N',N'-tetrametiluronio (62 mg, 0.165 mmol), la amina apropiada (1.65 mmol) and DIEA (68 mg, 0.525 mmol) a temperatura ambiente durante 1.5 hora. La mezcla de la reacción se diluyó entonces con agua (4 ml) y una solución acuosa de bicarbonato de sodio (1 ml). El sólido se recuperó por filtración, se disolvió nuevamente en tetrahidrofurano, cloruro de metileno, y se concentró, el sólido precipitado se recuperó, se lavó con éter, se secó bajo vacío, para producir el compuesto del título.

Ejemplo 92. Preparación del Compuesto 252 en Tabla 9

Compuesto de Ejemplo **1** se obtuvo por reacción del éster de N-hidroxibenzotriazol de **3** (56 mg, 0.1 mmol) con anilina (11 mg, 0.12 mmol) en DMF (1 ml) a 105°C durante 3 horas. Se agregó agua a la mezcla de reacción enfriada, la cual se extrajo con acetato de etilo, se lavó la fase orgánica con agua, se secó sobre $MgSO_4$, se filtró y se concentró para producir el compuesto del título (12 mg, 23 %). El éster de N-hidroxibenzotriazol se obtuvo como se describe en el procedimiento general del Ejemplo 91.

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.97 (s, 3H); 4.02 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 7.08 (t, 1H); 7.33 (m, 3H); 7.4 (s, 1H); 7.63 (s, 1H); 7.74 (d, 2H); 8.1 (s, 1H); 8.93 (s, 1H).

MS ES^+: 517 $(M_+H)^+$

Ejemplo 93. Preparación de Compuesto 253 en Tabla 9

Una reacción análoga a la descrita en el Ejemplo 92, pero comenzando con 4-fluoroanilina (22 mg, 0.195 mmol) produjo el compuesto del título (40 mg, 57 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.72 (t, 2H); 3.97 (s, 3H); 4.02 (s, 3H); 4.04 (d, 2H); 4.3 (t, 2H); 7.18 (t, 2H); 7.34 (s, 1H); 7.4 (d, 1H), 7.63 (d, 1H), 7.76 (m, 1H), 8.11 (s, 1H), 8.94 (s, lH).

MS ES^+: 535 $(M_+H)^+$

Ejemplo 94. Preparación de Compuesto 254 en Tabla 9

Una reacción análoga a la descrita en Ejemplo 92, pero comenzando con ciclohexilamina (16 5 mg, 0.17 mmol) produjo el compuesto del título (60 mg, 76 %).

^{1}HNMR (DMSO-d_6, TFA): 1.14 (m, 1H); 1.3 (m, 4H); 1.62 (m, 1H); 1.8 (m, 4H); 2.29 (m, 2H); 3.15 (t, 2H); 3.34 (t, 2H); 3.54 (d, 2H); 3.68 (m, 3H); 3.9 (s, 3H); 4.0 (s, 3H); 4.03 (d, 2H); 4.28 (t, 2H); 7.14 (d, 1H); 7.31 (s, 1H); 7.49 (d, 1H); 8.07 (s, 1H); 8.9 (s, 1H).

MS ES^+: 523 $(M_+H)^+$

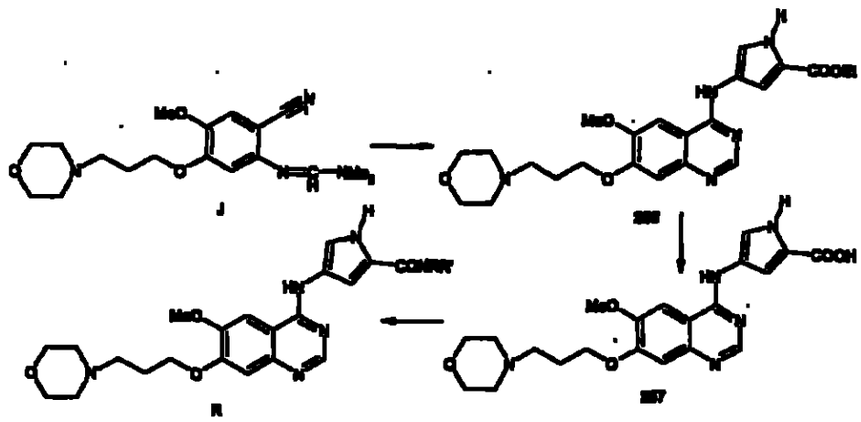
Ejemplo 95. Preparación de Compuesto 255 in Tabla 9

Una reacción análoga a la descrita en Ejemplo 92, pero comenzando con N,N-dimetil-1,4-fenilendiamina (23 mg, 0.17 mmol) produjo el compuesto del título (61 mg, 73 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.21 (s, 6H); 3.35 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3.97 (s, 3H); 4.01 (s, 3H); 4.03 (d, 2H); 4.29 (t, 2H); 7.35 (s, 1H); 7.45 (d, 1H); 7.66 (m, 3H); 7.93 (d, 2H); 8.1 (s, 1H); 8.93 (s, 1H).

MS ES^+: 560 $(M_+H)^+$

Esquema General 10



Ejemplo 96. Preparación de Compuesto 256 en Tabla 9

Amidina **J** (1.38 g, 4 mmol) en ácido acético (14 ml) se hizo reaccionar con 4-amino-2-pirrolcarboxilato de etilo (0.702 g, 4.56 mmol) a 130°C durante 5 horas. La solución se concentró, el sólido se recuperó por filtración y se lavó con éter. Este sólido se trató entonces con una solución diluida de bicarbonato de sodio, se filtró, se lavó con agua y se secó bajo vacío sobre P_2O_5 para producir el compuesto del título (1.34 g, 73 %).

^{1}HNMR (DMSO-d_6): 1.3 (t, 3H); 1.95 (t, 2H); 2.38 (m, 4H); 2.44 (t, 2H); 3.58 (m, 4H); 3.94 (s, 3H); 4.16 (d, 2H); 4.23 (q, 2H); 7.05 (d, 1H); 7.14 (s, 1H); 7.59 (d, 1H); 7.75 (s, 1H); 8.46 (s, 1H); 9.53 (s, 1H); 11.72 (s, 1H).

MS ES$^+$: 456 $(M_+H)^+$

Ejemplo 96. Preparación de Compuesto 257 en Tabla 9

Éster **256** (1.34 g, 3 mmol) en etanol (25 ml) se trató con hidróxido de sodio (6N, 3 ml) a 75°C durante 2 horas. La solución se enfrió, y se acidificó con ácido clorhídrico (6N) a pH 3. El precipitado se filtró, se lavó con etanol, éter, se secó bajo vacío sobre P_2O_5, para producir el compuesto del título (0.63 g, 42 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.34 (t, 2H); 3.54 (d, 2H); 3.72 (t, 2H); 4.02 (s, 3H); 4.03 (d, 2H); 4.3 (t, 2H); 7.19 (d, 1H); 7.32 (s, 1H); 7.62 (d, 1H); 8.17 (s, 1H); 8.93 (s, 1H).

MS ES^+: 428 $(M+H)^+$

Ejemplo 97. Preparación de Compuesto 258 en Tabla 9

Ácido **256** (75 mg, 0.15 mmol) en DMF (0.7 ml) se hizo reaccionar con hexafluorofosfato de O-(benzotriazol-1-il)-N,N,N',N'-tetrametiluronio (68 mg, 0.18 mmol), anilina (17 mg, 0.18 mmol) y DIEA (62 mg, 0.48 mmol) a temperatura ambiente de un día para otro. La mezcla de la reacción se diluyó entonces con una solución saturada de bicarbonato de sodio (5 ml), y se agitó durante 1 hora. El sólido se filtró, se lavó con agua, se secó bajo vacío sobre sobre P_2O_5, para producir el compuesto del título (30 mg, 40 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.16 (t, 2H); 3.37 (t, 2H); 3.54 (d, 2H); 3.69 (t, 2H); 4.01 (s, 3H); 4.03 (d, 2H); 4.31 (t, 2H); 7.08 (t, 1H); 7.35 (m, 3H); 7.46 (d, 1H); 7.56 (d, 1H); 7.77 (d, 1H); 8.1 (s, 1H); 8.93 (s, 1H).

MS ES^+: 503 $(M+H)^+$

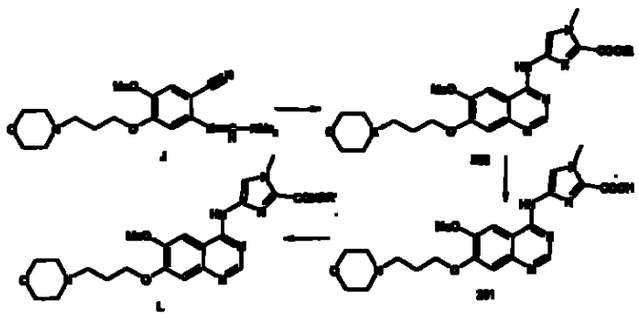
Ejemplo 98. Preparación de Compuesto 259 en Tabla 9

Una reacción análoga a la descrita en Ejemplo 97, pero comenzando con ciclohexilamina (18 mg, 0.18 mmol) produjo el compuesto del título (30 mg, 39 %).

^{1}HNMR (DMSO-d_6, TFA): 1.13 (m, 1H); 1.3 (m, 4H); 1.63 (m, 1H); 1.8 (m, 4H); 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.76 (m, 1H); 4.0 (s, 1h); 4.03 (d, 2H); 4.3 (t, 2H); 7.2 (d, 1H); 7.3 (s, 1H); 7.43 (d, 1H); 8.0 (s, 1H); 8.9 (s, 1H).

MS ES^+: 509 $(M+H)^+$

Esquema General 11



Ejemplo 99. Preparación de Compuesto 260 en Tabla 10

Amidina **J** (1.04 g, 3 mmol) en ácido acético (10 ml) se hizo reaccionar con ácido clorhídrico de etil 4-amino-1-metil-2-imidazolcarboxilato (0.74 g, 3.6 mmol) en presencia de dimetilamina / MeOR (1.25N, 2.9 ml, 3.6 mmol) a 130°C durante 3 horas. El solvente se evaporó, el residuo se trituró con éter y se filtró. El sólido se suspendió en agua, se ajustó el pH a 9 con una solución acuosa de bicarbonato de sodio, la suspensión se filtró, se lavó con agua, se secó bajo vacío sobre P_2O_5, para producir el compuesto del título (1.1 g, 78 %).

^{1}HNMR (DMSO-d_6): 1.32 (t, 3H); 1.96 (m, 2H); 2.37 (m, 4H); 2.44 (t, 2H); 3.58 (m, 4H); 3.94 (s, 3H); 4.0 (s, 3H); 4.17 (t, 2H); 4.28 (q, 2H); 7.16 (s, 1H); 7.99 (s, 1H); 8.07 (s, lH); 8.53 (s, 1H); 10.55 (s, 1H).

Ejemplo 100. Preparación de Compuesto 261 en Tabla 10

Ester **260** (1.1 g, 2.34 mmol) en etanol (23 ml) se hizo reaccionar con hidróxido de sodio (6N, 2.3 ml) a 80°C durante 2.5 horas. La mezcla se enfrió, y se acidificó con ácido clorhídrico (6N) a pH 3. La suspensión se recuperó por centrifugación, se lavó con etanol, éter, se secó bajo vacío sobre P_2O_5, para producir el compuesto del título (930 mg, 73 %).

^{1}HNMR (DMSO-d_6, TFA): 2.31 (m, 2H); 3.16 (t, 2H); 3.35 (t,2H); 3.54 (d, 2H); 3.76 (t, 2H); 4.01 (s, 3H); 4.05 (m, SH); 4.32 (t, 2H); 7.41 (s, 1H); 8.03 (s, 1H); 8.38 (s, 1H); 9.0 (s, 1H).

MS ES$^+$: 443 $(M_+H)^+$

Ejemplo 101. Preparación de Compuestos de Estructura General L

Ácido **261** (88 mg, 0.16 mmol) in DMF (1 ml) se hizo reaccionar con hexafluorofosfato de O-(benzotriazol-1-il)-N,N,N',N'-tetrametiluronio (73 mg, 0.19 mmol), la amina apropiada (0.18 mmol) y DIEA (82 mg, 0.4 mmol) a temperatura ambiente durante 3 horas. La solución se diluyó entonces con una solución saturada de bicarbonato de sodio (4 ml) y se agitó a temperatura ambiente durante 3 horas. El precipitado se filtró, se lavó con agua, se secó bajo vacío sobre P_2O_5, para producir el compuesto del título.

Ejemplo 102. Preparación de Compuesto 262 en Tabla 10

Una reacción análoga a la descrita en Ejemplo 101, pero comenzando con anilina (17 mg, 0.18 mmol) produjo el compuesto del título (37 mg, 44 %).
^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.02 (m, 5H); 4.06 (s, 3H); 4.31 (t, 2H); 7.13 (t, 1H); 7.38 (m, 3H); 7.78 (d, 2H); 7.99 (s, 1H); 8.27 (s, 1H); 9.01 (s, 1H).
MS ES$^+$: 518 $(M_+H)^+$

Ejemplo 103. Preparación de Compuesto 263 en Tabla 10

Una reacción análoga a la descrita en Ejemplo 101, pero comenzando con 4-fluoroanilina (20 mg, 0.18 mmol) produjo el compuesto del título (84 mg, 97 %).
^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.02 (s, 3H); 4.04 (d, 2H); 4.1 (s, 3H); 4.31 (t, 2H); 7.2.1 (t, 2H); 7.39 (s, 1H); 7.82 (m, 2H); 7.98 (5, 1H); 8.32 (5, 1H); 9.01 (5, 1H).
MS ES$^+$: 536 $(M_+H)^+$

Ejemplo 104. Preparación de Compuesto 264 en Tabla 10

Una reacción análoga a la descrita en Ejemplo 101, pero comenzando con 4-N,N-dimetil-1,4-fenilendiamina (24 mg, 0.18 mmol) produjo el Compuesto del título (80 mg, 88 %).
^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.17 (t, 2H); 3.21 (s, 6H); 3.35 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.02 (m, 5H); 4.1 (s, 3H); 4.31 (t, 2H); 7.4

(s, 1H); 7.66 (d, 2H); 7.98 (d, 2H); 8.01 (s, 1H); 8.32 (s, 1H); 9.01 (s, 1H).
MS ES^+: 561 $(M+H)^+$

Ejemplo 105. Preparación de Compuesto 265 en Tabla 10

Una reacción análoga a la descrita en Ejemplo 101, pero comenzando con 4-cloroanilina (23 mg, 0.18 mmol) produjo el compuesto del título (55 mg, 62 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.17 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.69 (t, 10 2H); 4.02 (s, 3H); 4.04 (d, 2H); 4.1 (s, 3H); 4.32 (t, 2H); 7.39 (s, 1H); 7.43 (d, 2H); 7.84 (d, 2H); 7.99 (s, 1H); 8.32 (s, 1H); 9.01 (s, 1H).

MS ES^+: 552, 554 $(M+H)^+$

Ejemplo 106. Preparación de Compuesto 266 en Tabla 10

Una reacción análoga a la descrita en Ejemplo 101, pero comenzando con pirrolidina (13 mg, . 0.18 mmol) produjo el compuesto del título (50 mg, 62 %).

^{1}HNMR (DMSO-d_6, TFA): 1.85 (m, 4H); 2.28 (m, 2H); 3.15 (t, 2H); 3.32 (t, 2H); 3.5 (m, 4H); 3.66 (t, 2H); 3.89 (m, 5H); 3.98 (m, 5H); 4.27 (t, 2H); 7.33 (s, 1H); 7.85 (s, 1H); 8.29 (s, 1H); 8.96 (s, 1H).

MS ES^+: 496 $(M+H)^+$

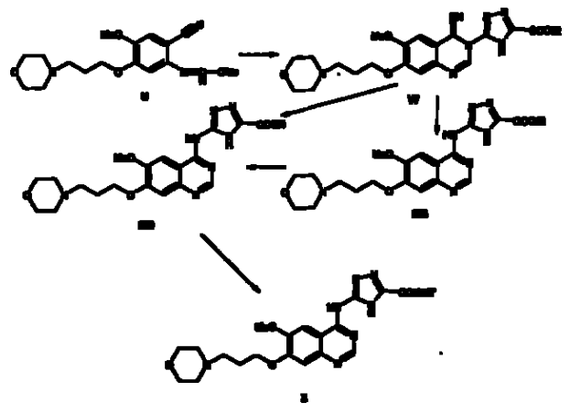
Ejemplo 107. Preparación de Compuesto 267 en Tabla 10

Una reacción análoga a la descrita en Ejemplo 101, pero comenzando con ciclohexilamina (18 mg, 0.18 mmol) produjo el compuesto del título (54 mg, 64 %).

^{1}HNMR (DMSO-d_6, TFA): 1.19 (m, 1H); 1.35 (m, 4H); 1.61 (m, 1H); 1.71 (m, 2H); 1.85 (m, 2H); 2.31 (m, 2H); 3.16 (t, 2H); 3.34 (t, 2H); 3.54 (d, 2H); 3.69 (t, 2H); 3.75 (m, 1H); 4.01 (s, 3H); 4.04 (m, 5H); 4.3 (t, 2H); 7.37 (s, 1H); 7.9 (s, 1H); 8.29 (s, 1H); 8.99 (s, 1H).

MS ES^+: 524 $(M+H)^+$

Esquema General 12



Ejemplo 108.

Paso (a) Preparación de Intermedios de la fórmula General W

Imidato U (2 g, 6 mmol) en dimetilformamida (40 ml) se hizo reaccionar con ácido clorhídrico de etil 5-amino-4H-1,2,4-triazol-3-carboxilato (1.16 g, 6 mmol) en presencia de hidruro de sodio (60 %, 504 mg, 12.6 mmol) a 110°C durante 7 horas, bajo argón. La mezcla se enfrió entonces a temperatura ambiente, y se añadió ácido acético (1.03 ml, 18 mmol), el solvente se evaporó bajo vacío, el residuo se purificó por cromatografía de gel de sílice, eluyente: CH_2Cl_2 / MeOH, 90/10 para producir el compuesto del título (1.07 g, 39 %).

^{1}HNMR (DMSO-d_6, TFA): 1.39 (t, 3H); 2.28 (m, 2H); 3.15 (t, 2H); 3.32 (t,2H); 3.56 (d, 2H); 3.68 (t, 2H); 3.98 (s, 3H); 4.05 (d, 2H); 4.37 (t, 2H); 4.52 (q, 2H); 7.49 (s, 1H); 8.1 (s, 1H); 8.71 (s, 1H).

MS ES$^+$: 458 $[M_+H]^+$

Paso (b): Preparación de Compuesto 268 en Tabla 11

Triazol éster W (80 mg, 0.17 mmol) en dimetilformamida (3 ml) se trató con acetato de dimetilamina (0.52 mmol) a 70°C durante 20 minutos. La mezcla se enfrió, el solvente se evaporó, y el residuo se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH / NH3, 90/10/1 para producir el producto del título (60 mg, 75 %).

^{1}HNMR (DMSO-d_6, TFA): 1.34 (t, 3H); 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t,

2H); 3.54 (d, 2H); 3.68 (t, 2H); 4.0 (s, 3H); 4.04 (d, 2H); 4.36 (m, 4H); 7.48 (s, 1H); 8.26 (s, 1H); 9.01 (s, 1H).
MS ES^+: 458 $(M+H)^+$

Ejemplo 109. Preparación de Compuesto 269 en Tabla 11

Triazol éster **268** (900 mg, 1.97 mmol) en metanol (20 ml), se trató con hidróxido de sodio (2N, 20 ml) a 80°C durante 1.5 hora. La mezcla se enfrió, y se acidificó a pH 2.5 con ácido clorhídrico (6N), el sólido se recuperó por filtración, se secó bajo vacío sobre P_2O_5 para producir el compuesto del título (843 mg, 100 %).
^{1}HNMR (DMSO-d_6, TFA): 2.37 (m, 2H); 3.12 (t, 2H); 3.3 (t, 2H); 3.5 (d, 2H); 3.87 (t, 2H); 3.97 (d, 2H); 4.01 (s, 3H); 4.35 (t, 2H); 7.63 (s, 1H); 8.32 (s, 1H); 8.97 (s, 1H).
MS ES^+: 430 $(M+H)^+$

Ejemplo 110. Preparación de Compuesto 270 en Tabla 11

Ácido **269** (120 mg, 0.28 mmol) en DMF (2 ml) se hizo reaccionar con anilina (0.025 ml, 0.28 mmol) en presencia de hexafluorofosfato de O-(7 - azabenzotriazol-1-il) N,N,N',N',-tetrametiluronio (106 mg, 0.28 mmol) y DIEA (0.12 ml, 0.7 mmol) a temperatura ambiente durante 4 horas. El solvente se evaporó, el residuo se disolvió en cloruro de metileno / metanol, y se trató con una solución metanólica de dimetilamina (2M, 1 ml) a temperatura ambiente de un día para otro. El solvente se evaporó, y el residuo se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH, 90/10 para producir el compuesto del título (12 mg, 9 %).
^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.18 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 4.01 (s, 3H); 4.03 (d, 2H); 4.33 (t, 2H); 7.16 (t, 1H); 7.39 (t, 2H); 7.45 (s, IH); 7.83 (d,2R); 8.2 (s, IH); 8.95 (s, IH).
MS ES^+: 505 $(M+H)^+$

Ejemplo 111. Preparación de Compuesto 271 en Tabla 11

Una reacción análoga a la descrita en Ejemplo 110, pero comenzando con

4-fluoroanilina (0.13 ml, 1.4 mmol) produjo el compuesto del título (44 mg, 18 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 4.0 (s, 3H); 4.04 (d, 2H); 4.33 (t, 2H); 7.23 (t, 2H); 7.44 (s, 1H); 7.86 (m, 1H); 8.18 (s, 1H); 8.93 (s, 1H).

MS ES^+: 523 $(M+H)^+$

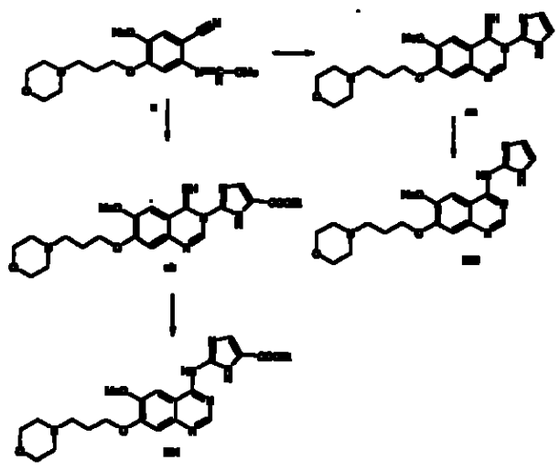
Ejemplo 112. Preparación de Compuesto 272 en Tabla 11

Una reacción análoga a la descrita en Ejemplo 110, pero comenzando con alilamina (0.13 ml, 1.75 mmol) produjo el compuesto del título (26 mg, 10 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.16 (t, 2H); 3.34 (, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.94 (d, 2H); 3.99 (s, 3H); 4.03 (d, 2H); 4.32 (t, 2H); 5.13 (d, 1H); 5.18 (d, 1H); 5.92 (m, 1H); 7.41 (s, 1H); 8.17 (s, 1H); 8.91 (s, 1H).

MS ES^+: 469 $(M+H)^+$

Esquema General 13



Ejemplo 113. Preparación de Compuesto 300 en Tabla 12

Paso 1 Preparación de Compuesto aa

Imidato u, (200 mg, 0.6 mmol) en DMF (4 ml) se condensó con 2-aminoimidazol, sulfato (160 mg, 0.6 mmol) en presencia de hidruro de sodio (60 %, 50 mg, 1.26 mmol) a 90°C durante 2 horas. La mezcla se

enfrió, se añadió ácido acético (0.01 ml, 1.8 mmol), el solvente se evaporó, y el residuo se purifico por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH, 90/10 para producir el compuesto del título (112 mg, 48 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.33 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.97 (s, 3H); 4.03 (d, 2H); 4.36 (t, 2H); 7.41 (s, 2H); 7.47 (s, 1H); 8.13 (s, 1H); 8.66 (s, 1H).

MS ES^+: 385 $(M+H)^+$

Paso 2: Preparación de Compuesto 300

Imidazol aa (105 mg, 0.273 mmol) en DMF (2 ml) se calentó a 80°C durante 0.3 hora en presencia de acetato de dimetilamina (0.819 mmol), el solvente se evaporó, y el residuo se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOR sat. NH_3, 90/10 para producir el compuesto del título (78 mg, 74 %).

^{1}HNMR (DMSO): 1.96 (m, 2H); 2.39 (m, 4H); 2.46 (t, 2H); 3.6 (m, 4H); 3.9 (s, 3H); 4.18 (t, 2H) . 6.9 (s, 2H); 7.14 (s, 1H); 7.84 (s, 1H); 8.39 (s, 1H).

MS ES^+: 385 $(M+H)^+$

Ejemplo 114. Preoaración de Compuesto 301 en Tabla 12

Paso 1: Preparación de Compuesto ab

Imidato u (250 mg, 0.751 mmol) en DMF (4 ml) se hizo reaccionar con etil 2-aminoimidazol-4-carboxilato (117 mg, 0.751 mmol) en presencia de hidruro de sodio (60 %, 30 mg, 0.826 mmol) a 100° C durante 3 horas. La mezcla se enfrió, se agregó ácido acético (0.13 ml, 2.25 mmol), el solvente se evaporó, y el residuo se purificó por cromatografía de gel de sílice para producir el compuesto del título (125 mg, 36 %).

^{1}HNMR (DMSO-d_6, TFA): 1.32 (t, 3H); 2.3 (m, 2H); 3.15 (t, 2H); 3.34 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.98 (s, 3H); 4.03 (d, 2H); 4.33 (q, 2H); 4.37 (t, 2H); 7.49 (s, 1H); 8.11 (s, 1H); 8.2 (s, 1H); 8.65 (s, 1H).

MS ES^+: 457 $(M+H)^+$

Paso 2: Preparación de Compuesto 301 en Tabla 12

Imidazol 3 (122 mg, 0.268 mmol) en DMF (2 ml) se calentó a 80°C durante 0.3 horas en presencia de acetato de dimetilamina (0.802 mmol). El solvente se evaporó, y el residuo se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH sat. NH_3 95/5 a 90/10 para producir el compuesto del título (105 mg, 86 %).

^{1}HNMR (DMSO-d_6, TFA): 1.32 (t, 3H); 2.3 (m, 2H); 3.15 (t, 2H); 3.34 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.94 (s, 3H); 4.03 (d, 2H); 4.27 (t, 2H); 4.33 (q, 2H); 7.27 (s, 1H); 7.84 (s, 1H); 7.92 (s, 1H); 8.76 (s, 1H).

MS ES$^+$: 457 $(M_+H)^+$

Ejemplo 115. Preparación de Compuesto 302 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 4-metoxianilina (32 mg, 0.26 mmol) produjo el compuesto 302 en Tabla 13 (24 mg, 21 %).

MS ES$^+$: 551 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3.76 (s, 3H); 4.02 (s, 3H); 4.04 (d, 2H); 4.33 (t, 2H); 6.96 (d, 2H); 7.38 (s, 1H); 7.62 (d, 2H); 8.04 (s, 1H); 8.55 (s, 1H); 9.27 (s, 1H).

Ejemplo 116. Preparación de Compuesto 303 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 4-metilanilina (28 mg, 0.26 mmol) produjo el compuesto 303 en Tabla 13 (23 mg, 22%).

MS ES$^+$: 535 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.29 (s, 3H); 2.33 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.01 (s, 3H); 4.04 (d, 2H); 4.33 (t, 2H); 7.19 (d, 2H); 7.38 (s, 1H); 7.60 (d, 2H); 8.05 (s, 1H); 8.58 (s, 1H); 9.28 (s, 1H).

Ejemplo 117. Preparación de Compuesto 304 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 2-aminopiridina 30 (24 mg, 0.26 mmol) produjo el compuesto 304 en Tabla

13 (12 mg, 11 %).

MS ES$^+$: 522 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.02 (s, 3H); 4.04 (d, 2H); 4.34 (t, 2H); 7.33 (m, 1H); 7.41 (s, 1H); 8.07 (m, 2H); 8.09 (s, 1H); 8.46 (d, 1H); 8.81 (s, 1H); 9.30 (s, 1H).

Ejemplo 118. Preparación de Compuesto 305 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con alcohol 2-aminobencílico (32 mg, 0.26 mmol) produjo el compuesto 305 en Tabla 13 (54 mg, 60%).

MS ES$^+$: 551 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2,33 (t, 2H); 3.18 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 3.78 (s, 2H); 4.02 (s, 3H); 4.05 (d, 2H); 4.34 (t, 2H); 6.73 (d, 1H); 7.30 (m, 2H); 7.39 (s, 1H); 7.40 (m, 1H); 8.07 (s, 1H); 8.62 (s, 1H); 9.3 (s, 1H).

Ejemplo 119. Preparación de Compuesto 306 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 4-

metoxbencilamina (36 mg, 0.26 mmol) produjo el compuesto 306 en Tabla 13 (29 mg, 26%).

MS ES$^+$: 565 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.28 (t, 2H); 3.14 (t, 2H); 3.31 (t, 2H); 3.50 (d, 2H); 3.68 (t, 2H); 3.69 (s, 3H); 3.94 (s, 3H); 3.98 (d, 2H); 4.26 (t, 2H); 4.37 (s, 2H); 6.89 (m, 2H); 7.12 (m, 2H); 7.35 (s, 1H); 7.90 (s, 1H); 8.31 (s, 1H); 9.15 (s, 1H).

Ejemplo 120. Preparación de Compuesto 307 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 3-nitroanilina (36 mg, 0.26 mmol) produjo el compuesto 307 en Tabla 13 (27 mg, 24%).

MS ES$^+$: 566 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.30 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.02 (s, 3H); 4.04 (d, 2H); 4..33 (t, 2H); 7.40 (s, 1H); 7.71 (t, 1H); 7.99 (d, 1H); 8.08 (s, 1H); 8.14 (d, 1H); 8.64 (s, 1H); 8.71 (s, 1H); 9.31 (s, 1H).

Ejemplo 121. Preparación de Compuesto 308 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con aminoacetonitrilo (24 mg, 0.26 mmol) produjo el compuesto 308 en Tabla 13 (29 mg, 30%).

MS ES$^+$: 484 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 4.00 (s, 3H); 4.02 (d, 2H); 4.32 (t, 2H); 4.37 (s, 2H); 7.39 (s, 1H); 8.06 (s, 1H); 8.36 (s, 1H); 9.27 (s, 1H).

Ejemplo 122. Preparación de Compuesto 309 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 2-metil-5-nitroanilina (40 mg, 0.26 mmol) produjo el compuesto 309 en Tabla 13 (14 mg, 12%).

MS ES$^+$: 580 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 4.01 (s, 3H); 4.03 (d, 2H); 4.32 (t, 2H); 7.39 (s, 1H); 7.58 (d, 1H); 8.04 (d, 1H); 8.08 (s, 1H); 8.34 (d, 1H); 8.62 (s, 1H); 9.29 (s, 1H).

Ejemplo 123. Preparación de Compuesto 310 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con ciclopropilamina 15 (15 mg, 0.26 mmol) produjo el compuesto 310 en Tabla 13 (6 mg, 6%).

MS ES$^+$: 485 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 0.68 (m, 2H); 0.74 (m, 2H); 2.27 (t, 2H); 2.67 (m, 1H); 3.12 (t, 2H); 3.31 (t, 2H); 3.51 (d, 2H); 3.69 (t, 2H); 3.95 (s, 3H); 3.98 (d, 2H); 4.29 (t, 2H); 7.32 (s, 1H); 7.96 (s, 1H); 8.24 (s, 1H); 9.20 (s,

1H).

Ejemplo 124. Preparación de Compuesto 311 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 4-nitrobencilamina (49 mg, 0.26 mmol) produjo el compuesto 311 en Tabla 13 (5 mg, 4%).

MS ES^+: 580 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.00 (s, 3H); 4.03 (d, 2H); 4.32 (t, 2H); 4.63 (s, 2H); 7.38 (s, 1H); 7.62 (d, 2H); 8.04 (s, 1H); 8.23 (d, 2H); 8.40 (s, 1H); 9.25 (s, 1H).

Ejemplo 125. Preparación de Compuesto 312 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 2-anilinoetanol (36 mg, 0.26 mmol) produjo el compuesto 312 en Tabla 13 (49 mg, 44%).

MS ES^+: 565 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.7 (m, 4H); 4.01 (s, 3H); 4.03 (d, 2H); 4.33 (t, 2H); 4.49 (t, 2H); 7.15 (t, 1H); 7.26 (d, 2H); 7.41 (t, 2H); 7.43 (s, 1H); 8.15 (s, 1H); 8.48 (s, 1H); 9.31 (s, 1H).

Ejemplo 126. Preparación de Compuesto 313 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con furfurilamina (25 mg, *0.26* mmol) produjo el compuesto 313 en Tabla 13 (20 mg, 19%).

MS ES^+: 525 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.69 (t, 2H); 3.99 (s, 3H); 4.02 (d, 2H); 4.32 (t, 2H); 4.48 (s, 2H); 6.33 (d, 1H); 6.41 (d, 1H); 7.37 (s, 1H); 7.59 (s, 1H); 8.01 (s, 1H); 8.37 (s, 1H); 9.24 (s, 1H).

Ejemplo 127. Preparación de Compuesto 314 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 3-cloroanilina (33 mg, 0.26 mmol) produjo el compuesto 314 en Tabla 13 (21 mg, 19%).

MS ES^+: 555, 557 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.54 (d, 2H); 3.69 (t, 2H); 4.02 (s, 3H); 4.04 (d, 2H); 4.32 (t, 2H); 7.20 (d, 1H); 7.39 (s, 1H); 7.42 (t, 1H); 7.63 (d, 1H); 7.91 (s, 1H); 8.07 (s, 1H); 8.61 (s, 1H); 9.30 (s, 1H).

Ejemplo 128. Preparación de Compuesto 315 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 2-metoxianilina ,5 (32 mg, 0.26 mmol) produjo el compuesto 315 en Tabla 13 (67 mg, 61 %).

MS ES^+: 551 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 3.87 (s, 3H); 4.02 (s, 3H); 4.04 (d, 2H); 4.33 (t, 2H); 6.99 (t, 1H); 7.13 (d, 1H); 7.23 (t, 1H); 7.40 (s, 1H); 7.66 (d, 1H); 8.04 (s, 1H); 8.64 (s, 1H); 9.27 (s, 1H).

Ejemplo 139. Preparación de Compuesto 316 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con tiofen-2-metilamina (29 mg, 0.26 mmol) produjo compuesto 316 en Tabla 13 (25 mg, 23%).

MS ES^+: 541 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.18 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 4.01 (s, 3H); 4.04 (d, 2H); 4.34 (t, 2H); 4.67 (s, 2H); 6.99 (m, 1H); 7.08 (m, 1H); 7.39 (s, 1H); 7.41 (d, 1H); 8.04 (s, 1H); 8.36 (s, 1H); 9.27 (s, 1H).

Ejemplo 140. Preparación de Compuesto 317 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con neopentilamina (23 mg, 0.26 mmol) produjo el compuesto 317 en Tabla 13

(31 mg,30%).

MS ES^+: 515 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 0.91 (s, 9H); 2.31 (t, 2H); 3.10 (s, 2H); 3.17 (t, 2H); 3.35 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.00 (s, 3H); 4.03 (d, 2H); 4.32 (t, 2H); 7.35 (s, 1H); 8.00 (s, 1H); 8.45 (s, 1H); 9.23 (s, 1H).

Ejemplo 141. Preparación de Compuesto 318 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 2,6- difluorobencilamina (37 mg, 0.26 mmol) produjo el compuesto 318 en Tabla 13 (35 mg, 31 %).

MS ES^+: 571 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.99 (s, 3H); 4.03 (d, 2H); 4.31 (t, 2H); 4.54 (s, 2H); 7.11 (t, 2H); 7.36 (s, 1H); 7.42 (m, 1H); 8.00 (s, 1H); 8.35 (s, 1H); 9.24 (s, 1H).

Ejemplo 142. Preparación de Compuesto 319 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 2-metilalilamina (28 mg, 0.26 mmol) produjo el compuesto 319 en Tabla 13 (16 mg, 16%).

MS ES^+: 499 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.72 (s, 3H); 2.31 (t, 1H); 3.15 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3.72 (s, 2H); 3.99 (s, 3H); 4.02 (d, 2H); 4.31 (t, 2H); 4.82 (s, 1H); 4.86 (s, 1H); 7.36 (s, 1H); 8.01 (s, 1H); 8.37 (s, 1H); 9.23 (s, 1H).

Ejemplo 143. Preparación de Compuesto 320 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 2-metil-4-fluoroanilina (33 mg, 0.26 mmol) produjo el compuesto 320 en Tabla 13 (47 mg, 43%).

MS ES^+: 553 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.26 (s, 3H); 2.31 (t, 1H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 4.01 (s, 3H); 4.03 (d, 2H); 4.33 (t, 2H); 7.07

(m, 1H); 7.18 (d, 1H); 7.36 (m, 1H); 7.38 (s, 1H); 8.06 (s, 1H); 8.53 (s, 1H); 9,27 (s, 1H).

Ejemplo 144. Preparación de Compuesto 321 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 2-fluoro-5-metilanilina (33 mg, 0.26 mmol) produjo el compuesto 321 en Tabla 13 (60 mg, 54%).

MS ES^+: 553 $(M_+H)^+$.

Ejemplo 145. Preparación de Compuesto 322 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 4- fluorobencillamina (33 mg, 0.26 mmol) produjo el compuesto 322 en Tabla 13 (33 mg, 30%).

MS ES^+: 553 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 1H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3.99 (s, 3H); 4.02 (d, 2H); 4.33 (t, 2H); 4.47 (s, 2H); 7.15 (t, 2H); 7.36 (s, 1H); 7.37 (m, 2H); 8.02 (s, 1H); 8.36 (s, 1H); 9.24 (s, 1H).

Ejemplo 146. Preparación de Compuesto 323 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 3,4-difluorobencilamina (37 mg, 0.26 mmol) produjo el compuesto 323 en Tabla 13 (17 mg, 15%).

MS ES^+: 571 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.00 (s, 3H); 4.04 (d, 2H); 4.33 (t, 2H); 4.48 (s, 2H); 7.21 (m, 1H); 7.38 (s, 1H); 7.38 (m, 2H); 8.03 (s, 1H); 8.38 (s, 1H); 9.24 (s, 1H).

Ejemplo 147. Preparación de Compuesto 324 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 3-metilanilinae (28 mg, 0.26 mmol) produjo el compuesto 324 en Tabla 13 (57 mg, 53%).

MS ES^+: 535 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (m, 5H); 3.17 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.01 (s, 3H); 4.04 (d, 2H); 6.95 (d, 1H); 7.24 (t, 1H); 7.38 (s, 1H); 7.53 (m, 2H); 8.04 (s, 1H); 8.59 (s, 1H); 9.28 (s, 1H).

Ejemplo 148. Preparación de Compuesto 325 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 2-

(metiltio)anilina (36 mg, 0.26 mmol) produjo el compuesto 325 en Tabla 13 (73 mg, 64%).

MS ES$^+$: 567 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.44 (s, 3H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 4.01 (s, 3H); 4.03 (d, 2H); 4.32 (t, 2H); 7.22 (t, 1H); 7.37 (m, 4H); 8.06 (s, 1H); 8.52 (s, 1H); 9.27 (s, 1H).

Ejemplo 149. Preparación de Compuesto 326 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 5-aminoindol (34 mg, 0.26 mmol) produjo el compuesto 326 en Tabla 13 (16 mg, 15%).

MS ES$^+$: 560 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3:37 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.02 (s, 3H); 4.04 (d, 2H); 4.32 (t, 2H); 7.36 (m, 5H); 7.94 (s, 1H); 8.04 (s, 1H); 8.28 (s, 1H); 9.28 (s, 1H).

Ejemplo 150. Preparación de Compuesto 327 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 3- aminobenzonitrilo (31 mg, 0.26 mmol) produjo el compuesto 327 en Tabla 13 (30 mg, 28%). MS ES$^+$: 546 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.67 (t, 30 2H); 4.02 (s, 3H); 4.04 (d, 2H); 4.33 (t, 2H); 7.40 (s, 1H); 7.60 (m, 2H); 7.97 (m, 1H); 8.08 (s, 1H); 8.21 (s, 1H); 8.61 (s, 1H); 9.30 (s, 1H).

Ejemplo 151. Preparación de Compuesto 328 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 2,4-difluorobencilamina (37 mg, 0.26 mmol) produjo el compuesto 328 en Tabla 13 (27 mg, 24%).

MS ES^+: 571 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.70 (t, 2H); 4.00 (s, 3H); 4.03 (d, 2H); 4.32 (t, 2H); 4.49 (s, 2H); 7.09 (m, 1H); 7.21 (m, 1H); 7.38 (s, 1H); 8.02 (s, 1h); 8.38 (s, 1H); 9.24 (s, 1h).

Ejemplo 152. Preparación de Compuesto 329 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 3-(2- aminoetil)piridina (32 mg, 0.26 mmol) produjo el compuesto 329 en Tabla 13 (33 mg, 30%).

MS ES^+: 550 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.33 (t, 2H); 3.11 (t, 2H); 3.18 (t, 2H); 3.35 (t, 2H); 3.57 (d, 2H); 3.66 (t, 2H); 3.68 (t, 2H); 4.01 (s, 3H); 4.05 (d, 2H); 4.34 (t, 2H); 7.41 (s, 1H); 8.05 15 (s, 1H); 8.08 (dd, 2H); 8.28 (s, 1H); 8.59 (d, 1H); 8.87 (d, 1H); 8.95 (s, 1H); 9.25 (s, 1H).

Ejemplo 153. Preparación de Compuesto 330 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con N-metilisobutilamina (23 mg, 0.26 mmol) produjo el compuesto 330 en Tabla 13 (23 mg, 22%).

MS ES^+: 515 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 0.88 (d, 6H); 2.02 (m, 1H); 2.31 (t, 2H); 3.16 (t, 2H); 3.27 (m, 5H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.00 (s, 3H); 4.03 (d, 2H); 4.32 (t, 2H); 7.37 (s, 1H); 8.03 (s, 1H); 8.18 (s, 1H); 9.23 (s, 1H).

Ejemplo 154. Preparación de Compuesto 331 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 2-aminobencilamina (32 mg, 0.26 mmol) produjo el compuesto 331 en Tabla 13 (6 mg, 6%).

MS ES$^+$: 550 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 30 2H); 4.00 (s, 3H); 4.03 (d, 2H); 4.32 (t, 2H); 4.47 (s, 2H); 7.41 (s, 1H); 7.46 (m, 4H); 8.06 (s, 1H); 8.42 (s, 1H); 9.24 (s, 1H).

Ejemplo 155. Preparación de Compuesto 332 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 3-

metilbutilamina (23 mg, 0.26 mmol) produjo el compuesto 332 en Tabla 13 (48 mg, 47%).

MS ES$^+$: 515 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 0.90 (d, 6H); 1.43 (q, 2H); 1.62 (m, 1H); 2.31 (t, 2H); 3.15 (t, 2H); 3.28(t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.99 (s, 3H); 4.02 (d, 2H); 4.31 (t, 2H); 7.35 (s, 1H); 8.00 (s, 1H); 8.31 (s, 1H); 9.23 (s, 1H).

Ejemplo 156. Preparación de Compuesto 333 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 1-aminometil-1-ciclohexanol (43 mg, 0.26 mmol) produjo el compuesto 333 en Tabla 13 (7 mg, 6%).

MS ES$^+$: 557 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.37 (m, 10H); 2.28 (t, 2H); 3.11 (t, 2H); 3.23 (s, 2H); 3.32 (t, 2H); 3.51 (d, 2H); 3.65 (t, 2H); 3.96 (s, 3H); 3.99 (d, 2H); 4.28 (t,2H); 7.32 (s, 1H); 7.95 (s, 1H); 8.43 (s, 1H); 9.19 (s, 1H).

Ejemplo 157. Preparación de Compuesto 334 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 2- aminometilpirazina (38 mg, 0.26 mmol) produjo el compuesto 334 en Tabla 13 (25 mg, 24%).

MS ES$^+$: 537 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.33 (t, 2H); 3.13 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.00 (s, 3H); 4.05 (d, 2H); 4.30 (t, 2H); 4.65 (s, 2H); 7.38

(s, 1H); 8.03 (s, 1H); 8.40 (s, 1H); 8.57 (d, 1H); 8.62 (d, 1H); 8.70 (s, 1H); 9.24 (s, 1H).

Ejemplo 158. Preparación de Compuesto 335 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 3-metoxianilina (32 mg, 0.26 mmol) produjo el compuesto 335 en Tabla 13 (60 mg, 54%). MS ES^+: 551 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.58 (d, 2H); 3.70 (t, 2H); 3.79 (s, 3H); 4.03 (s, 3H); 4.06 (d, 2H); 4.34 (t, 2H); 6.73 (d, 1H); 7.29 (d, 1H); 7.32 (d, 1H); 7.41 (m, 2H); 8.07 (s, 1H); 8.62 (s, 1H); 9.30 (s, 1H).

Ejemplo 159. Preparación de Compuesto 336 en Tabla 13

Una reacción análoga a la descrita en Esquema General 5, comenzando con 4- clorobencilamina (19 mg, 0.26 mmol) produjo el compuesto 336 en Tabla 13 (31 mg, 54%).

MS ES^+: 569 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2h); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.69 (t, 10 2H); 4.00 (s, 3H); 4.03 (d, 2H); 4.32 (t, 1H); 4.48 (s, 2H); 7.42 (m, 5H); 8.02 (s, 1H); 8.37 (s, 1H); 9.24 (s, 1H).

Ejemplo 160. Preparación de Compuesto 337 en Tabla 14

4-((2-amino-1,3-tiazol-5-il)ácido acético)-6-metoxi-7-(3-morfolinopropoxi)quinazolina 15 (78 mg, 0.17 mmol) en DMF (1 ml), se hizo reaccionar con anilina (19 mg, 0.2 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (76 mg, 0.2 mmol) y DIEA (44 mg, 0.34 mmol) a 50°C de un día para otro. La mezcla de la reacción se enfrió, se trató con NaHCO3 (1 ml), se concentró. El sólido amarillo se recuperó, disolvió en una mezcla de CH_2Cl_2 / MeOH (60/40) 20 mol. Alúmina (3 g) se agregó a la mezcla, el solvente se evaporó, y el sólido se agregó en la parte superior de una columna de alúmina que se eluyó con CH_2Cl_2 / MeOH (10/0 a 9/1) para

producir el compuesto del título (43 mg, 47 %):

MS ES^+: 535 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3.37 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3.99 (m, 5H); 4.04 (d, 2H); 4.30 (t, 2H); 7.08 (t, 1H); 7.32 (m, 3H); 7.62 (m, 3H); 7.91 (s, 1H); 9.09 (s, 1H).

4-(etil(2-amino-1,3-tiazol-5-il)acetato)-6-metoxi-7-(3-morfolinopropoxi)quinazolina. Amidina J de Esquema 2 (4.5 g, 13 mmol) en ácido acético (45 ml) se hizo reaccionar con etil (2- amino-1,3-tiazol-il)acetato (2.54 g, 13.65 mmol) a reflujo durante 5.5 horas bajo argón. La mezcla se concentró, y el residuo se purificó sobre cromatografía de gel de sílice, eluyente

CH_2Cl_2 / MeOH, 95/5 a 90/10 para producir el compuesto del título (4.5 g, 63 %).

^{1}HNMR (DMSO-d_6): 1.22 (t, 3H); 1.96 (t, 2H); 2.37 (m, 4H); 2.35 (t, 2H); 3.58 (m, 4H); 3.91 (s, 2H); 3.95 (s, 3H); 4.13 (q, 2H); 4.20 (t, 2H); 7.25 (s, 1H); 7.36 (s, 1H); 8.10 (s, 1H); 8.66 (s, 1H).

4-((2-amino-1,3-tiazol-5-il)acétic ácido)-6-metoxi-7-(3-morfolinopropoxi)quinazolina. 4-(etil(2-amino-1,3-tiazol-5-il)acetato)-6-metoxi- 7-(3-morfolinopropoxi)quinazolina (4.38 g, 8 mmol) en etanol (44 ml) se trató con hidróxido de sodio (2N, 10 ml) a 50°C durante 4 horas. La mezcla se enfrió a temperatura ambiente y se ajustó el pH a 3.5 con 2N HCl. El residuo se disolvió en CH_2Cl_2 / MeOH, 60/40, se agregó DIEA (3 g, 24 mmoles). La mezcla se agitó durante 10 minutos, se filtró, y la solución se concentró para producir un residuo oleoso. Este residuo se disolvió en etanol, y el solvente se evaporó parcialmente. Se recuperó un sólido cristalino, se suspendió en etanol, se lavó con éter y se secó bajo vacío para producir el compuesto del título (3.7 g, 100 %).

^{1}HNMR (DMSO-d_6, TFA): 2.28 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.70 (t, 2H); 3.92 (s, 2H); 3.99 (s, 3H); 4.03 (d, 2H); 4.30 (t, 2H); 7.32 (s, 1H); 7.60 (s, 1H); 7.90 (s, 1H); 9.08 (s, 1H).

Ejemplo 161. Preparación de Compuesto 338 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 3-cloro-4-fluoroanilina (30 mg, 0.2 mmol) produjo el compuesto del título (24 mg, 24 %).

MS ES^+: 587 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3.34 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 3.99 (m, 5H); 4.03 (d, 2H); 4.30 (t, 2H); 7.30 (s, 1H); 7.39 (t, 1H); 7.50 (m, 1H); 7.65 (s, 1H); 7.85 (s, 1H); 7.97 (d, 1H); 9.09 (s, 1H).

Ejemplo 162. Preparación del Compuesto 339 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 4-cloroanilina (26 mg, 0.2 mmol) produjo el compuesto del título (73 mg, 76 %). MS ES^+: 569 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3.89 (m, 5H); 4.04 (d, 2H); 4.30 (t, 2H); 7.30 (s, 1H); 7.39 (d, 2H); 7.64 (s, 1H); 7.65 (d, 2H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 163. Preparación de Compuesto 340 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 3,4-difluoroanilina (26 mg, 0.2 mmol) produjo el compuesto del título (75 mg, 77 %). MS ES^+: 571 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.72 (t, 2H); 3.99 (m, 5H); 4.04 (d, 2H); 4.30 (t, 2H); 7.31 (s, 1H); 7.32 (m, 1H); 7.41 (q, 1H); 7.65 (s, 1H); 7.81 (m, 1H); 7.92 (s, 1H); 9.09 (s, 1H).

Ejemplo 164. Preparación de Compuesto 341 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 3-metoxianilina (25 mg, 0.2 mmol) produjo el compuesto del título (40 mg, 42 %). MS ES^+: 565 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.70 (t,2H) 15 ; 3.74 (s, 3H); 3.97 (s, 2H); 3.99 (s, 3H); 4.04 (d, 2H);

4.31 (t, 2H); 6.68 (d, 1H); 7.15 (d, lH); 7.23 (t, 1H); 7.29 (s, 1H); 7.33 (s, lH); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 165. Preparación de Compuesto 342 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-cloroanilina (26 20 mg, *0.2* mmol) produjo el compuesto del título (15 mg, 16 %).

MS ES^+: 569 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.30 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 3.99 (s, 3H); 4.05 (m, 4H); 4.31 (t, 2H);,7.22 (t, 1H); 7.30 (s, 1H); 7.35 (t, 1H); 7.51 (d, 1H); 7.65 (s, 1H); 7.75 (d, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 166. Preparación de Compuesto 343 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 4-metoxianilina (26 mg, 0.21 mmol) produjo el compuesto del título (55 mg, 57 %).

MS ES^+: 565.6 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 3.19 (t, 2H); 3.39 (t, 2H); 3.58 (d, 2H); 3.73 (t, 2H); 3.80 (s, 3H); 3.97 (s, 2H); 4.02 (s, 3H); 4.07 (d, 2H); 4.33 (t, 2H); 6.93 (d, 2H); 7.09 (s, 1H); 7.33 (s, 1H); 7.56 (d, 2H); 7.66 (s, 1H); 7.94 (s, 1H); 9.12 (s, 1H).

Ejemplo 167. Preparación de Compuesto 344 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 4-metilanilina (23 mg, 0.21 mmol) produjo el compuesto del título (5; mg, 54 %).

MS ES^+: 549.7 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.29 (s, 3H); 2.31 (t, 2H); 3.19 (t, 2H); 3.38 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 3.99 (s, 2H); 4.02 (s, 3H); 4.04 (d, 2H); 4.33 (t, 2H); 7.16 (d, 2H); 7.33 (s, 1H); 7.54 (d, 2H); 7.67 (s, 1H); 7.94 (s, 1H); 9.12 (s, 1H).

Ejemplo 168. Preparación de Compuesto 345 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-metilanilina (23 mg, 0.21 mmol) produjo el compuesto del título (42 mg, 45 %). MS ES^+: 549.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.24 (s, 3H); 2.31 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H: ; 3.69 (t, 2H); 3.99 (s, 2H); 4.02 (s, 3H); 4.04 (d, 2H); 4.30 (t, 2H); 7.12 (t, 1H); 7.19 (t, 1H); 7.24 (d, 1H); 7.31 (s, 1H); 7.43 (t, 1H); 7.66 (s, 1H); 7.92 (s, 1H); 9.08 (s, 1H).

Ejemplo 169. Preparación de Compuesto 346 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-aminopiridina (20 mg, 0.21 mmol) produjo el compuesto del título (12 mg, 13 %).

MS ES^+: 536.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.18 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 4.00 (m, 5H); 4.04 (d, 2H); 4.33 (t,2H); 7.34 (s, 1IH); 7.37 (t, 1H); 7.68 (s, 1H); 7.93 (d, 1H); 7.94 (s, 1H); 8.10 (t, 1H); 8.42 (d, 1H); 9.10 (s, 1H).

Ejemplo 170. Preparación de Compuesto 347 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con alcohol 2-aminobencílico (26 mg, 0.21 mmol) produjo el compuesto del título (24 mg, 24 %).

MS ES^+: 565.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6): 1.97 (t, 2H); 2.41 (m, 6H); 3.59 (m, 4H); 3.91 (s, 2H); 3.97 (s, 3H); 30 4.21 (t, 2H); 4.50 (d, 2H); 5.27 (t, 1H); 7.18 (t, 1H); 7.25 (d, 1H); 7.26 (s, 1H); 7.42 (m, 2H); 7.52 (d, 1H); 8.67 (s, 1H); 9.59 (s, 1H).

Ejemplo 171. Preparación de Compuesto 348 en TabIe 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-amino-3-metil-1-butanol (22 mg, 0.21 mmol) produjo el compuesto del

título (25 mg, 27 %).

MS ES$^+$: 545.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 0.87 (d, 3H); 0.89 (d, 3H); 1.86 (m, 1H); 2.31 (t, 2H); 3.18 (t, 2H); 3.37 (t, 2H); 3.44 (2s, 2H); 3.57 (d, 2H); 3.63 (q, 1H); 3.70 (t, 2H); 3.80 (d, 2H); 4.01 (t, 3H); 4.07 (d, 2H); 4.31 (t, 2H); 7.32 (s, 1H); 7.58 (s, 1H); 7.92 (s, 1H); 9.09 (s, 1H).

Ejemplo 172. Preparación de Compuesto 349 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-anilinoetanol (29 mg, 0.21 mmol) produjo el compuesto del título (11 mg, 11 %). MS ES$^+$: 579.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.38 (t, 2H); 3.40 (m, 2H); 3.50 (t, 2H); 3.54 (d, 2H); 3.67 (m, 2H); 3.75 (t, 2H); 3.98 (s, 3H); 4.07 (d, 2H); 4.31 (t, 2H); 7.30 (s, 1H); 7.40 (s, 1H); 7.45 (m, 2H); 7.52 (m, 3H); 7.89 (s, 1H); 9.08 (s, 1H).

Ejemplo 173. Preparación de Compuesto 350 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 3-cloro-4-metilamina (30 mg, 0.21 mmol) produjo el compuesto del título (3 mg, 3 %).

MS ES$^+$: 583.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (m, 5H); 3.20 (t, 2H); 3.40 (t, 2H); 3.60 (d, 2H); 3.72 (t, 2H); 4.01 (s, 2H); 4.02 (s, 3H); 4.07 (d, 2H); 4.33 (t, 2H); 7.32 (m, 2H); 7.42 (d, 1H); 7.68 (s, 1H); 7.87 (s, 1H); 7.95 (s, 1H); 9.13 (s, 1H).

Ejemplo 174. Preparación de Compuesto 351 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 3-nitroanilina (29 mg, 0.21 mmol) produjo el compuesto del título (20 mg, 21 %). MS ES$^+$: 580.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.33 (t, 2H); 3.20 (t, 2H); 3.39 (t, 2H); 3.60 (d, 2H); 3.73 (t, 2H); 4.02 (s, 3H); 4.06 (d, 2H); 4.09 (s, 2H); 4.34 (t, 2H); 7.34 (s, 1H); 7.67 (d, 1H); 7.70 (s, 1H); 7.95 (s, 1H); 7.98 (m, 2H); 8.74 (s, 1H);

9.15 (s, 1H).

Ejemplo 175. Preparación de Compuesto 352 en Tabla 14.

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con aminoacetonitrilo (19 mg, 0.21 mmol) produjo el compuesto del título (28 mg, 31 %).

MS ES^+: 498.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.18 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 3.84 (s, 2H); 3.99 (s, 3H); 4.04 (d, 2H); 4.21 (s, 2H); 4.31 (t, 2H); 7.31 (s, 1H); 7.60 (s, 1H); 9.10 (s, 1H).

Ejemplo 176. Preparación de Compuesto 353 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-metil-5-nitroanilina (32 mg, 0.21 mmol) produjo el compuesto del título (11 mg, 11 %).

MS ES^+: 594.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 2.44 (s, 3H); 3.19 (t, 2H); 3.40 (t, 2H); 3.59 (d, 2H); 3.73 (t, 2H); 4.03 (s, 3H); 4.07 (d, 2H); 4.16 (s, 2H); 4.34 (t, 2H); 7.34 (s, 1H); 7.57 (d, 1H); 7.71 (s, 1H); 7.95 (s, 1H); 8.01 (d, 1H); 8.58 (s, 1H); 9.13 (s, 1H).

Ejemplo 177. Preparación de Compuesto 354 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-amino-5-cloropiridina (27 mg, 0.21 mmol) produjo el compuesto del título (13 mg, 13 %).

MS ES^+: 570.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 3.99 (s, 3H); 4.04 (d, 2H); 4.07 (s, 2H); 4.31 (t, 2H); 7.02 (d, 1H); 7.36 (s, 1H); 7.64 (s, 1H); 7.92 (s, 1H); 7.98 (dd, 1H); 8.21 (d, 1H); 9.1 (s, 1H).

Ejemplo 178. Preparación de Compuesto 355 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 4-trifluorometilanilina (34 mg, 0.21 mmol) produjo el compuesto del título (26 mg, 25 %);

MS ES^+: 603.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.30 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.72 (t, 2H) 30 ; 3.99 (s, 3H); 4.05 (m, 4H); 4.31 (t, 2H); 7.31 (s, 1H); 7.66 (s, 1H); 7.70 (d, 2H); 7.84 (d, 2H); 7.92 (s, 1H); 9.10 (s, 1H).

Ejemplo 179. Preparación de Compuesto 356 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 3-cloroanilina (27 mg, 0.21 mmol) produjo el compuesto del título (47 mg, 48 %).

MS ES^+: 569.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2 H); 3.69 (t, 2H); 3.99 (s, 3H); 4.00 (s,.2H); 4.04 (d, 2H); 4.31 (t, 2H); 7.14 (d, 1H); 7.30 (s, 1H); 7.37 (t, 1H); 7.47 (d, 1H); 7.65 (s, 1H); 7.87 (s, 1H); 7.92 (s, 1H); 9.10 (s, 1H).

Ejemplo 180. Preparación de Compuesto 357 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-metoxianilina (26 mg, 0.21 mmol) produjo el compuesto del título (44 mg, 46 %).

MS ES^+: 565.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.33 (t, 2H); 3.20 (t, 2H); 3.40 (t, 2H); 3.60 (d, 2H); 3.73 (t, 2H); 3.91 (s, 3H); 4.03 (s, 3H); 4.08 (d, 2H); 4.11 (s, 2H); 4.34 (t, 2H); 6.96 (t, 1H); 7.12 (m, 2H); 7.34 (s, 1H); 7.66 (s, 1H); 7.95 (s, 1H); 8.01 (d, 1H); 9.12 (s, 1H).

Ejemplo 181. Preparación de Compuesto 358 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-fluoroanilina (23 20 mg, 0.21 mmol) produjo el compuesto del título (43 mg, 46 %).

MS ES$^+$: 553.7 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.18 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 4.00 (s, 3H); 4.05 (d, 2H); 4.08 (s, 2H); 4.31 (t, 2H); 7.19 (m, 2H); 7.28 (m, 1H); 7.31 (s, 1H); 7.64 (s, 1H); 7.93 (m, 2H); 9.06 (, 1H).

Ejemplo 182. Preparación of Compuesto 359 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con tifen-2-metilamina (24 mg, 0.21 mmol) produjo el compuesto del título (50 mg, 53 %).

MS ES$^+$: 555.7 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 3.18 (t, 2H); 3.38 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 3.80 (s, 2H); 4.01 (s, 3H); 4.06 (d, 2H); 4.33 (t, 2H); 4.52 (s, 2H), 6.98 (dd, 1H); 7.02 (dd, 1H); 7.32 (s, 1H); 7.41 (dd, 1H); 7.60 (sq, 1H); 7.93 (s, 1H); 9.11 (s, 1H).

Ejemplo 183. Preparación de Compuesto 360 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-amino-1-feniletanol (29 mg, 0.21 mmol) produjo el compuesto del título (32 mg, 33 %).

MS ES$^+$: 579.7 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2R); 3.18 (m, 3H); 3.36 (m, 3H); 3.56 (d, 2H); 3.69 (t, 2H); 3.74 (s, 2H); 3.99 (s, 3H); 4.05 (d, 2H); 4.30 (t, 2H); 4.66 (m, 1H); 7.3 (m, 6H); 7 .53 (s, 1H); 7.90 (s, 1H); 9.09 (s, 1H).

Ejemplo 184. Preparación of Compuesto 361 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 3-(1- hidroxietil)anilina (29 mg, 0.21 mmol) produjo el compuesto del título (50 mg, 50 %).

MS ES$^+$: 579.7 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.34 (d, 3H); 2.31 (t, 2H); 3.18 (t, 2H); 3.38 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 4.00 (s, 2H); 4.02 (s, 3H); 4.07 (d, 2H); 4.33 (t, 2H); 4.72 (q, 1H); 7.07 (d, 1H); 7.29 (t, 1H); 7.33 (s, 1H); 7.53 (d, 1H);

7.67 (s, 2H); 7.93 (s, 1H); 9.12 (s, 1H).

Ejemplo 185. Preparación de Compuesto 362 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con neopentilamina (18 mg, 0.21 mmol) produjo el compuesto del título (57 mg, 64 %).

MS ES$^+$: 529.7 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 0.89 (s, 9H); 2.33 (t, 2H); 2.97 (s, 2H); 3.19 (t, 2H); 3.39 (t, 2H); 3.59 (d, 2H); 3.80 (s, 2H); 4.02 (s, 3H); 4.07 (d, 2H); 4.32 (t, 2H); 7.33 (s, 1H); 7.60 (s, 1H); 7.93 (s, 1H); 9.11 (s, 1H).

Ejemplo 186. Preparación de Compuesto 363 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 3-fluoro-4-metoxianilina (30 mg, 0.21 mmol) produjo el compuesto del título (64 mg, 65 %).

MS ES$^+$: 583.7 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H) .30 ; 3.82 (s, 3H); 3.96 (s, 2H); 4.00 (s, 3H); 4.04 (d, 2H); 4.31 (t, 2H); 7.15 (t, 1H); 7.30 (d, 1H); 7.31 (8, 1H); 7.61 (8, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 9.10 (s, lH).

Ejemplo 187. Preparación de Compuesto 364 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-metil-4-fluoroanilina (26 mg, 0.21 mmol) produjo el compuesto del título (60 mg, 62 %).

MS ES$^+$: 567.7 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 4.00 (s, 3H); 4.01 (s, 2H); 4.04 (d, 2H); 4.31 (t, 2H); 7.02 (t, 1H); 7.10 (d, 1H); 7.31 (s, 1H); 7.41 (q, 1H); 7.66 (s, 1H); 7.92 (s, 1H); 9.09 (s, 1H).

Ejemplo 188. Preparación de Compuesto 365 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2,5-difluoroanilina (27 mg, 0.21 mmol) produjo el compuesto del título (14 mg, 14 %).

MS ES^+: 571.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.19 (t, 2H); 3.39 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 4.01 (s, 3H); 4.06 (d, 2H); 4.12 (s, 2H); 4.33 (t, 2H); 7.00 (m, 1H); 7.33 (m, 2H); 7.65 (s, 1H);7.95 (m, 2H); 9.11 (s, 1H).

Ejemplo 189. Preparación de Compuesto 366 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-fluoro-4-cloroanilina (31 mg, 0.21 mmol) produjo el compuesto del título (12 mg, 12 %).

MS ES^+: 587.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 3.99 (s, 3H); 4.04 (m, 4H); 4.31 (t, 2H); 7.29 (d, 1H); 7.52 (dd, 1H); 7.64 (s, 1H); 7.97 (d, 1H); 9.09 (s, 1H).

Ejemplo 190. Preparación de Compuesto 367 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-fluoro-4-metilanilina (26 mg, 0.21 mmol) produjo el compuesto del título (20 mg, 20 %).

MS ES^+: 567.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (s, 3H); 2.32 (t, 2H); 3.20 (t, 2H); 3.39 (t, 2H); 3.59 (d, 2H); 3.73 (t, 2H); 4.03 (s, 3H); 4.07 (d, 2H); 4.09 (s, 2H); 4.34 (t, 2H); 7.02 (m, 1H); 7.18 (dd, 1H); 7.34 (s, 1H); 7.67 (s, 1H); 7.77 (d, 1H); 7.95 (s, 1H); 9.12 (s, 1H).

Ejemplo 191. Preparación de Compuesto 368 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 3-metilanilina (23 mg, 0.21 mmol) produjo el compuesto del título (45 mg, 48 %).

MS ES$^+$: 549.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (m, 5H); 3.19 (t, 2H); 3.39 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 4.00 (s, 2H); 4.02 (s, 3H); 4.07 (d, 2H); 4.33 (t, 2H); 6.93 (d, 1H); 7.24 (t, 1H); 7.33 (s, 1H); 7.43 (d, 1H); 7.51 (s, 1H); 7.67 (s, 1H); 7.94 (s, 1H); 9.12 (s, 1H).

Ejemplo 192. Preparación de Compuesto 369 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-(metilltio)anilina (29 mg, 0.21 mmol) produjo el compuesto del título (13 mg, 13 %).

MS ES$^+$: 581.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.46 (s, 3H); 3.19 (t, 2H); 3.39 (t, 2H); 3.59 (d, 2H); 3.72 (t, 2H); 3.99 (s, 3H); 4.02 (s, 2H); 4.07 (d, 2H); 4.33 (t, 2H); 7.22 (t, 1H); 7.27 (t, 1H); 7.34 (s, 1H); 7.39 (d, 1H); 7.45 (d, 1H); 7.68 (s, 1H); 7.93 (s, 1H); 9.10 (s, 1H).

Ejemplo 193. Preparación de Compuesto 370 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 5-aminoindol (28 20 mg, 0.21 mmol) produjo el compuesto del título (33 mg, 34 %).

MS ES$^+$: 574.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.18 (t, 2H); 3.36 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 3.97 (s, 2H); 4.00 (s, 3H); 4.03 (d, 2H); 4.31 (t, 2H); 7.32 (m, 6H); 7.65 (8, 1H); 7.91 (s, 1H); 9.10 (8, 1H).

Ejemplo 194. Preparación de Compuesto 371 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2,4-difluoroanilina (27 mg, 0.21 mmol) produjo el compuesto del título (28 mg, 29 %).

MS ES$^+$: 571.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 3.19 (t, 2H); 3.39 (t, 2H); 3.59 (d, 2H); 3.72 (t, 2H); 4.02 (s, 3H); 4.07 (d, 2H); 4.08 (s, 2H); 4.34 (t, 2H); 7.12

(t, 1H); 7.34 (s, 1H); 7.36 (m, 1H); 7.89 (m, 1H); 7.95 (s, 1H); 9.12 (s, 1H).

Ejemplo 195. Preparación de Compuesto 372 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-fluoro-4-metilanilina (26 mg, 0.21 mmol) produjo el compuesto del título (35 mg, 37 %).

MS ES^+: 567.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.33 (s, 5H); 3.19 (t, 2H); 3.39 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 4.02 (s, 3H); 4.07 (s, 2H); 4.08 (d, 2H); 4.33 (t, 2H); 7.04 (d, 1H); 7.12 (d, 1H); 7.34 (s, 1H); 7.66 (s, 1H); 7.78 (t, 1H); 7.94 (s, 1H); 9.12 (s, 1H).

Ejemplo 196. Preparación de Compuesto 373 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 3-cianoanilina (25 mg, 0.21 mmol) produjo el compuesto del título (21 mg, 22 %). MS ES^+: 560.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.19 (t, 2H); 3.39 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 4.02 (s, 3H); 4.06 (s, 2H); 4.07 (d, 2H); 4.33 (t, 2H); 7.34 (s, 1H); 7.6 (m, 2H); 7.69 (s, 1H); 7.85 (m, 1h); 7.95 (s, 1h); 8.18 (s, 1H); 9.13 (s, 1H).

Ejemplo 197. Preparación de Compuesto 374 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-metil-5-fluoroanilina (26 mg, 0.21 mmol) produjo el compuesto del título (15 mg, 16 %).

MS ES^+: 567.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.27 (s, 3H); 2.32 (t, 2H); 3.20 (t, 2H); 3.39 (t, 2H); 3.59 (d, 2H); 3.72 (t, 2H); 4.02 (s, 3H); 4.07 (d, 2H); 4.09 (s, 2H); 4.33 (t, 2H); 6.96 (t, 1H); 7.29 (t, 1H); 7.34 (s, 1H); 7.48 (d, 1H); 7.69 (s, 1H); 7.95 (s, 1H); 9.12 (s, 1H).

Ejemplo 198. Preparación de Compuesto 375 en Tabla 14

Una reacción análoga a la descrita en Ejemplo 36 pero comenzando con 2-metil-5-cloroanilina (30 mg, 0.21 mmol) produjo el compuesto del título (20 mg, 21 %).

MS ES^+: 583.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.26 (s, 3H); 2.32 (t, 2H); 3.17 (t, 2H); 3.38 (t 2H); 3.58 (d, 2H); 3.71 (t, 2H); 4.01 (s, 3H); 4.05 (d, 2H); 4.07 (s, 2H); 4.32 (t, 2H); 7.16 (dd, 1H); 7.27 (d, 1H); 7.31 (s, 1H); 7.65 (d, 1H); 7.65 (s, 1H); 7.93 (s, 1H); 9.10 (s, 1H).

Ejemplo 199. Preparación de Compuesto 376 en Tabla 15

4-((2-amino-1,3-tiazol-5-il)ácido acético)-6-metoxi-7-((1-metil-piperidin-4-il)metoxi)quinazolina (89 mg, 0.2 mmol) en DMF (1.5 ml), se hizo reaccionar con anilina (22 mg, 0.24 mmol) en presencia de hexatluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (99 mg, 0.26 mmol) y DIEA (50 mg, 0.4 mmol) a 60°C de un día para otro. Luego de enfriar a temperatura ambiente la mezcla de la reacción se diluyó con diclorometano, y se purificó por cromatografía de gel de sílice, eluyendo sucesivamente conh CH_2Cl_2, CH_2Cl_2 / MeOH 90/10, y CH_2Cl_2 / MeOH sat. NH_3 90/10 para producir el compuesto del título (50 mg, 42 %).

MS ES^+: 519.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.58 (m, 2H); 2.02 (m, 2H); 2.13 (m, 1H); 2.80 (s, 3H); 3.03 (t, 2H); 3.52 (d, 2H); 3.98 (s, 2H); 3.98 (s, 3H); 4.10 (d, 2H); 7.06 (t, 1H); 7.29 (s, 1H); 7.33 (t, 2H); 7.60 (d, 2H); 7.61 (s, 1H); 7.90 (s, 1H); 9.08 (s, 1H).

El espectro NMR de Ejemplo 75 en presencia de ácido muestra la existencia de 2 formas en una proporción de aproximadamente 9:1. Señales debidas a la forma menor se aprecian a 1.95 (m) 3.23 (m) 3.32 (m) 4.28 (d) 9.38 (m). Todos los demás ejemplos, hasta Ejemplo 101, despliegan de manera similar 2 formas; en ejemplos subsiguientes sólo se describe la forma mayor.

4-benciloxi- 3 -metoxibenzonitrilo.

4-benciloxi-3-metoxibenzaldehído (4.84 g, 20 mmol) en ácido acético (25 ml) y acetato de sodio (3.3 g, 40 mmol) se hicieron reaccionar con clorhidrato de hidroxilamina (2.8 g, 40 mmol) a reflujo durante 6 horas. La mezcla se enfrió, se dilujó con agua, se extrajo con cloruro de metileno, se secó sobre $MgSO_4$, se concentró para producir el compuesto del título (4.8 g, 100 %).

^{1}HNMR (DMSO-d_6,): 3.83 (s, 3H); 5.20 (s, 2H); 7.21 (d, 1H); 7.40 (m, 7H).

2-nitro-4-benciloxi-5-metoxibenzonitrilo.

4-benciloxi-3-metoxibenzonitrilo (4.78 g, 20 mmol) en ácido acético (10 ml) se agregó lentamente a ácido nítrico (25 ml) a 20°C hasta 30°C. La mezcla se agitó a temperatura ambiente durante 6 horas, se basificó (pH 10-11) con enfriamiento (KOH 10N), se extrajo con cloruro de metileno, se secó sobre $MgSO_4$, se evaporó. El sólido se recristalizó en EtOAc caliente, se obtuvo un sólido amarillo del compuesto del título (3.62 g, 64 %).

MS ES^+: 285 $(M+H)^+$

^{1}HNMR (DMSO-d_6): 3.97 (s, 3H); 5.33 (s, 2H); 7.40 (m, 5H); 7.71 (s, 1H); 8.01 (s, 1H).

2-nitro-4-hidroxi-5-metoxibenzonitrilo

2-nitro-4-benciloxi-5-metoxibenzonitrilo (3 g, 10.6 mmol) se trató con trifluoroácido acético (30 ml) a reflujo durante 0.5 hora. El solvente se evaporó, el residuo se trituró con éter para producir un sólido amarillo del compuesto del título (1.27 g, 62 %).

^{1}HNMR (DMSO-d_6): 3.95 (s, 3H); 7.63 (s, 1H); 7.70 (s, 1H).

2-nitro-4-((1-tert-butiloxicarbonilpiperidin-4-il)metoxi)-5-metoxibenzonitrilo.

2-nitro-4-hidroxi-5-metoxibenzonitrilo (388 mg, 2 mmol) en DMF (5 ml) y acetonitrilo (5 ml) se hicieron reaccionar con 4-(4-tolilsulfoniloximetil)-1-tert-butiloxicarbonil-piperidina (738 mg, 2 mmol) y K_2CO_3 (414 mg, 3 mmol) a 110°C durante 3.5 horas. La mezcla se diluyó con agua, se extrajo con acetato de etilo, se lavó HCl (2N), se secó sobre $MgSO_4$, se evaporó para producir el compuesto del título (630 mg, 80 %).

^{1}HNMR ($CDCl_3$): 1.31 (m, 2H); 1.47 (s, 9H); 1.85 (m, 2H); 2.07 (m, 1H);

2.77 (m, 2H); 3.96 (d, 2H); 3.99 (s, 3H); 4.19 (m, 2H); 7.19 (s, 1H); 7.75 (s, 1H).

2 - nitro-4-(1-piperidin-4-ilmetoxi)-5-metoxibenzonitrilo.

2-nitro-4-((1-tert-butiloxicarbonilpiperidin-4-il)metoxi)-5-metoxibenzonitrilo (1.17 g, 3 mmol) en CH_2Cl_2 (12 ml) se trató con TFA (2.4 ml) durante 1 hora a temperatura ambiente. El solvente se evaporó, el residuo se absorbió en una mezcla de CH_2Cl_2 y se concentró en bicarbonato de sodio, se extrajo con CH_2Cl_2. La fase orgánica se secó sobre $MgSO_4$, se concentró para producir el compuesto del título como un sólido (770 mg, 88 %).

^{1}HNMR ($CDCl_3$): 1.33 (m, 2H); 1.86 (d, 2H); 2.03 (m, 1H); 2.71 (t, 2H); 3.15 (d, 2H); 3.96 (d, 2H); 3.99 (s, 3H); 7.18 (s, 1H); 7.76 (s, 1H).

2-nitro-4-(1-metilpiperidin-4-ilmetoxi)-5-metoxibenzonitrilo.

2-nitro-4-(1-piperidin-4-ilmetoxi)-5-metoxibenzonitrilo (771 mg, 2.65 mmol) en CH_2Cl_2 (8 ml) y MeOH (4 ml) se hizo reaccionar durante 0.5 hora con formaldehído (13.3 M, 300 µl, 4 mmol), ácido acético (191 mg, 3.18 mmol) y $NaBH(OAc)_3$ (674 mg, 3.18 mmol) se añadió lentamente durante 15 minutos. La solución se evaporó, el residuo oleoso se absorbió en una mezcla de Na_2CO_3 y acetato de etilo, se extrajo con acetato de etilo. La fase orgánica se secó sobre $MgSO_4$, se evaporó para producir el compuesto del título como un sólido amarillo (698 mg, 86 %).

^{1}HNMR ($CDCl_3$): 4.7 (m, 2H); 1.88 (d, 2H); 1.90 (m, IH); 2.0 (m, 2H); 2.3 (s, 3H); 2.91 (d, 2H); 2.95 (d, 2H); 2.99 (s, 3H); 7.18 (s, 1H); 7.76 (s, 1H).

2-amino-4-(1- metilpiperidin-4-ilmetoxi)-5-metoxibenzonitrilo.

2-nitro-4-(1-metilpiperidin-4-ilmetoxi)-5-metoxibenzonitrilo (1.1 g, 3.6 mmol) en THF (20 ml) en presencia de cloruro de benciltrimetilamonio (334 mg, 1.8 mmol) se trató mediante una adición lenta de $Na_2S_2O_4$ (3.1 g, 18 mmol) en agua (20 ml). Luego de 0.5 horas , HCl (6N, 20 ml) a la mezcla, la cual se agitó a 60°C durante 5 horas. La mezcla se enfrió a temperatura ambiente, se extrajo con acetato de etilo. La fase acuosa se hizo básica con Na_2CO_3 (sólido), y se extrajo con acetato de etilo. La fase orgánica se secó sobre $MgSO_4$, se concentró, para producir un sólido

amarillo (748 mg, 75 %) del compuesto del título.

^{1}HNMR ($DMSOd_6$): 1.29 (m, 2H); 1.70 (m, 3H); 1.85 (t, 2H); 2.14 (s, 3H); 2.76 (d, 2H); 3.64 (s, 3H); 3.75 (d, 2H); 5.57 (s, 2H); 6.40 (s, 1H); 6.87 (s, 1H).

N'-(2-ciano-4-metoxi-5-(1-metillpiperidin-4-ilmetoxi)fenil)-N,N-dimetilimidoformamida.

2-amino-4-(1-metilpiperidin-4-ilmetoxi)-5-metoxi-benzonitrilo (710 mg, 2.58 mmol) se hizo reaccionar con DMF DMA (414 mg, 3.5 mmol) en tolueno (15 ml) a reflujo durante 5 horas. La solución se concentró, el residuo oleoso se trituró con éter para producir un sólido amarillo del compuesto del título (680 mg, 80 %).

^{1}HNMR ($DMSOd_6$): 1.28 (m, 2H); 1.72 (m, 3H); 1.85 (t, 2H); 2.14 (s, 3H); 2.76 (d, 2H); 2.95 (s, 3H); 3.05 (s, 3H); 3.72 (s, 3H); 3.86 (d, 2H); 6.71 (s, 1H); 7.07 (s, 1H); 7.89 (s, 1H).

4-(metil(2-amino-1,3-tiazol-5-il)acetato)-6-metoxi-7-((1-metilpiperidin-4-il)metoxi) quinazolina.

N'-(2-ciano-4-metoxi-5-(1-metilpiperidin-4-ilmetoxi)fenil)-N,N-dimetilimidoformamida (627 mg, 1.9 mmol) se hizo reaccionar con metil-2-amino-1,3-tiazol-5-acetato (360 mg, 2.1 mmol) en ácido acético (6.3 ml) a reflujo durante 4.5 horas bajo nitrógeno. La mezcla se concentró, y el residuo oleoso se purificó por cromatografía de gel de sílice, eluyente: CH_2Cl_2 / MeOH 90/10 y CH_2Cl_2 / MeOH sat. NH_3 90/10 para producir el compuesto del título (552 mg, 63 %).

^{1}HNMR ($DMSOd_6$): 1.35 (m, 2H); 1.76 (m, 3H); 1.87 (t, 2H); 2.16 (d, 2H); 2.78 (d, 2H); 25 3.67 (s, 3H); 3.93 (s, 2H); 3.96 (s, 3H); 4.01 (d, 2H); 7.24 (s, 1H); 7.36 (s, 1H); 8.10 (s, 1H); 8.66 (s, 1H).

4-((2-amino-1,3-tiazol-5-il)ácido acético)-6-metoxi-7-((1-metilpiperidin-4-il)metoxi)quinazolina.

4-(metil(2-amino-1,3-tiazol-5-il)acetato)-6-metoxi-7-((1-metilpiperidin-4-il)metoxi)quinazolina (137 mg, 0.3 mmol) en etanol (1.4 ml) se trató con NaOH (2N, 3.75 ml, 7.5 mmol) a temperatura ambiente durante 0.5 hora. HCl (2N) se agregó para ajustar el pH a 3. La solución se evaporó, se

agregó (exceso) el sólido solubilizado en CH_2Cl_2 (6 ml) MeOH (4 ml) DIEA. El insoluble se filtró, el filtrado se concentró, se añadió etanol, el sólido se filtró, se lavó con éter, para producir el compuesto del título (102 mg, 77 %).

MS ES^+: 444.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.61 (m, 2H); 2.03 (d, 2H); 2.16 (m, 1H); 2.80 (s, 3H); 3.03 (t, 2H); 3.5 (d, 2H); 3.92 (s, 2H); 3.98 (s, 3H); 4.10 (d, 2H); 7.32 (s, 1H); 7.59 (s, 1H); 7.89 (s, 1H); 9.07 (s, 1H).

Ejemplo 200. Preparación de Compuesto 377 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 3-cloro-4-fluoroanilina (44 mg, 0.3 mmol) produjo el compuesto 76 en Tabla 3 (63 mg, 60 %)

MS ES^+: 571 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.64 (m; 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.8 (s, 3H); 3.04 (t, 2H); 3.51 (d, 2H); 3.99 (s, 3H); 4.0 (s, 2H); 4.11 (d, 2H); 7.34 (s, 1H); 7.39 (t, 1H); 7.5 (m, 1H); 7.65 (s, 1H); 7.91 (dd, 1H); 9.09 (s, 1H).

Ejemplo 201. Preparación de Compuesto 378 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 2-aminopiridina (40 mg, 0.42 mmol) produjo el compuesto 77 en Tabla 3 (100 mg, 53 %).

MS ES^+: 520 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.65 (m, 2H); 2.02 (m, 2H); 2.15 (m, 1H); 2.78 (s, 3H); 3.02 (t, 2H); 3.48 (d, 2H); 3.99 (s, 3H); 4.1 (d, 2H); 4.14 (s, 2H); 7.32 (m, 1H); 7.39 (s, 1H); 7.66 (s, 1H); 7.91 (s, 1H); 7.97 (d, 1H); 8.16 (t, 1H); 8.4 (d, 1H); 9.079 (s, 1H).

Ejemplo 202. Preparación de Compuesto 379 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 3,4-difluoroanilina (54 mg, 0.42 mmol) produjo el compuesto 78 en Tabla 3

(120 mg, 72 %)

MS ES$^+$: 555 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.63 (m, 2H); 2.02 (m, 2H); 2.15 (m, 1H); 2.79 (s, 3H); 3.03 (t, 2H); 3.49 (d, 2H); 3.99 (s, 3H); 4.0 (s, 2H); 4.10 (d, 2H); 7.35 (s, 1H); 7.39 (m, 2H); 7.64 (s, 1H);7.82 (dd, 1H); 7.90 (s, 1H); 9.08 (s, 1H).

Ejemplo 203. Preparación de Compuesto 380 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 2-cloroanilina (54 5 mg, 0.42 mmol) produjo el compuesto 79 en Tabla 3 (29 mg, 16 %)

MS ES$^+$: 553 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.62 (m, 2H); 2.03 (m, 2H); 2.15 (m, 1H); 2.81 (s, 3H); 3.04 (t, 2H); 3.51 (d, 2H); 4.0 (s, 3H);.4.08 (s, 2H); 4.11 (d, 2H); 7.24 (t, 1H); 7.31 (s, 1H); 7.34 (dd, 1H); 7.53 (d, 1H); 7.66 (s, 1H); 7.75 (d, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 204. Preparación de Compuesto 381 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 4-metilanilina (45 mg, 0.42 mmol) produjo el compuesto 80 en Tabla 3 (155 mg, 85 %)

MS ES$^+$: 533 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.65 (m, 2H); 2.02 (m, 2H); 2.16 (m, 1H); 2.27 (s, 3H); 2.8 (s, 3H); 3.05 (t, 2H); 3.50 (d, 2H); 3.97 (s, 2H); 3.99 (s, 3H); 4.11 (d, 2H); 7.14 (d, 2H); 7.34 (s, 1H); 7.52 (d, 2H); 7.63 (s, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 205. Preparación de Compuesto 382 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 2-metilanilina (45 mg, 0.42 romol) produjo el compuesto 81 en Tabla 3 (126 mg, 69 %)

MS ES$^+$: 533 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.62 (m, 2H); 2.02 (m, 2H); 2.15 (m, 1H); 2.24 (s, 3H); 2.8 (s, 3H); 3.04 (t, 2H); 3.51 (d, 2H); 3.99 (s, 3H); 4.02 (s, 2H); 4.10 (d, 2H); 7.11 (t, 1H); 7.19 (t, 1H); 7.24 (d, 1H); 7.33 (s, 1H); 7.43 (d, 1H); 7.65 (s, 1H); 7.91 (s, 1H); 9.07 (s, 1H).

Ejemplo 206. Preparación de Compuesto 383 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 4-cloroanilina (54 mg, 0.42 mmol) produjo el compuesto 82 en Tabla 3 (128 mg, 68 %)

MS ES$^+$: 553 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.65 (m, 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.79 (s, 3H); 3.04 (t, 2H); 3.50 (d, 2H); 3.99 (s, 3H); 4.0.(s, 2H); 4.1 (d, 2H); 7.36 (s, 1H); 7.38 (d, 2H); 7.64 (s, 1H); 7.68 (d, 2H); 7.9 (s, 1H); 9.08 (s, 1H).

Ejemplo 207. Preparación de Compuesto 384 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 4-fluoroanilina (47 mg, 0.42 mmol) produjo el compuesto 83 en Tabla 3 (136 mg, 84 %)

MS ES$^+$: 537 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.62 (m, 2H); 2.02 (m, 2H); 2.15 (m, 1H); 2.79 (s, 3H); 3.03 (t, 2H); 3.50 (d, 2H); 3.97 (s, 2H); 3.98 (s, 3H); 4.1 (d, 2H); 7;16 (t, 2H); 7.34 (s, 1H); 7.63 (s, 1H); 7.65 (m, 2H); 7.9 (s, 1H); 9.07 (s, 1H).

Ejemplo 208. Preparación de Compuesto 385 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 2-amino-6-metilpirimidina (45 mg, 0.42 mmol) produjo el compuesto 84 en Tabla 3 (91 mg, 57 %)

MS ES$^+$: 534 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.61 (m, 2H); 2.05 (m, 2H); 2.15 (m, 1H); 2.50 (s, 3H); 2.8 (s, 3H); 3.03 (t, 2H); 3.52 (d, 2H); 4.02 (s, 3H); 4.1 (s, 2H);

4.11 (d, 2H); 7.15 (m, 1H); 7.33 (s, 1H); 7.65 (s, 1H); 7.8 (m, 2H); 7.91 (s, 1H); 9.07 (s, 1H).

Ejemplo 209. Preparación de Compuesto 386 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 3-metoxianilina (52 mg, 0.42 mmol) produjo el compuesto 85 en Tabla 3 (125 mg, 67 %)

MS ES^+: 549 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.63 (m, 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.8 (s, 3H); 3.04 (t, 2H); 3.52 (d, 2H); 3.75 (s, 3H); 3.98 (s, 2H); 3.99 (s, 3H); 4.11 (d, 2H); 6.68 (m, 1H); 7.17 (d, 1H); 7.24 (t, 1H); 7.33 (s, 1H); 7.35 (d, 1H); 7.64 (s, 1H); 7.92 (s, 1H); 9.09 (s, 1H).

Ejemplo 210. Preparación de Compuesto 387 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 2-amino-5-cloropiridina (54 mg, 0.42 mmol) produjo el compuesto 86 en Tabla 3 (22 mg, 11 %)

MS ES^+: 554 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.61 (m, 2H); 2.03 (m, 2H); 2.15 (m, 1H); 2.8 (s, 3H); 3.03 (t, 2H); 3.5 (d, 2H); 3.98 (s, 3H); 4.07 (s, 2H); 4.11 (d, 2H); 7.30 (s, 1H); 7.63 (s, 1H); 7.9 (s, 1H); 7.93 (dd, 1H); 8.12 (d, 1H); 8.41 (d, 1H).

Ejemplo 211 Preparación de Compuesto 388 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 3-cloroanilina (54 mg, 0.42 mmol) produjo el compuesto 87 en Tabla 2 (130 mg, 69 %).

MS ES^+: 553 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.62 (m, 2H); 2.02 (m, 2H); 2.15 (m, 1H); 2.78 (s, 3H); 3.02 (t, 2H); 3.49 (d, 2H); 3.97 (s, 3H); 3.99 (s, 2H); 4.08 (d, 2H); 7.13 (d, 1H); 7.3 (s, 1H); 7.38 (t, 1H); 7.64 (s, 1H); 7.86 (s, 1H); 7.90 (s, 1H); 9.07 (s, 1H).

Ejemplo 212. Preparación de Compuesto 389 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 2-fluoroanilina (47 mg, 0.42 mmol) produjo el compuesto 88 en Tabla 3 (116 mg, 63 %).

MS ES^+: 537 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.64 (m, 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.79 (s, 3H); 3.03 (t, 15 2H); 3.50 (d, 2H); 3.99 (s, 3H); 4.07 (s, 2H); 4.10 (d, 2H); 7.19 (m, 2H); 7.25 (m, 1H); 7.35 (s, 1H); 7.63 (s, 1H); 7.90 (s, 1H); 7.91 (m, 1H); 9.07 (s, 1H).

Ejemplo 213. Preparación de Compuesto 390 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 3-fluoro-4-metoxianilina (59 mg, 0.42 mmol) produjo el compuesto 89 en Tabla 3 (151 mg, 85 %).

MS ES^+: 567 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.62 (m, 2H); 2.01 (m, 2H); 2.15 (m, 1H); 2.79 (s, 3H); 3.03 (t, 2H); 3.51 (d, 2H); 3.81 (s, 3H); 3.96 (s, 2H); 3.98 (s, 3H); 4.10 (d, 2H); 7.14 (t, 1H); 7.28 (d, 1H); 7.34 (s, 1H); 7.59 (dd, 1H); 7.6 (s, 1H); 7.90 (s, 1H); 9.07 (s, 1H).

Ejemplo 214. Preparación de Compuesto 391 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 2-metil-4-fluoroanilina (53 mg, 0.42 mmol) produjo el compuesto 90 en Tabla 3 (151 mg, 81 %).

MS ES^+: 551 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.62 (m, 2H); 2.02 (m, 2H); 2.15 (m, 1H); 2.33 (s, 3H); 2.79 (s, 3H); 2.93 (t, 2H); 3.48 (d, 2H); 3.97 (s, 3H); 3.99 (s, 2H) ,4.09 (d, 2H); 7.01 (dt, 1H); 7.1 (dd, 1H); 7.37 (s, 1H); 7.39 (m, 1H); 7.64 (s, 1H); 7.89 (s, 1H); 9.05 (s, 1H).

Ejemplo 215. Preparación de Compuesto 392 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 2-amino-4-metilpiridina (45 mg, 0.42 mmol) produjo el compuesto 91 en Tabla 3 (119 mg, 66 %).

MS ES^+: 534 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.66 (m, 2H); 2.05 (m, 2H); 2.15 (m, 1H); 2.77 (s, 3H); 3.03 (t, 2H); 3.48 (d, 2H); 3.97 (s, 3H); 4.09 (d, 2H); 4.21 (s, 2H); 7.35 (m, 1H); 7.45 (s, 1H); 7.69 (s, 1H); 7.70 (s, 1H); 7.90 (s, 1H); 8.31 (d, 1H); 9.06 (s, 1H).

Ejemplo 216. Preparación de Compuesto 393 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 2,5-difluoroanilina (54 mg, 0.42 mmol) produjo el compuesto 92 en Tabla 3 (42 mg, 22 %).

MS ES^+: 555 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.60 (m, 2H); 2.02 (m, 2H); 2.15 (m, 1H); 2.81 (s, 3H); 3.04 (t, 2H); 3.52 (d, 2H); 3.99 (s, 3H); 4.10 (s, 2H); 4.11 (d, 2H); 7.02 (m, 2H); 7.32 (s, 1H); 7.34 (m, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 7.92 (m, 1H); 9.08 (s, 1H).

Ejemplo 217. Preparación de Compuesto 394 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 2-fluoro-4-cloroanilina (61 mg, 0.42 mmol) produjo el compuesto 93 en Tabla 3 (97 mg, *50* %).

MS ES^+: 571 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.63 (m, 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.77 (s, 3H); 3.03 (t, 2H); 3.48 (d, 2H); 3.98 (s, 3H); 4.07 (s, 2H); 4.09 (d, 2H); 7.26 (d, 1H); 7.38 (s, 1H); 7.5 (dd, 1H); 7.62 (s, 1H); 7.89 (s, 1H); 7.96 (t, 1H); 9.06 (s, 1H).

Ejemplo 218. Preparación de Compuesto 395 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 2-fluoro-5-metilanilina (53 mg, 0.42 mmol) produjo el compuesto 94 en Tabla

3 (119 mg, 63 %).

MS ES$^+$: 551 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.63 (m, 2H); 2.03 (m, 2H); 2.15 (m, 1H); 2.28 (s, 3H); 2.77 (s, 3H); 3.03 (t, 2H); 3.49 (d, 2H); 3.98 (s, 3H); 4.05 (s, 2H); 4.09 (d, 2H); 6.98 (m, 1H); 7.15 (dd, 1H); 7.38 (s, 1H); 7.62 (s, 1H); 7.72 (m, 1H); 7.89 (s, 1H); 9.06 (s, 1H).

Ejemplo 219. Preparación de Compuesto 396 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 3-metilanilina (45 mg, 0.42 mmol) produjo el compuesto 95 en Tabla 3 (144 g, 79 %).

MS ES$^+$: 533 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.64 (m, 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.3 (s, 3H); 2.79 (s, 3H); 3.04 (t, 2H); 3.51 (d, 2H); 3.98 (s, 2H); 3.99 (3H); 4.10 (d, 2H); 6.90 (d, 1H); 7.21 (t, 1H); 7.36 (s, 1H); 7.42 (d, 1H); 7.49 (s, 1H); 7.63 (s, 1H); 7.9 (s, 1H); 9.07 (s, 1H).

Ejemplo 220. Preparación de Compuesto 397 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 2,4- difluoroanilina (54 mg, 0.42 mmol) produjo el compuesto 96 en Tabla 3 (121 mg, 74 %).

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.63 (m, 2H); 2.03 (m, 2H); 2.15 (m, 1H); 2.78 (s, 3H); 3.03 (t, 2H); 3.5 (d, 2H); 3.98 (s, 3H); 4.04 (s, 2H); 4.1 (d, 2H); 7.08 (m, 1H); 7.36 (s, 1H); 7.63 (s, 1H); 7.86 (m, 1H); 7.90 (s, 1H); 9.07 (s, 1H).

Ejemplo 221. Preparación de Compuesto 398 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 2-fluoro-4-metilanilina (53 mg, 0.42 mmol) produjo el compuesto 97 en Tabla 3 (147 mg, 79 %).

MS ES$^+$: 551 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.63 (m, 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.3 (s, 3H); 2.79 (s, 3H); 3.04 (t, 2H); 3.51 (d, 2H); 3.99 (s, 3H); 4.04 (s, 2H); 4.1 (d, 2H); 6.99 (d, 1H); 7.10 (d, 1H); 7.35 (s, 1H); 7.62 (s, 1H); 7.75 (t, 1H); 7.90 (s, 1H); 9.07 (s, 1H).

Ejemplo 222. Preparación de Compuesto 399 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 3-cianoanilina (50 mg, 0.42 mmol) produjo el compuesto 98 en Tabla 3 (118 mg, 71 %).

MS ES$^+$: 544 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.66 (m, 2H); 2.07 (m, 2H); 2.17 (m, 1H); 2.81 (s, 3H); 3.06 (t, 2H); 3.53 (d, 2H); 4.0 (s, 3H); 4.05 (s, 2H); 4.11 (d, 2H); 7.36 (s, 1H); 7.54 (m, 2H); 7.65 (s, 1H); 7.86 (dd, 1H); 7.92 (s, 1H); 8.18 (s, 1H), 9.09 (s, 1H).

Ejemplo 223. Preparación de Compuesto 400 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 2-metil-5-fluoroanilina (53 mg, 0.42 mmol) produjo el compuesto 99 en Tabla 3 (107 mg, 57 %).

MS ES$^+$: 551 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.65 (m, 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.24 (s, 3H); 2.76 (s, 3H); 3.02 (t, 2H); 3.47 (d, 2H); 3.98 (s, 3H); 4.07 (s, 2H); 4.08 (d, 2H); 6.92 (m, 1H); 7.25 (t, 1H); 7.4 (s, 1H); 7.43 (m, 1H); 7.64 (s, 1H); 7.88 (s, 1H); 9.04 (s, IH).

Ejemplo 224. Preparación de Compuesto 401 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 3,5-difluoroanilina (54 mg, 0.42 mmol) produjo el compuesto 100 en Tabla 3 (83 mg, 44 %).

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.66 (m, 2H); 2.02 (m, 2H); 2.16 (m, 1H); 2.76 (s, 3H); 3.03 (t, 2H); 3.45 (d, 2H); 3.97 (s, 3H); 4.03 (s, 2H); 4.08 (d, 2H);

6.90 (dd, 1H); 7.38 (m, 2H); 7.39 (s, 1H); 7.87 (s, 1H); 9.05 (s, 1H).

Ejemplo 225. Preparación de Compuesto 402 en Tabla 15

Una reacción análoga a la descrita en Ejemplo 75 pero comenzando con 3-fluoroanilina (47 mg, 0.42 mmol) produjo el compuesto 101 en Tabla 3 (142 mg, 77 %).

MS ES^+: 537 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.62 (m, 2H); 2.03 (m, 2H); 2.15 (m, 1H); 2.78 (s, 3H); 3.02 (t, 2H); 3.49 (d, 2H); 3.98 (s, 3H); 4.0 (s, 2H); 4.1 (d, 2H); 6.9 (s, 1H); 7.35 (s, 1H); 7.36 (m, 2H); 7.62 (m, 1H); 7.64 (s, 1H); 7.9 (s, 1H); 9.08 (s, 1H).

Ejemplo 226. Preparación de Compuesto 403 en Tabla 16

4-((2-amino-1,3-tiazol-5-il)ácido acético)-6-metoxi-7-(3-N-metilpiperazinilpropoxi)quinazolina (142 mg, 0.3 mmol) en NMP (1.5 ml) se hizo reaccionar con anilina (42 µl, 0.45 mmol) en presencia de hexafluorofosfiato de O-(7-azabenzotriazol-l-ilo)-N,N,N',N',tetrametiluronio (173 mg, 0.45 mmol) y diisopropiletilamina (105 µl, 0.6 mmol) a 65°C bajo nitrógeno de un día para otro. Luego de enfriar a temperatura ambiente, la mezcla de la reacción se diluyó con diclorometano y se purificó por cromatografía de gel de sílice) eluyente CH_2Cl_2, CH_2Cl_2 / MeOH, 9/1, CH_2Cl_2 / MeOH sat. NH_3, 9/1 para producir el compuesto del título (24 mg, 15 %).

MS ES^+: 548.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.94 (s, 3H); 3.2-4.2 (m, 8H); 3.45 (t, 2H); 3.99 (s, 5H); 4.30 (t, 2H); 7.08 (t, 1H); 7.31 (s, 1H); 7.33 (, 2H); 7,.62 (d, 2H); 7.64 (s, 1H); 7.90 5 (s, 1H); 9.09 (s, 1H).

2-nitro-4-(3-N-metilpiperazinilpropoxi)-5-metoxibenzonitrilo.

2-nitro-4-hidroxi-5-metoxibenzonitrilo (45 g, 25 mmol) en CH_2Cl_2 (125 ml) se hizo reaccionar con diterciobutilazodicarboxilato (6.9 g, 30 mmol) trifenilfosfina (7.86 g, 30 mmol) a temperatura ambiente durante 2 horas. Se agregó una solución de éter (2.3N HCl, 55 ml). El sólido se recuperó, se

lavó con CH_2Cl_2, éter. El sólido se disolvió en $MeOH_2$, se trató con MeOH / NH_3, el solvente se evaporó, y el residuo se purificó por cromatografía de gel de sílice: CH_2Cl_2 / AcOEt 50/50, CH_2Cl_2 / MeOH 90/10, para producir el compuesto del título (8.2 g, 98 %).

MS ES^+: 335.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.29 (t, 2H); 3.95 (s, 3H); 3.2-4 (m, 8H); 3.38 (t, 2H); 3.98 (s, 3H); 4.32 (t, 2H); 7.70 (s, 1H); 7.89 (s, 1H).

2-amino-4-(3-N-metilpiperazinilpropoxi)-5-metoxi-benzonitrilo.

2-nitro-4-(3-N-metilpiperazinilpropoxi)-5-metoxibenzonitriloe (1.67 g, 5 mmol), cloruro de benciltrimetilamonio (0.46 g, 2.5 mmol) en cloruro de metilo (40 ml) se trató con hidrosulfito de sodio (4.35 g, 5 mmol) en agua (40 ml) a temperatura ambiente durante 1 hora. HCl (6N, 28 ml) se añadió a la mezcla que se calentó a 60°C durante 2.5 horas. La mezcla se enfrió, se extrajo con acetato de etilo. La fase acuosa se trató con Na_2CO_3 (sólido), se extrajo con acetato de etilo. La fase orgánica se secó sobre $MgSO_4$, se concentró para producir el compuesto del título (0.93 g, 61 %).

MS ES^+: 305.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.18 (t, 2H); 2.93 (s, 3H); 3.1-4.1 (m, 8H); 3.39 (t, 2H); 3.66 (s, 3H); 4.05 (t, 2H); 6.54 (s, 1H); 7.00 (s, 1H).

N'-(2-ciano-4-metoxi-5-(3-N-metilpiperazinilpropoxi)fenil)-N,N-dimetilimidoformamida.

2-amino-4-(3-N-metilpiperazinilporpoxi)-5-metoxibenzonitrilo (16.4 g, 54 mmol) se hizo reaccionar con dimetolformamida dimetil acetal (12 ml, 90 mmol) en tolueno (400 ml) a reflujo durante 4 horas. El solvente se evaporó para producir el compuesto del título (19.4 g, 100 %).

MS ES^+: 360.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.28 (t, 2H); 2.96 (s, 3H); 3.26 (s, 3H); 3.35 (s, 3H); 3.40 (t, 2H); 3.1-4 (m, 8H); 3.88 (s, 3H); 4.21 (t, 2H); 7.32 (s, 1H); 7.53 (s, 1H); 8.56 (s, 1H).

4-(metil(2-amino-1,3-tiazoñ-5-il)acetato)-6-metoxi-4-((3-N-metilpiperazinilpropoxi)quinazolina.

N'-(2-ciano-4-metoxi-5-(3-N-piperazinilpropoxi)fenil)-N,N-

dimetilimidoformamida (9.7 g, 27 mmol) en ácido acético (100 ml) se hizo reaccionar con metil (2-amino-1,3-tiazol-5-il)acetato (5.2 g, 30 mmol) a reflujo durante 4 horas. El solvente se evaporó y el residuo se purificó por cromatografía de gel de sílice. Eluyente: CH_2Cl_2 / MeOH 99/1 a 97/3 para producir el compuesto del título (9.15 g, 70 %).

MS ES^+: 487.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 2.97 (s, 3H); 3.2-4.2 (m, 8H); 3.48 (t, 2H); 3.97 (s, 2H); 4.00 (s, 3H); 4.33 (t, 2H); 7.36 (s, 1H); 7.61 (s, 1H); 7.93 (s, 1H); 9.10 (s, 1H).

4-((2-amino-1,3-tiazol-5-il)ácido acético)-6-metoxi-7-(3-(N-metilpiperazinilpropoxi) quinazolina (8.25 g, 17 mmol) en etanol (80 ml) se trató con hidróxido de sodio (2N, 42.5 ml, 85 mmol) a temperatura ambiente durante 1 hora. Ácido de clohidrato (2N) se añadió a la solución (pH 3). La solución se evaporó, el residuo se disolvió en etanol y N-etil diisopropil amina (8.9 ml, 51 mmol). Se agregó éter a la solución, se recuperó el sólido, se secó, para producir el compuesto del título (7.44 g, 93 %).

MS ES^+: 473.5 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.30 (t, 2H); 2.94 (s, 3H); 3.2-4.1 (m, 8H); 3.45 (t, 2H); 3.89 (s, 2H); 3.97 (s, 3H); 4.29 (t, 2H); 7.30 (s, 1H); 7.56 (s, 1H); 7.90 (s, 1H); 9.06 (s, 1H).

Ejemplo 227. Preparación de Compuesto 404 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 3,4-difluoroanilina (77 mg, 0.6 mmol) produjo el compuesto del título (105 mg, 60 %).

MS ES^+: 584.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 2.94 (s, 3H); 3.2-4.1 (m, 8H); 3.44 (t, 2H); 3.99 (s, 5H); 4.30 (t, 2H); 7.32 (s, 1H); 7.32 (m, 1H); 7.40 (q, 1H); 7.65 (s, 1H); 7.81 (m, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 228. Preparación de Compuesto 405 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 2-aminopiridina (56 mg, 0.6 mmol) produjo el compuesto del título (53 mg, 36 %). MS ES^+: 549.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.30 (t, 2H); 2.94 (s, 3H); 3.1-4.1 (m, 8H); 3.41 (t, 2H); 3.99 (s, 3H); 4.02 (s, 2H); 4.32 (t, 2H); 7.21 (m, 1H); 7.34 (s, 1H); 7.64 (s, 1H); 7.91 (m, 2H); 8.03 (d, 1H); 8.37 (m, 1H); 9.98 (s, 1H).

Ejemplo 229. Preparación de Compuesto 406 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 3-cloro-4-fluoroanilina (87 mg, 0.6 mmol) produjo el compuesto del título (134 mg, 74 %).

MS ES^+: 600.5 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.94 (s, 3H); 3.43 (t, 2H); 3.1-4.1 (m, 8H); 3,99 (s, 5H); 4.32 (t, 2H); 7.33 (s, 1H); 7.38 (t, 1H); 7.50 (m, 1H); 7.64 (s, 1H); 7.90 (s, 1H); 7.96 (m, 1H); 9.09 (s, 1H).

Ejemplo 230. Preparación de Compuesto 407 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 3-cloroanilina (77 mg, 0.6 mmol) produjo el compuesto del título (46 mg, 26 %).

MS ES^+: 582.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2,95 (s, 3H); 3.2-4.1 (m, 8H); 3.45 (t, 2H); 3.99 (s, 3H); 4.07 (s, 2H); 4.30 (t, 2H); 7.22 (t, 1H); 7.31 (s, 1H); 7.35 (t, 1H); 7.53 (d, 1H); 7.65 (s, 1H); 7.74 (d, 1H); 7.92 (s, 1H); 9.08 (s, 1H).

Ejemplo 231. Preparación de Compuesto 408 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 4-metilanilina (64 mg, 0.6 mmol) produjo el compuesto del título (105 mg, 62 %). MS ES^+: 562.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.26 (s, 3H); 2.31 (t, 2H); 2.95 (s, 3H); 3.1-4.1

(m, 8H); 3.43 (t, 30 2H); 3.95 (s, 2H); 3.98 (s, 3H); 4.30 (t, 2H); 7.12 (d, 2H); 7.31 (s, 1H); 7.50 (d, 2H); 7.63 (s, 1H); 7.90 (s, 1H); 9.08 (s, 1H).

Ejemplo 232. Preparación de Compuesto 409 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 2-metilanilina (64 mg, 0.6 mmol) produjo el compuesto del título (127 mg, 75 %). MS ES^+: 562.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.24 (s, 3H); 2.31 (t, 2H); 2.95 (s, 3H); 3.2-4.1 (m, 8H); 3.44 (t, 2H); 3.99 (s, 3H); 4.02 (s, 2H); 4.31 (t, 2H); 7.12 (t, 1H); 7.19 (t, 1H); 7.24 (d, 1H); 7.33 (s, 1H); 7.44 (d, 1H); 7.66 (s, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 233. Preparación de Compuesto 410 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 4-cloroanilina (77 mg, 0.6 mmol) produjo el compuesto del título (101 mg, 58 %). MS ES^+: 582.5 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 2.95 (s, 3H); 3.1-4.1 (m, 8H); 3.44 (t, 2H); 4.00 (s, 5H); 4.31 (t, 2H); 7.33 (s, 1H); 7.40 (d, 2H); 7.65 (s, 1H); 7.66 (d, 2H); 7.92 (s, 1H); 9.10 (s, 1H).

Ejemplo 234. Preparación de Compuesto 411 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 4-fluoroanilina (67 mg, 0.6 mmol) produjo el compuesto del título (97 mg, 57 %). MS ES^+: 566.5 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.94 (s, 3H); 3.1-4.1 (m, 8H); 3.44 (t, 2H); 3.97 (s, 2H); 3.99 (s, 3H); 4.30 (t, 2H); 7.17 (t, 2H); 7.34 (s 1H); 7.64 (m, 3H); 7.90 (s, 1H); 9.09 (s, 1H).

Ejemplo 235. Preparación de Compuesto 412 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 2-amino-6-metilpiridina (65 mg, 0.6 mmol) produjo el compuesto del título (70 mg, 42 %).

MS ES$^+$: 563.6 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.30 (t, 2H); 2.46 (s, 3H); 2.94 (s, 3H); 3.10-4.10 (m, 8R); 3.43 (t, 2H); 3.98 (s, 3H); 4.06 (s, 2H); 4.30 (t, 2H); 7.08 (d, 1H); 7.32 (s, 1H); 7.63 (s, 1H); 7.79 (t, 1H); 7.88 (d, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 236. Preparación de Compuesto 413 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 2-metoxianilina (74 mg) 0.6 mmol) produjo el compuesto del título (99 mg) 57 %). MS ES$^+$: 578.6 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.30 (t) 2H); 2.94 (s) 3H); 3.1-4.1 (m) 8H); 3.43 (t, 2H); 3.74 (s, 3H); 3.97 (s, 2H); 3.99 (s, 3H); 4.30 (t, 2H); 6.67 (d, 1H); 7.15 (d, 1H); 7.24 (t, 1H); 7.33 (s, 2H); 7.64 (s, 1H); 7.90 (s, 1H); 9.09 (s, 1H).

Ejemplo 237. Preparación de Compuesto 414 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 2-amino-5-cloropiridina (77 mg, 0.6 mmol) produjo el compuesto del título (23 mg, 13 %).

MS ES$^+$: 583.5 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.30 (t, 2H); 2.94 (s, 3H); 3.10-4.10 (m, 8H); 3.45 (t, 2H); 3.98 (s, 3H); 4.06 (s, 2H); 4.30 (t, 2HR); 7.31 (s, 1H); 7.63 (s, 1H); 7.90 (s, 1H); 7.91 (dd, 1H); 8.11 (d, 1H); 8.40 (d, 1H); 9.09 (s, 1H).

Ejemplo 238. Preparación de Compuesto 415 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 3-cloroanilina (77 mg, 0.6 mmol) produjo el compuesto del título (96 mg, 55 %).

MS ES$^+$: 582.5 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.94 (s, 3H); 3.2-4.2 (m, 8H); 3.45 (t, 2H); 3.98 (s, 5H); 4.28 (t, 2H); 7.12 (d, 1H); 7.31 (s, 1H); 7.34 (t, 1H); 7.46 (d, 1H); 7.62 (s, 1H); 7.85 (s, 1H); 7.91 (s, 1H); 9.07 (s, 1H).

Ejemplo 239. Preparación de Compuesto 416 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 2-fluoroanilina (67 mg, 0.6 mmol) produjo el compuesto del título (68 mg, 40 %). MS ES^+: 596.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.28 (t, 2H); 2.91 (s, 3H); 3.1-4.1 (m, 8H); 3.40 (t, 2H); 3.95 (s, 3H); 4.03 (s, 2H); 4.26 (t, 2H); 7.13 (m, 2H); 7.25 (m, 2H); 7.28 (s, 1H); 7.60 (s, 1H); 7.87 (s, 1H); 9.05 (s, 1H).

Ejemplo 240. Preparación de Compuesto 417 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 3-cianoanilina (71 mg, 0.6 mmol) produjo el compuesto del título (101 mg, 63 %). MS ES^+: 573.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.95 (s, 3H); 3.1-4.1 (m, 8H); 3.45 (t, 2H); 4.00 (s, 3H); 4.04 (s, 2H); 4.31 (t, 2H); 7.33 (s, 1H); 7.56 (s, 1H); 7.57 (m, 1H); 7.66 (s, 1H); 7.82 (m, 1H); 7.92 (s, 1H); 8.15 (s, 1H); 9.10 (s, 1H).

Ejemplo 241. Preparación de Compuesto 418 en Tabla 16:

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 2-fluoro-4-metilanilina (75 mg, 0.6 mmol) produjo el compuesto del título (109 mg, 63 %).

MS ES^+: 580.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.29 (m, 5H); 2.94 (s, 3H); 3.1-4.1 (m, 8H); 3.44 (t, 2H); 3.98 (s, 3H); 4.03 (s, 2H); 4.30 (t, 2H); 6.98 (d, 1H); 7.09 (d, 1H); 7.32 (s, 1H); 7.63 (s, 1H); 7.74 (t, 1H); 7.90 (s, 1H); 9.08 (s, 1H).

Ejemplo 242. Preparación de Compuesto 419 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 3-fluoro-4-metoxianilina (85 mg, 0.6 mmol) produjo el compuesto del título (121 mg, 68 %).

MS ES^+: 596.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.95 (s, 3H); 3.1-4.1 (m, 8H); 3.44 (t, 2H); 3.81 (s, 3H); 3.95 (s, 2H); 3.99 (s, 3H); 4.30 (t, 2H); 7.13 (t, 1H); 7.27 (m, 1H); 7.31 (s, 1H); 7.60 (m, 1H); 7.64 (s, 1H); 7.90 (s, 1H); 9.09 (s, 1H).

Ejemplo 243. Preparación de Compuesto 420 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 2-metil-4-fluoroanilina (75 mg, 0.6 mmol) produjo el compuesto del título (130 mg, 75 %).

MS ES$^+$: 580.6 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.23 (s, 3H); 2.29 (t, 2H); 2.95 (s, 3H); 3.1-4.1 (m, 8H); 3.44 (t, 2H); 3.99 (s, 3H); 4.00 (s, 2H); 4.30 (t, 2H); 7.01 (m, 1H); 7.09 (dd, 1H); 7.32 (s, 1H); 7.40 (m, 1H); 7.65 (s, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 244. Preparación de Compuesto 421 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 2-amino-4-metilpiridina (65 mg, 0.6 mmol) produjo el compuesto del título (87 mg, 52 %).

MS ES$^+$: 563.6 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.29 (t, 2H); 2.45 (s, 3H); 2.94 (s, 3H); 3.1-4.1 (m, 8H); 3.44 (t, 2H); 3.99 (s, 3H); 4.15 (s, 2H); 4.30 (t, 2H); 7.24 (d, 1H); 7.37 (s, 1H); 7.67 (s, 1H); 7.72 (s, 1H); 7.92 (s, 1H); 8.29 (d, 1H); 9.08 (s, 1H);

Ejemplo 245. Preparación de Compuesto 422 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 2,5-difluoroanilina (77 mg, 0.6 mmol) produjo el compuesto del título (56 mg, 32 %). MS ES$^+$: 584.6 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.30 (t, 2H); 2.94 (s, 3H); 3.1-4.1 (m, 8H); 3.43 (t, 2H); 3.98 (s, 3H); 4.10 (s, 2H); 4.30 (t, 2H); 7.0 (m, 1H); 7.32 (s, 1H); 7.33 (m, 1H); 7.64 (s, 1H); 7.91 (m, 2H); 9.09 (s, 1H).

Ejemplo 246. Preparación de Compuesto 423 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 2-fluoro-4-cloroanilina (87 mg, 0.6 mmol) produjo el compuesto del título (69 mg, 38 %).

MS ES^+: 600.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32.(t, 2H); 2.94 (s, 3H); 3.2-4.2 (m, 8H); 3.44 (t, 2H); 3.99 (s, 3H); 4.07 (s, 2H); 4.30 (t, 2H); 7.20 (dd, 1H); 7.33 (s, 1H); 7.51 (dd, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 7.97 (t, 1H); 9.09 (s, 1H).

Ejemplo 247. Preparación de Compuesto 424 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 2-fluoro-5-metilanilina (75 mg, 0.6 mmol) produjo el compuesto del título (81 mg, 46 %).

MS ES^+: 580.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.27 (s, 3H); 2.32 (t, 2H); 2.94 (s, 3H); 3.1-4.1 (m, 8H); 3.44 (t, 30 2H); 3.99 (s, 3H); 4.05 (s, 2H); 4.30 (t, 2H); 6.97 (m, 1H); 7.13 (dd, 1H); 7.34 (s, 1H); 7.63 (s, 1H);7.74 (d, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 248. Preparación de Compuesto 425 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 3-metilanilina (64 mg, 0.6 mmol) produjo el compuesto del título (116 mg, 69 %). MS ES^+: 584.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.28 (s, 3H); 2.31 (t, 2H); 2.95 (s, 3H); 3.1-4.1 (m, 8H); 3.45 (t, 2H); 3.96 (s, 2H); 3.98 (s, 3H); 4.30 (t, 2H); 6.88 (d, 1H); 7.19 (t, 1H); 7.30 (s, 1H); 7.39 (d, 1H); 7.47 (s, 1H); 7.62 (s, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 249. Preparación de Compuesto 426 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 2,4-difluoroanilina (77 mg, 0.6 mmol) produjo el compuesto del título (84

mg, 48 %). MS ES^+: 584.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.95 (s, 3H); 3.1-4.1 (m, 8H); 3.99 (s, 3H); 4.05 (s, 2H); 4.30 (t, 2H); 7.07 (t, 1H); 7.32 (m, 2H); 7.64 (s, 1H); 7.86 (m, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 250. PreParación de Compuesto 427 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 2-metil-5-fluoroanilina (75 mg, 0.6 mmol) produjo el compuesto del título (98 mg, 57 %).

MS ES^+: 580.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.23 (s, 3H); 2.31 (t, 2H); 2.94 (s, 3H); 3.1-4.1 (m, 8H); 3.43 (t, 2H); 3.98 (s, 3H); 4.05 (s, 2H); 4.30 (t, 2H); 6.91 (m, 1H); 7.25 (t, 1H); 7.32 (s, 1H); 7.44 (dd, 1H); 7.65 (s, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 251. Preparación de Compuesto 428 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 3,5-difluoroanilina (77 mg, 0.6 mmol) produjo el compuesto del título (54 mg, 31 %). MS ES^+: 584.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.95 (s, 3H); 3.1-4.1 (m, 8H); 3.45 (t, 2H); 3.99 (s, 3H); 4.02 (s, 2H); 4.31 (t, 2H); 6.92 (m, 1H); 7.33 (s, 1H); 7.35 (m, 2H); 7.66 (s, 1H); 7.92 (s, 1H); 9.10 (s, 1H).

Ejemplo 252. Preparación de Compuesto 429 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 103 pero comenzando con 3-fluoroanilina (67 mg, 0.6 mmol) produjo el compuesto del título (120 mg, 70 %). MS ES^+: 566.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.94 (s, 3H); 3.2-4.2 (m, 8H); 3.44 (t, 2H); 3.98 (s, 3H); 3.99 (s, 2H); 4.30 (t, 2H); 6.90 (s, 1H); 7.34 (s, 1H); 7.36 (m, 2H); 7.61 (m, 1h); 7.64 (s, 1h); 7.90 (s, 1h); 9.09 (s, 1h).

Ejemplo 253. Preparación DE Compuesto 430 en Tabla 17

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N-(3-clorofenil)-2-(2-(7-(3-cloropropox)-6-metoxiquinazolin-4-il-amino)1,3- tiazol-5-il)acetamida (141 mg, 0.22 mmol) en acetonitrilo (2 ml) se hizo reaccionar con pirrolidina (3.3 mmol) en presencia de yoduro de potasio (100 mg, 0.6 mmol) a 80°C durante 15 / 30 horas. Una vez concluida la reacción (tlc) DMF (2 ml), se añadió gel de sílice (2 g), la mezcla se evaporó, y el residuo se purificó por cromatografía de gel de sílice, eluyente: CH_2Cl_2 / MeOH 95/5, CH_2Cl_2 / MeOH sat. NH_3 90/10 para producir el compuesto del título (81 mg, 29 %).

MS ES^+: 553.4 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.90 (m, 2H); 2.06 (m, 2H); 2.26 (t, 2H); 3.09 (m, 2H); 3.36 (t, 2H); 3.67 (m, 2H); 3.99 (s, 3H); 4.00 (s, 2H); 4.29 (t, 2H); 7.14 (d, 1H); 7.30 (s, 1H); 7.37 (t, 1H); 7.47 (d, 1H); 7.65 (s, 1H); 7.85 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

3-metoxi-4-benciloxibenzonitrilo.

3-metoxi-4-benciloxibenzoldehído (4.87 g, 20 mmol) en ácido acético (25 ml) se trató con hidroxiamina HCl (2.8 g, 40 mmol), acetato de sodio (3.3 g, 40 mmol) a reflujo durante 6 horas. La mezcla se enfrió, se extrajo con agua y cloruro de metileno, se secó sobrer $MgSO_4$, se evaporó, para producir el compuesto del título (4.8 g, 100 %).

^{1}HNMR (DMSO-d_6, TFA): 3.72 (s, 3H); 5.15 (s, 2H); 7.18 (d, 1H); 7.39 (m, 7H).

2-nitro-4-benciloxi-5-metoxibenzonitrilo.

3-metoxi-4-benciloxibenzonitrilo (4.78 g, 20 mmol) en ácido acético (10 ml) se adicionó lentamente a ácido nítrico (d = 1.42, 25 ml) a 20-30° con enfriamiento en un baño de hielo. La mezcla se agitó luego a temperatura ambiente durante 6 horas. La mezcla de la reacción se trató con hidróxido de potasio (10N) a O°C. La mezcla básica (pH 10) se extrajo con CH_2Cl_2, la fase orgánica se secó sobre $MgSO_4$, se concentró para producir el compuesto del título (3.62 g, 64 %). MS ES^+: 285 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 3.97 (s, 3H); 5.33 (s, 2H); 7.42 (m, 5H); 7.70 (s, 1H); 8.03 (s, 1H).

2-amino-4-benciloxi-5-metoxibenzonitrilo.

2-nitro-4-benciloxi-5-metoxibenzonitrilo (40 g, 125 mmol), cloruro de tetrabutilamonio (21 g, 75 mmol) en cloruro de metileno (500 ml) se trató con $Na_2S_2O_4$ (180 g, 87.9 mmol) en H_2O (700 ml), se agregó hidrosulfito de sodio durante 45 minutos, y la mezcla se agitó durante 2 horas a temperatura ambiente. Se adicionó hidróxido de sodio (pH 8.2), la mezcla se extrajo con cloruro de metileno. La fase orgánica se acidificó con HCl-éter (2.3N, 250 ml), el sólido se recuperó, se suspendió en metaanol (250 ml) y se trató con una solución saturada de bicarbonato de sodio (pH 8.1). El sólido se recuperó, se lavó con agua, éter para producir el compuesto del título (30.7 g, 97 %).

^{1}HNMR (DMSO-d_6): 3.65 (s, 3H); 5.04 (s, 2H); 5.61 (s, 2H); 6.51 (s, 1H); 6.91 (s, 1H); 7.40 (m, 5H).

N'-(2-ciano-4-metoxi-5-benciloxifenil-N,N-dimetilimidoformamida.

2-amino-4-benciloxi-5-metoxi benzonitrilo (102 g, 400 mmol) en tolueno (1.5 1) se hizo reaccionar con DMF-DMA (110 ml, 780 mmol) a reflujo durante 5 horas. El solvente se evaporó, el residuo se trituró con éter para producir el compuesto del título como sólido amarillo.

^{1}HNMR (DMSO-d_6): 2.96 (s, 3H); 3.06 (s, 3H); 3.73 (s, 3H); 5.15 (s, 2H); 6.87 (s, 1H); 7.11 (s, 1H); 7.40 (m, 5H); 7.89 (s, 1H).

N'-(2-ciano-4-metoxi-5-hidroxifenil)-N,N-dimetilimidoformamida.

N'-(2-ciano-4-metoxi-5-benciloxifenil)-N,N-dimetilimidoformamida (15.45 g, 50 mmol) en TFA (200 ml) se irradió en un horno microondas a 75°C durante 45 minutos. El solvente se evaporó, el residuo disuelto en diclorometano se lavó con bicarbonato de sodio, se secó sobre sulfato de magnesio, se eaporó para producir un sólido amarillo pálido (10.26 g, 94 %).

^{1}HNMR (DMSO-d_6, TFA): 3.24 (s, 3H); 3.34 (s, 3H); 3.87 (s, 3H); 7.02 (s, 1H); 7.49 (s, 1H); 8.56 (s, 1H).

N'-(2-ciano-4-metoxi-5-(3-cloropropoxifenil)-N,N-dimetilimidoformamida.

N'-(2-ciano-4-metoxi-5-hidroxifenil)-N,N-dimetilimidoformamida (439 mg, 2 mmol) en acetonitrilo (5 ml) se hizo reaccionar con 1-bromo-3-cloropropano (0.22 ml, 2.2 mmol) y carbonato de cesio (1.95 g, 5.98 mmol)

a 85°C durante 0.5 hora. La mezcla de la reacción se evaporó, se absorbión en cloruro de metileno, agua, se extrajo con CH_2Cl_2, se secó sobre $MgSO_4$, se evaporó para producir el compuesto del título como un sólido amarillo pálido (450 mg, 76 %).

MS ES^+: 296.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.26 (t, 2H); 3.26 (s, 3H); 3.37 (s, 3H); 3.81 (t, 2H); 3.87 (s, 3H); 4.23 (t, 2H); 7.34 (s, 1H); 7.53 (s, 1H); 8.56 (s, 1H).

g) N-(3-clorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4-ilamino)1,3- tiazol-5- il)acetamida.

N'-(2-ciano-4-metoxi-5-(3-cloropropoxifenil)-N,N-dimetilimidoformamida (296 mg, 1 mmol) y 2-(2-amino-1,3-tiazol-5-il)-N-(3-clorofenil)acetamida (268 mg, 1 mmol) en AcOH (1.5 ml), se irradió en un horno microondas a 120°C durante 40 minutos. La mezcla se enfrió, el sólido se filtró para producir el compuesto del título (445 mg, 72 %).

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.84 (t, 2H); 3.98 (s, 3H); 3.99 (s, 2H); 4.32 (t, 2H); 7.13 (d, 1H); 7.29 (s, 1H); 7.36 (t, 1H); 7.46 (d, 1H); 7.63 (s, 1H); 7.85 (s, 1H); 7.88 (s, 1H); 9.07 (s, 1H).

Ejemplo 254. Preparación de Compuesto 431 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130 pero comenzando con N-(3,4-difluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4-il-amino)1,3- tiazol-5-il)acetamida (52 mg, 0.1 mmol) y pirrolidina (150µ, 1.8 mmol) produjo el compuesto del título (26 mg, 47 %).

^{1}HNMR (DMSO-d_6, TFA): 1.91 (m, 2H); 2.07 (m, 2H); 2.28 (t, 2H); 3.10 (m, 2H); 3.37 (t, 2H); 3.67 (m, 2H); 3.99 (s, 5H); 4.30 (t, 2H); 7.30 (s, 1H); 7.33 (m, 1H); 7.40 (q, 1H); 7.65 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Material inicial: N-(3,4-difluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxi quinazolin-4-il-amino)1,3-tiazol-5-il)acetamida se obtuvo por una reacción análoga a la descrita en Ejemplo 130 pero comenzando con 2-(2-amino-1,3-tiazol-5-il)-N-(3,4-difluorofenil)acetamida (540 mg, 2 mmol) para producir el compuesto del título (980 mg, 78 %).

MS ES$^+$: 520.4, 522.4 $(M_+H)^+$

^{1}HNMR (DMSO-d_6): 1.26 (t, 2H); 3.82 (t, 2H); 3.88 (s, 2H); 3.97 (s, 3H); 4.29 (t, 2H); 7.29 (s, 1H); 7.32 (m, 1H); 7.36 (s, 1H); 7.39 (t, 1H); 7.80 (m, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

Ejemplo 255. Preparación de Compuesto 432 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130 pero comenzando con N-(3,5-difluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4-il-amino)1,3-tiazol-5-il)acetamida (138 mg, 0.22 mmol) y dimetilamina (3.6 M en CH_2Cl_2, 3 ml, 3.6 mmol) produjo el compuesto del título (47 mg, 40 %).

MS ES$^+$: 529.5 $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.25 (t, 2H); 3.28 (t, 2H); 3.99 (s, 3H); 4.01 (s, 2H); 4.28 (t, 2H); 6.93 (m, 1H); 7.30 (s, 1H); 7.34 (m, 2H); 7.65 (s, 1H); 7.90 (s, 1H); 9.09 (s, 1H).

Material inicial: N-(3,5-difluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4-il-amino)1,3-tiazol-5-il)acetamida se obtuvo por reacción análoga a la descrita en Ejemplo 130 pero comenzando con 2-(2-amino-1,3-tiazol-5-il)-N-(3,5-difluorofenil)acetamida (810 mg, 3 mmol) para producir el compuesto del título (630 mg, 40 %).

MS ES$^+$: 520.4, 522.4 $(M_+H)^+$

^{1}HNMR (DMSO-d_6): 2.26 (t, 2H); 3.84 (t, 2H); 3.92 (s, 2H); 3.98 (s, 3H); 4.30 (t, 2H);; 6.94 (m, 1H); 7.30 (5, 1H); 7.35 (m, 2H); 7.40 (s, 1H); 8.14 (5, 1H); 8.69 (s, 1H); 10.64 (5, 1H).

Ejemplo 256. Preparación de Compuesto 433 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130 pero comenzando con N-(3-cloro-4-fluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4-il-amino)1,3-tiazol-5-il)acetamida (123 mg, 0.22 mmol) y 2-amino-2-metil-1-propanol (89.1 mg, 3.3 mmol) produjo el compuesto del título (6 mg, 5 %).

MS ES$^+$: 589.4, $(M_+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.24 (s, 6H); 2.22 (t, 2H); 3.10 (t, 2H); 3.45 (s,

2H); 3.98 (s, 3H); 4.31 (t, 2H); 7.29 (s, 1H); 7.38 (t, 1R); 7.50 (m, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 7.97 (s, 1H); 9.09 (s, 1H).

Material inicial: N-(3.cloro-4-fluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4-il-amino)1,3-tiazol-5-il)acetamida se obtuvo por reacción análoga a la descrita en Ejemplo 130 pero comenzando con 2-(2-amino-1,3-tiazol-5-il)-N-(3-cloro-4-fluorofenil)acetamida (2.29 g, 8.0 mmol) para producir el compuesto del título (3.62 g, 84 %). MS ES^+: 536.3, 538.3 $(M+H)^+$

1HNMR ($DMSOd_6$): 2.26 (t, 2H); 3.82 (t, 2H); 3.88 (s, 2H); 3.96 (s, 3H); 4.29 (t, 2H); 7.28 (s, 1H); 7.38 (t, 1H); 7.39 (s, 1H); 7.48 (m, 1H); 7.93 (m, 1H); 8.12 (s, 1H); 8.67 (s, 1H); 10.47 (s, 1H).

Ejemplo 257. Preparación de Compuesto 434 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con N-(3-fluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4-il-amino)1,3-tiazol-5-il)acetamida (116 mg, 0.22 mmol) y 2-amino-2-metil-1-propanol (89 mg, 3.3 mmol) produjo el compuesto del título (40 mg, 33 %).

MS ES^+: 555.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.22 (t, 2H); 3.09 (t, 2H); 3.16 (s, 2H); 3.97 (s, 3H); 4.30 (t, 2H); 6.86 (t, 1H); 7.28 (s, 1H); 7.33 (m, 2H); 7.58 (m, 1H); 7.62 (s, 1H); 7.91 (s, 1H); 9.07 (s, 1H).

Material inicial: N-(3-fluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4- il-amino)1,3-tiazol-5-il)acetamida se obtuvo mediante una reacción análoga a la descrita en Ejemplo 130 pero comenzando con 2-(2-amino-1,3-tiazol-5-il)-N-(3-fluorofenil)acetamida (2.01 g, 8 mmol) para producir el compuesto del título (3.08 g, 77 %).

MS ES^+: 502.4, 504.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.28 (t, 2H); 3.84 (t, 2H); 3.90 (s, 2H); 3.98 (s, 3H); 4.31 (t, 2H); 6.91 20 (t, 1H); 7.30 (s, 1H); 7.35 (m, 2H); 7.39 (s, 1H); 7.63 (d, 1H); 8.14 (s, 1H); 8.69 (s, 1H); 10.48 (s, 1H).

Ejemplo 258. Preparación de Compuesto 435 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con 4-hidroxiperidina 25 (405 mg, 4.0 mmol) produjo el compuesto 135 en Tabla 17 (82 mg, 70 %).

MS ES^+: 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.43 (m, 2H); 1.73 (m, 2H); 1.95 (m, 2H); 2.03 (t, 2H); 2.44 (t, 2H); 2.74 (m, 2H); 3.38 (m, 1H); 3.90 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.53 (d, 1H); 7.26 (s, 1H); 7.31 (m, 1H); 7.39 (s, 1H); 7.42 (ddd, 1H); 7.83 (m, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.50 (s, 1H).

Ejemplo 259. Preparación de Compuesto 436 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con N,N- dimetilendiamina (0.44 ml, 4.0 mmol) produjo el compuesto 136 en Tabla 17 (40 mg, 35 %).

MS ES^+: 572.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.95 (m, 2H); 2.14 (s, 6H); 2.33 (t, 2H); 2.63 (t, 2H); 2.73 (t,2H); 3.89 (s, 2H); 3.97 (s, 3H); 4.22 (t, 2H); 7.26 (s, 1H); 7.34 (m, 1H); 7.38 (s, 1H); 7.41 (ddd, 1H); 7.82 (m, 1H); 8.11 (s, 1H); 8.67 (s, 1H); 10.50 (s, 1H).

Ejemplo 260. Preparación de Compuesto 437 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con piperidina (0.4 ml, 3.0 mmol) produjo el compuesto 137 en Tabla 17 (67 mg, 59 %).

MS ES^+: 569.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H); 1.52 (m, 4H); 1.95 (m, 2H); 2.42 (m, 4H); 2.48 (t,2H); 3.89 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 7.25 (s, 1H); 7.33 (m, 1H); 7.39 (8, 1H); 7.41 (ddd, 1H); 7.82 (m, 1H); 8.11 (s, 1H); 8.68 (s, 1H); 10.51 (s, 1H).

Ejemplo 261. Preparación de Compuesto 438 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con 2-

metilaminoetanol (248 mg, 3.3 mmol) produjo el compuesto 138 en Tabla 17 (23 mg, 19 %).

MS ES^+: 559 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.95 (m, 2H); 2.23 (s, 3H); 2.47 (m, 2H); 3.32 (m, 2H); 3.49 (m, 2H); 3.90 (s, 2H); 3.98 (s, 3H); 4.21 (t, 2H); 4.37 (m, 1H); 7.27 (s, 1H); 7.34 (m, 1H); 7.38 (s, 1H); 7.40 (dd, 1H); 7.82 (ddd, 1H); 8.13 (brs, 1H); 8.68 (s, 1H); 10.50 (s, 1H).

Ejemplo 262. Preparación de Compuesto 439 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con 1,2-diamino-2-metilpropano (291 mg, 3.3 mmol) produjo el compuesto 139 en Tabla 17 (16 mg, 13 %).

MS ES^+: 572 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.10 (s, 6H); 1.96 (m, 2H); 2.48 (s, 2H); 2.75 (t, 2H); 3.89 (s, 2H); 3.97 (s, 3H); 4.26 (t, 2H); 7.27 (s, 1H); 7.34 (m, 1H); 7.37 (s, 1H); 7.42 (dd, 1H); 7.83 (ddd, 1H); 8.10 (s, 1H); 8.66 (s, 1H); 10.50 (s, 1H).

Ejemplo 263. Preparación de Compuesto 440 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con ciclohexilamina (327 mg, 3.3 mmol) produjo el compuesto 140 en Tabla 17 (70 mg, 55 %).

MS ES^+: 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.12 (m, 1H); 1.27 (m, 4H); 1.63 (brd, 1H); 1.78 (m, 2H); 2.04 (m, 2H); 2.16 (m, 2H); 3.03 (m, 1H); 3.16 (t, 2H); 3.90 (s, 2H); 3.98 (s, 3H); 4.29 (t, 2H); 7.31 (s, 1H); 7.34 (m, 1H); 7.40 (s, 1H); 7.42 (dd, 1H); 7.82 (ddd, 1H); 8.16 (brs, 1H); 8.70 (s, 1H); 10.51 (s, 1H).

Ejemplo 264. Preparación de Compuesto 441 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con N,N, N'-trimetiletilendiamina (337 mg, 3.3 mmol) produjo el compuesto 141 en Tabla 17 (63 mg, 49 %).

MS ES^+: 587 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (m, 2H); 2.88 (s, 6H); 2.93 (s, 3H); 3.38 (m, 2H); 3.56 (m, 4H); 3.98 (s, 5H); 4.30 (t, 2H); 7.29 (m, 1H); 7.33 (s, 1H); 7.35 (dd, 1H); 7.63 (5, 1H); 7.80 (ddd, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 265. Preparación de Compuesto 442 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con (R)-(-)-2-pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 142 en Tabla 17 (90 mg, 70 %).

MS ES$^+$: 585 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.79 (m, 1H); 1.91 (m, 1H); 2.03 (m, 1H); 2.11 (m, 1H); 2.29 25 (m, 2H); 3.21 (m, 2H); 3.62 (m, 4H); 3.77 (m, 1H); 3.98 (s, 5H); 4.29 (t, 2H); 7.30 (s, 1H); 7.32 (m, 1H); 7.39 (dd, 1H); 7.64 (s, 1H); 7.80 (ddd, 1H); 7.90 (s, 1H); 9.08 (s, 1H).

Ejemplo 266. Preparación de Compuesto 443 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con (S)-(+)-2-pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 143 en Tabla 17 (82 mg, 63 %).

MS ES$^+$: 585 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.76 (m, 1H); 1.88 (m, 1H); 2.01 (m, 1H); 2.10 (m, 1H); 2.26 (m, 2H); 3.21 (m, 2H); 3.59 (m, 4H); 3.74 (dd, 1H); 3.95 (s, 5H); 4.27 (t, 2H); 7.27 (s, 1H); 7.28 (m, 1H); 7.34 (dd, 1H); 7.60 (s, 1H); 7.77 (ddd, 1H); 7.88 (s, 1H); 9.05 (s, 1H).

Ejemplo 267. Preparación de Compuesto 444 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con 3-pirrolidinol (288 mg, 3.3 mmol) produjo el compuesto 144 en Tabla 17 (15 mg, 12 %).

MS ES$^+$: 571 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.85-2.04 (m, 2H); 2.28 (m, 2H); 3.03-3.54 (m, 4H); 3.75 (m, 2H); 3.99 (s, 5H); 4.28 (m, 2H); 4.40-4.52 (m, 1H); 7.29 (s, 1H); 7.33 (m, 1H); 7.39 (dd, 1H); 7.64 (s, 1H); 7.81 (ddd, 1H); 7.91 (s, 1H);

9.08 (s, 1H).

Ejemplo 268. Preparación de Compuesto 445 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con 1-(2-aminoetil)pirrolidina (377 mg, 3.3 mmol) produjo el compuesto 145 en Tabla 17 (20 mg, 15 %).

MS ES^+: 598 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.92 (m, 2H); 2.06 (m, 2H); 2.24 (m, 2H); 3.11 (m,2H); 3.23 (t, 2H); 3.42 (m, 2H); 3.49 (m, 2H); 3.52 (m, 2H); 4.00 (3, 5H); 4.32 (t, 2H); 7.32 (s, 1H); 7.33 (m, 1H); 7.39 (dd, 1H); 7.65 (s, 1H); 7.81 (ddd, 1H); 7.92 (s, 1H); 9.10 (s, 1H).

Ejemplo 269. Preparación de Compuesto 446 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con 1-acetilpiperazina (423 mg, 3.3 mmol) produjo el compuesto 146 en Tabla 17 (100 mg, 74 %).

MS ES^+: 612 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.00 (s, 5H); 2.35 (m, 2H); 2.42 (m, 2H); 3.92-3.06 (m, 1H); 3.45 (m, 4H); 3.56 (t, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4.23 (t, 2H); 7.28 (s, 1H); 7.34 (m, 1H); 7.40 (s, 1H); 7.42 (dd, 1H); 7.83 (ddd, 1H); 8.13 (brs, 1H); 8.69 (s, 1H).

Ejemplo 270. Preparación de Compuesto 447 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con 1-(2-morfolinoetil)-piperazina (658 mg, 3.3 mmol) produjo el compuesto 147 en Tabla 17 (44 mg, 29%).

MS ES^+: 683 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.98 (m, 2H); 2.30-2.70 (m, 18H); 3.58 (m, 4H); 3.90 (s, 2H); 3.97 (s, 3H); 4.21 (t, 2H); 7.26 (s, 1H); 7.33 (m, 1H); 7.40 (s, 1H); 7.41 (dd, 1H); 7.82 (ddd, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.54 (s, 1H).

Ejemplo 271. Preparación de Compuesto 448 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con 2-piperidinetanol (426 mg, 3.3 mmol) produjo el compuesto 148 en Tabla 17 (19 mg, 14 %).

MS ES^+: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.45-1.92 (m, 7H); 2.00-2.15 (m, 1H); 2.20-2.40 (m, 2H); 3.10-3.70 (m, 7H); 3.99 (s, 5H); 4.30 (m, 2H); 7.30 (s, 1H); 7.34 (m, 1H); 7.40 (dd, 1H); 7.64 (s, 1H); 7.81 (ddd, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 272. Preparación de Compuesto 449 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con 1-(2-hidroxietil)piperazina (430 mg, 3.3 mmol) produjo el compuesto 149 en Tabla 17 (90 mg, 66 %).

MS ES^+: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H); 2.35-2.47 (m, 12H); 3.49 (q, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.20 (t, 1H); 4.37 (t, 1H); 7.25 (s, 1H); 7.33 (m, 1H); 7.39 (s, 1H); 7.41 (dd, 1H); 7.81 (ddd, 1H); 8.12 (brs, 1H); 8.68 (s, 1H); 10.50 (s, 1H); 12.03 (brs, 1H).

Ejemplo 273. Preparación de Compuesto 450 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con ciclopentilamina (281 mg, 3.3 mmol) produjo el compuesto 150 en Tabla 17 (43 mg, 34 %).

MS ES^+: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.53 (m, 4H); 1.69 (m, 2H); 1.93 (m, 2H); 2.10 (m, 2H); 3.00 (m, 2H); 3.38 (m,2H); 3.90 (s, 2H); 3.98 (s, 3H); 4.28 (t, 2H); 7.30 (s, 1H); 7.32 (m, 1H); 7.42 (dd, 1H); 7.81 (ddd, 1H); 8.15 (brs, 1H); 8.70 (s, 1H); 10.51 (s, 1H).

Ejemplo 274. Preparación de Compuesto 451 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con

4-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 151 En Tabla 17 (53 mg, 39 %).

MS ES^+: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H); 1.36 (m, 3H); 1.63 (brd, 2H); 1.87 (m, 2H); 1.95 (m, 2H); 2.45 (m, 1H); 2.86 (m, 2H); 3.44 (m, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.32 (t, 1H); 7.26 (s, 1H); 7.31 (m, 1H); 7.40 (s, 1H); 7.42 (dd, 1H); 7.82 (ddd, 1H); 8.13 (brs, 1H); 8.68 (s, 1H); 10.50 (s, 1H); 12.02 (brs, 1H).

Ejemplo 275. Preparación de Compuesto 452 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con clorhidrato de L-alanin-T-butiléster (599 mg, 3.3 mmol) y tratando la mezcla de la reacción cruda con una solución 1:1 de CH_2Cl_2-TFA (4 ml) produjo el compuesto 152 en Tabla 17 (75 mg, 60 %).

MS ES^+: 573 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.48 (d, 3H); 2.24 (m, 2H); 3.22 (m, 2H); 3.97 (s, 5H); 4.15 (q, 1H); 4.30 (m, 2H); 7.30 (s, 1H); 7.34 (m, 1H); 7.40 (dd, 1H); 7.64 (s, 1H); 7.81 (ddd, 1H); 7.90 (s, 1H); 9.08 (s, 1H); 10.60 (s, 1H).

Ejemplo 276. Preparación de Compuesto 453 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con 3-hidroxipiperidina (334 mg, 3.3 mmol) produjo el compuesto 153 en Tabla 17 (84 mg, 65 %).

MS ES^+: 585 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.07 (m, 1H); 1.41 (m, 1H); 1.62 (m, 1H); 1.76 (m, 2H); 1.87 (m, 1H); 1.95 (m, 2H); 2.47 (m, 2H); 2.68 (m, 1H); 2.85 (m, 1H); 3.48 (m, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4.20 (t, 2H); 4.59 (d, 1H); 7.26 (s, 1H); 7.31 (m, 1H); 7.39 (s, 1H); 7.42 (dd, 1H); 7.81 (ddd, 1H); 8.12 (brs, 1H); 8.68 (s, 1H); 10.50 (s, 1H); 12.02 (brs, 1H).

Ejemplo 277. Preparación de Compuesto 454 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con

4- hidroximetilpiperidina (380 mg, 3.3 mmol) produjo el compuesto 154 en Tabla 17 (42 mg, 32 5 %).

MS ES^+: 599 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.13 (m, 2H); 1.33 (m, 1H); 1.62 (brd, 2H); 1.90 (m, 2H); 1.95 (m, 2H); 2.44 (m, 2H); 2.88 (m, 2H); 3.22 (t, 2H); 3.86 (s, 2H); 3.93 (s, 3H); 4.17 (t, 2H); 4.38 (t, 1H); 7.22 (s, 1H); 7.31 (m, 1H); 7.36 (s, 1H); 7.38 (dd, 1H); 7.80 (ddd, 1H); 8.09 (brs, 1H); 8.65 (s, 1H); 10.46 (s, 1H); 12.00 (brs, 1H).

Ejemplo 278. Preparación de Compuesto 455 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con 1-amino-2-propanol (248 mg, 3.3 mmol) produjo el compuesto 155 en Tabla 17 (52 mg, 42 %).

MS ES^+: 573 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H); 1.95 (m, 2H); 2.48 (m, 2H); 2.72 (t, 2H); 3.68 (m, 1H); 3.89 (s, 2H); 3.97 (s, 3H); 4.23 (t, 2H); 4.46 (m, 1H); 7.26 (s, 1H); 7.32 (m, 1H); 7.38 (s, 1H); 7.41 (dd, 1H); 7.81 (ddd, 1H); 8.11 (s, 1H); 8.67 (s, 1H); 10.49 (s, 1H).

Ejemplo 279. Preparación de Compuesto 456 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con clorhidrato de L-alamin-t-butiléster (599 mg, 3.3 mmol) y tratando la mezcla de la reacción cruda con CH_2Cl_2-TFA (1/1, 4 ml) produjo el compuesto 156 en Tabla 17 (106 mg, 84 %).

MS ES^+: 571 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.40 (d, 3H); 2.25 (m, 2H); 3.20 (m, 2H); 3.98 (s, 3H); 4.00 (s, 2H); 4.14 (m, 1H); 4.31 (t, 2H); 7.13 (dd, 1H); 7.32 (s, 1H); 7.35 (t, 1H); 7.47 (dd, 1H); 7.63 (s, 1H); 7.86 (t, 1H); 7.90 (s, 1H); 8.30 (m, 1H); 9.08 (s, 1H); 10.60 (s, 1H).

Ejemplo 280. Preparación de Compuesto 457 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con

2- metilaminoetanol (248 mg, 3.3 mmol) produjo el compuesto 157 en Tabla 17 (86 mg, 70 %).

MS ES^+: 557 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.93 (m, 2H); 2.20 (s, 3H); 2.43 (t, 2H); 2.48 (m, 1H); 2.55 (m, 1H); 3.47 (dd, 2H); 3.89 (s, 2H); 3.96 (s, 3H); 4.19 (t, 2H); 4.34 (t, 1H); 7.13 (brd, 1H); 7.25 (s, 1H); 7.35 (t, 1H); 7.38 (s, 1H); 7.47 (s, 1H); 7.84 (s, 1H); 8.11 (dd, 1H); 8.66 (s, 1H); 10.44 (s, 1H); 12.00 (dd, 1H).

Ejemplo 281. Preparación oí Compuesto 458 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con 1,2-diamino-2-metilpropano (291 mg, 3.3 mmol) produjo el compuesto 158 en Tabla 17 (21 mg, 17 %).

MS ES^+: 570 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.39 (s, 1H); 2.28 (m, 2H); 3.23 (m, 4H); 3.98 (s, 3H); 4.00 (s, 2H); 4.32 (m, 2H); 7.14 (ddd, 1H); 7.31 (s, 1H); 7.36 (t, 1H); 7.47 (ddd, 1H); 7.64 (s, 1H); 7.86 (t, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 282. Preparación de Compuesto 459 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con ciclohexilamina (327 mg, 3.3 mmol) produjo compuesto 159 en Tabla 17- 85 mg, 66 %).

MS ES^+: 581 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.13 (m, 1H); 1.26 (m, 4H); 1.62 (brd, 1H); 1.77 (m, 2H); 2.03 (m, 2H); 2.15 (m, 2H); 3.07 (m, 1H); 3.14 (t, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.29 (t, 2H); 7.13 (brd, 1H); 7.29 (s, 1H); 7.36 (t, 1H); 7.39 (s, 1H); 7.46 (dd, 1H); 8.16 (dd, 1H); 8.26 (brs, 1H); 8.69 (s, 1H); 10.45 (s, 1H).

Ejemplo 283. Preparación de Compuesto 460 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con N,N-dimetiletilendiamina (291 mg, 3.3 mmol) produjo el compuesto 160 en Tabla 17 (41 mg, 32 %)

MS ES$^+$: 570 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.00 (m, 1H); 2.17 (s, 6H); 2.38 (t, 2H); 2.72 (t, 2H); 2.81 (t, 2H); 3.91 (s, 2H); 3.98 (s, 3H); 4.24 (t, 2H); 7.14 (dd, 1H); 7.27 (s, 1H); 7.37 (t, 1H); 7.40 (s, 1H); 7.49 (dd, 1H); 7.86 (t, 1H); 8.13 (s, 1H); 8.69 (s, 1H); 10.50 (s, 1H).

Ejemplo 284. Preparación de Compuesto 461 en Tabla 11

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con N,N,N'-trimetiletilendiamina (337 mg, 3.3 mmol) produjo el compuesto 161 en Tabla 17 (11 mg, 8 %).

MS ES$^+$: 584 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.91 (m, 2H); 2.12 (s, 6H); 2.20 (s, 3H); 2.33 (m, 3H); 2.42 (m, 3H); 3.76 (s, 2H); 3.91 (s, 3H); 4.12 (t, 2H); 6.98 (s, 1H); 7.11 (dd, 1H); 7.16 (s, 4H); 7.35 (t, 1H); 7.52 (dd, 1H); 7.83 (s, 1H); 7.88 (t, 1H); 8.37 (s, 1H); 10.56 (s, 1H).

Ejemplo 285. Preparación de Compuesto 462 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con (R)-(-)-2-pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 162 en Tabla 17 (76 mg, 59 %).

MS ES$^+$: 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.77 (m, 1H); 1.89 (m, 1H); 2.02 (m, 1H); 2.4 (m, 1H); 2.29 (m, 2H); 3.21 (m, 2H); 3.62 (m, 4H); 3.76 (m, 1H); 3.98 (s, 3H); 3.99 (s, 2H); 4.29 (t, 2H); 7.13 (dd, 1H); 7.29 (s, 1H); 7.35 (t, 1H); 7.46 (dd, 1H); 7.63 (s, 1H); 7.85 (t, 1H); 7.90 (s, 1H); 9.08 (s, 1H).

Ejemplo 286. Preparación de Compuesto 463 en Tabla 11

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con (S)-(+)-2- pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 163 en Tabla 17 (72 mg, 56 %).

MS ES$^+$: 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.78 (m, 1H); 1.90 (m, 1H); 2.03 (m, 1H); 2.13

(m, 1H); 2.30 (m, 2H); 3.23 (m, 2H); 3.62 (m, 4H); 3.77 (m, 1H); 3.98 (s, 3H); 4.00 (s, 2H); 4.30 (t, 2H) 25 ; 7.14 (dd, 1H); 7.30 (s, 1H); 7.36 (t, 1H); 7.46 (dd, 1H); 7.64 (s, 1H); 7.85 (s, 1H); 7.90 (s, 1H); 9.09 (s, 1H).

Ejemplo 287. Preparación de Compuesto 464 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con 4-hidroxipiperidina 30 (334 mg, 3.3 mmol) produjo el compuesto 164 en Tabla 17 (63 mg, 49 %).

MS ES^+: 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.41 (m, 2H); 1.73 (m, 2H); 1.96 (m, 2H); 2.04 (m, 2H); 2.74 (m, 2H); 2.50 (m, 2H); 3.43 (s, 1H); 3.91 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.54 (d, 1H); 7.14 (d, 1H); 7.26 (s, 1H); 7.37 (t, 1H); 7.40 (s, 1H); 7.49 (d, 1H); 7.86 (t, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.46 (s, 1H).

Ejemplo 288. Preparación de Compuesto 465 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con 3-pirrolidinol (288 mg, 3.3 mmol) produjo el compuesto 165 en Tabla 17 (57 mg, 45 %).

MS ES^+: 569 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.56 (m, 1H); 1.99 (m, 4H); 2.36 (m, 1H); 2.56 (m, 4H); 2.74 (m, 1H); 3.91 (s, 2H); 3.98 (s, 3H); 4.21 (t, 2H); 4.70 (d, 1H); 7.14 (dd, 1H); 7.26 (s, 1H); 7.37 (t, 1H); 7.40 (s, 1H); 7.49 (dd, 1H); 7.86 (t, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.47 (s, 1H); 12.03 (brs, 1H).

Ejemplo 289. Preparación de Compuesto 466 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con 1-(2- aminoetil)pirrolidina (377 mg, 3.3 mmol) produjo el compuesto 166 en Tabla 17 (39 mg, 29 %).

MS ES^+: 596 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.91 (m,2H); 2.06 (m, 2H); 2.24 (m, 2H); 3.11 (m, 2H); 3.23 (t, 2H); 3.42 (m, 2H); 3.48 (m, 2H); 3.67 (m, 2H); 3.98 (s, 3H); 3.99 (s, 2H); 4.31 (t, 2H); 7.14 (d, 1H); 7.31 (s, 1H); 7.35 (t, 1H); 7.47

(d, 1H); 7.64 (s, 1H); 7.85 (t, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 290. Preparación de Compuesto 467 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con 4-hidroximetilpiperidina (380 mg, 3.3 mmol) produjo el compuesto 167 en Tabla 17 (64 mg, 49 %).

MS ES^+: 597 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H); 1.35 (m, 1H); 1.65 (brd, 2H); 1.88 (m, 2H); 1.97 (m, 2H); 2.47 (m, 2H); 2.90 (brd, 2H); 3.25 (t, 2H); 3.91 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.41 (t, 1H); 7.14 (d, 1H); 7.25 (s, 1H); 7.37 (t, 1H); 7.39 (s, 1H); 7.48 (s, 1H); 7.86 (s, 1H); 8.12 (brs, 1H); 8.68 (s, 1H); 10.46 (s, 1H); 12.03 (s, 1H).

Ejemplo 291. Preparación de Compuesto 468 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con 1-(2-hidroxietil)piperazina (430 mg, 3.3 mmol) produjo el compuesto 168 en Tabla 17 (63 mg, 47 %).

MS ES^+: 612 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H); 2.41 (m, 12H); 3.50 (q, 2H); 3.91 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.37 (t, 1H); 7.14 (dd, 1H); 7.25 (s, 1H); 7.37 (t, 1H); 7.39 (s, 1H); 7.48 (d, 1H); 7.86 (t, 1H); 8.12 (brs, 1H); 8.68 (s, 1H); 10.46 (s, 1H); 12.04 (s, 1H).

Ejemplo 292. Preparación de Compuesto 469 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con ciclopentilamina 281 mg, 3.3 mmol) produjo el compuesto 169 en Tabla 17 (77 mg, 61 %).

MS ES^+: 567 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.58 (m, 4H);1.73 (m, 2H); 2.00 (m, 2H); 2.17 (m, 2H); 3.12 (t, 2H); 3.56 (m, 1H); 3.92 (s, 3H); 3.99 (s, 3H); 4.31 (t, 2H); 7.15 (d, 1H); 7.31 (s, 1H); 7.37 (t, 1H); 7.41 (s, 1H); 7.48 (d, 1H); 7.86 (s, 1H); 8.16 (brs, 1H); 8.71 (s, 1H); 10.47 (s, 1H); 12.03 (brs, 1H).

Ejemplo 293. Preparación de Compuesto 470 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con 4-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 170 en Tabla 17 (78 mg, 58 %).

MS ES^+: 611 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.16 (m, 2H); 1.36 (m, 3H); 1.63 (d, 2H); 1.88 (t, 2H); 1.96 (m, 2H); 25 2.44 (t, 2H); 2.87 (d, 2H); 3.44 (m, 2H); 3.9 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.33 (t, 1H); 7.14 (d, 1H); 7.25 (s, 1H); 7.37 (t, 1H); 7.40 (s, 1H); 7.49 (d, 1H); 7.86 (t, 1H); 8.12 (brs, 1H); 8.68 (s, 1H); 10.46 (s, 1H); 12.04 (s, 1H).

Ejemplo 294. Preparación de Compuesto 471 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con 3-hidroxipiperidina (339 mg, 3.3 mmol) produjo el compuesto 171 en Tabla 17 (117 mg, 91 %).

MS ES^+: 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.07 (m, 1H); 1.41 (m, 1H); 1.62 (m, 1H); 1.70-1.90 (m, 3H); 1.95 (m, 2H); 2.46 (m, 2H); 2.67 (m, 1H); 2.83 (brd, 1H); 3.47 (m, 1H); 3.89 (s, 2H); 3.96 (s, 3H); 4.20 (t, 2H); 4.57 (d, 1H); 7.13 (ddd, 1H); 7.24 (s, 1H); 7.36 (t, 1H); 7.38 (s, 1H); 7.47 (d, 1H); 7.84 (t, 1H); 8.11 (brs, 1H); 8.67 (s, 1H); 10.46 (s, 1H); 12.00 (brs, 1H).

Ejemplo 295. Preparación de Compuesto 472 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con (S)-1-amino-2-propanol (248 mg, 3.3 mmol) produjo el compuesto 172 en Tabla 17 (55 mg, 45 %).

MS ES^+: 557 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H); 1.96 (m, 2H); 2.48 (m, 2H); 2.73 (t, 2H); 3.70 (m, 1H); 3.91 (s, 2H); 3.97 (s, 3H); 4.24 (t, 2H); 4.48 (brs, 1H); 7.14 (d, 1H); 7.27 (s, 1H); 7.37 (t, 1H); 7.39 (s, 1H); 7.49 (d, 1H); 7.86 (t, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.46 (s, 1H).

577

Ejemplo 296. Preparación de Compuesto 473 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con (R)-1-amino-2-propanol (248 mg, 3.3 mmol) produjo el compuesto 172 en Tabla 17 (84 mg, 68 %).

MS ES^+: 557 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.04 (d, 3H); 1.93 (m, 2H); 2.45 (m, 2H); 2.70 (t, 2H); 3.67 (m, 1H); 3.88 (5, 2H); 3.95 (s, 3H); 4.21 (t, 2H); 4.46 (brs, 1H); 7.12 (d, 1H); 7.24 (s, 1H); 7.35 (t, 1H); 7.37 (s, 1H); 7.47 (d, 1H); 7.84 (t, 1H); 8.09 (s, 1H); 8.65 (s, 1H); 10.45 (s, 1H).

Ejemplo 297. Preparación de Compuesto 474 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con tert-butil-1-piperazincarboxilato (615 mg, 3.3 mmol) y tratando la mezcla de la reacción cruda con ácido hidroclorhídrico 1,4 dioxano (4.0 M, 2 ml) produjo el compuesto 174 (3 HCl) en Tabla 17 (89 mg, 61 %.

(84 mg, 68 %).

MS ES^+: 568 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.34 (m, 2H); 3.25-3.68 (m, 10H); 3.99 (s, 3H); 4.01 (s, 2H); 4.33 (t, 2H); 7.14 (dd, 1H); 7.35 (5, 1H); 7.37 (t, 1H); 7.49 (d, 1H); 7.65 (s, 1H); 7.86 (t, 1H); 7.91 (s, 1H); 9.09 (s, 1H); 10.66 (s, 1H).

Ejemplo 298. Preparación de Compuesto 475 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con 2-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 175 en Tabla 17 (29 mg, 22

5 %).

MS ES^+: 611 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.30 (m, 2H); 1.48 (m, 4H); 1.60 (m ,2H); 1.76 (m, 1H); 1.93 (m, 2H); 2.26 (m, 1H); 2.48 (m, 1H); 2.79 (m, 2H); 3.46 (m, 2H); 3.89 (s, 2H); 3.96 (s, 3H); 4.18 (t, 2H); 4.40 (brs, 1H); 7.13 (d, 1H); 7.24 (s, 1H); 7.35 (t, 1H); 7.38 (s, 1H); 7.47 (d, 1H); 10 7.84 (s, 1H); 8.11 (brs, 1H);

8.67 (s, 1H); 10.44 (s, 1H).

Ejemplo 299. Preparación de Compuesto 476 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con 2-amino-2-metil-1-propanol (294 mg, 3.3 mmol) produjo el compuesto 176 en Tabla 17 (49 mg, 39 %).

MS ES^+: 571 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.25 (s, 6H); 2.22 (m, 2H); 3.10 (m, 2H); 3.46 (s, 2H); 3.99 (s, 3H); 4.00 (s, 2H); 4.32 (t, 2H); 7.15 (d, 1H); 7.30 (s, 1H); 7.37 (t, 1H); 7.47 (d, 1H); 7.65 (s, 1H); 7.86 (s, 1H); 7.91 (s, 1H); 9.09 (s, 4H); 10.56 (s, 1H).

Ejemplo 300. Preparación de Compuesto 477 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con 1-(2-dimetilaminoetilpiperazina (519 mg, 3.3 mmol) produjo el compuesto 177 en Tabla 17 (19 mg, 15 %).

MS ES^+: 639 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H); 2.13 *(s,* 6H); 2.30-2.52 (m, 14H); 3.89 (s, 2H); 3.95 (s, 3H); 4.18 (t, 2H); 7.13 (d, 1H); 7.23 (s, 1H); 7.35 (t, 1H); 7.38 (s, 1H); 7.84 (t, 1H); 8.10 (s, 1H); 8.67 (s, 1H); 10.45 (s, 1H).

Ejemplo 301. Preparación de Compuesto 478 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con una solución de dimetilamina en cloroformo (3,6M, 3 ml, 3.6 mmol) produjo el compuesto 178 en Tabla 17 (44 mg, 34 %).

MS ES^+: 527 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$): 1.95 (m, 2H); 2.17 (s, 6H); 2.41 (t,2H); 3.89 (s, 2H); 3.96 (s, 3H); 4.18 (t, 2H); 7.12 (d, 1H); 7.23 (s, 1H); 7.35 (t, 1H); 7.38 (s, 1H); 7.47 (d, 1H); 7.84 (t, 1H); 8.11 (s, 1H); 8.67 (s, 1H); 10.45 (s, 1H).

Ejemplo 302. Preparación de Compuesto 479 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con

aminometilciclopropano (234 mg, 3.3 mmol) produjo el compuesto 179 en Tabla 17 (88 mg, 65 %).

MS ES^+: 553 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 0.18 (m, 2H); 0.46 (m, 2H); 0.94 (m, 1H); 2.01 (m, 2H); 2.51 (d, 2H); 2.79 (t, 2H); 3.94 (s, 2H); 4.01 (s, 3H); 4.28 (t, 2H); 7.18 (d, 1H); 7.31 (s, 1H); 7.41 (t, 1H); 7.43 (s, 1H); 7.53 (d, 1H); 7.90 (s, 1H); 8.16 (s, 1H); 8.72 (s, 1H); 10.53 (s, 1H).

Ejemplo 303. Preparación de Compuesto 480 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con piperidina (344 mg, 4.0 mmol) produjo el compuesto 180 en Tabla 17 (52 mg, 40 %).

MS ES^+: 565 $(M+H)^+$.

^{1}HNMR ($DMSOd_6$, TFA): 1.43 (m, 1H); 1.69 (m, 3H); 1.87 (d, 2H); 2.30 (m, 2H); 2.96 (t, 2H); 3.27 (t, 2H); 3.55 (d, 2H); 3.99 (s, 3H); 4.00 (s, 2H); 4.31 (t, 2H); 7.15 (d, 1H); 7.31 (s, 1H); 7.37 (t, 1H); 7.47 (d, 1H); 7.65 (s, 1H); 7.86 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H); 10.56 (s, 1H).

Ejemplo 304. Preparación de Compuesto 481 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 130, pero comenzando con 1-(2-dimetilaminometil)piperazina (281 mg, 3.3 mmol) produjo el compuesto 181 en Tabla 17 (81 mg, 64 %).

MS ES^+: 641 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (m, 2H); 2.80-3.70 (m, 14H); 2.84 (s, 6H); 3.98 (s, 3H); 4.01 (s, 2H); 4.30 (brt, 1H); 6.90 (m, 1H); 7.32 (s, 2H); 7.35 (dd, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 305. Preparación de Compuesto 482 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con (S)-(+)-2-pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 182 en Tabla 17 (58 mg, 45 %).

MS ES^+: 585 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.79 (m, 1H); 1.90 (m, 1H); 2.02 (m, 1H); 2.13 (m, 1H); 2.30 (m, 2H); 3.33 (m, 2H); 3.62 (m, 4H); 3.77 (dd, 1H); 3.99 (s, 3H); 4.01 (s, 2H); 4.30 (brt, 2H); 6.91 (t, 1H); 7.30 (s, 1H); 7.35 (dd, 2H); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 306. Preparación de Compuesto 483 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con 4-hidroxipiperidina (334 mg, 3.3 mmol) produjo el compuesto 183 en Tabla 17 (28 mg, 22 %).

MS ES^+: 585 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H); 1.73 (m, 2H); 1.96 (m, 2H); 2.03 (m, 2H); 2.45 (m, 2H); 2.74 (m, 2H); 3.45 (m, 1H); 3.92 (s, 2H); 3.97 (s, 3H); 3.97 (t, 2H); 4.54 (d, 1H); 6.95 (m, 1H); 7.26 (s, 1H); 7.36 (dd, 2H); 7.40 (s, 1H); 8.14 (brs, 1H);8.68 (s, 1H); 10.65 (s, 1H); 12.04 (brs, 1H).

Ejemplo 307. Preparación de Compuesto 484 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con 3-pirrolidinol (288 20 mg, 3.3 mmol) produjo el compuesto 184 en Tabla 17 (30 mg, 23 %).

MS ES^+: 571 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.57 (m, 1H); 1.97 (m, 4H); 2.37 (m, 1H); 2.58 (m, 4H); 2.74 (m, 1H); 3.92 (s, 2H); 3.98 (s 3H); 4.22 (brt, 2H); 4.72 (brs, 1H); 6.95 (m, 1H); 7.26 (s, 1H); 7.36 (dd, 2H); 7.40 (s, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.65 (s, 1H); 12.04 (brs, 1H).

Ejemplo 308. Preparación de Compuesto 485 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con 1-(2-aminoetil)pirrolidina (377 mg, 3.3 mmol) produjo el compuesto 185 en Tabla 17 (25 mg, 19 %).

MS ES^+: 598 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.91 (m, 2H); 2.06 (m, 2H); 2.24 (m, 2H); 3.11 (m, 2H); 3.23 (t,2H); 3.41 (1m, 2H); 3.49 (m, 2H); 3.67 (m, 2H); 3.99 (s,

3H); 4.01 (s, 2H); 4.31 (t, 2H); 6.89 (t, 1H); 7.32 (s, 1H); 7.34 (d, 2H); 7.64 (s, 1H); 7.92 (s, 1H); 9.09 (s, 1H).

Ejemplo 309. Preparación de Compuesto 486 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con 4- hidroximetilpiperidina (380 mg, 3.3 mmol) produjo el compuesto 186 en Tabla 17 (62 mg, 47 %).

MS ES^+: 599 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H); 1.34 (m, 1H); 1.65 (d, 2H); 1.88 (t, 2H); 1.96 (m, 2H); 2.45 (t, 2H); 2.90 (d, 2H); 3.25 (t, 2H); 3.92 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.41 (t, 1H); 6.94 (m, 1H); 7.26 (s, 1H); 7.36 (dd, 2H); 7.40 (s, 1H); 8.13 (brs, 1H); 8.68 (s, 1H); 10.64 (s, 1H); 12.07 (brs, 1H).

Ejemplo 310. Preparación de Compuesto 487 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con 2-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 187 en Tabla 17 (61 mg, 45 %).

MS ES^+: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.47-1.90 (m, 7H); 2.09 (m, 1H); 2.27 (m, 2H); 3.08-3.70 (m, 7H); 3.99 (s, 3H); 4.00 (s, 2H); 4.30 (m, 2H); 6.84 (m, 1H); 7.29 (d, 1H); 7.34 (dd, 1H); 7.62 (s, 1H); 7.92 (s, 1H); 9.08 (s, 1H).

Ejemplo 311. Preparación de Compuesto 488 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con 1-(2- hidroxietil)piperazina (430 mg, 3.3 mmol) produjo el compuesto 188 en Tabla 17 (124 mg, 92 25 %).

MS ES^+: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.96 (m, 2H); 2.40 (m, 12H); 2.70 (m, 1H); 3.48 (m, 2H); 3.90 (s, 2H); 3.95 (s, 3H); 4.18 (t,2H); 4.35 (brt, 1H); 6.43 (m, 1H); 7.23 (s, 1H); 7.34 (dd, 2H); 7.38 (s, 1H); 8.10 (s, 1H); 8.66 (s, 1H); 10.63 (s, 1H).

Ejemplo 312. Preparación de Compuesto 489 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con 4-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 189 en Tabla 17 (54 mg, 40 %).

MS ES^+: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H); 1.36 (m, 3H); 1.63 (brd, 2H); 1.88 (m, 2H); 1.96 (m, 2H); 2.44 (m, 2H); 2.87 (brd, 2H); 3.44 (m, 2H); 3.92 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.33 (t, 1H); 6.95 (m, 1H); 7.26 (s, 1H); 7.36 (dd, 2H); 7.40 (s, 1H); 8.13 (brs, 1H); 8.68 (s, 1H); 10.64 (s, 1H); 12.04 (brs, 1H).

Ejemplo 313. Preparación de Compuesto 490 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con 3-hidroxipiperidina (334 mg, 3.3 mmol) produjo el compuesto en Tabla 17 (53 mg, 41 %).

MS ES^+: 559 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.09 (m, 1H); 1.43 (m, 1H); 1.64 (m, 1H); 1.79 (m, 2H); 1.87 (m, 1H); 1.96 (m, 2H); 2.47 (m, 2H); 2.69 (m, 2H); 2.85 (m, 2H); 3.49 (m, 1H); 3.92 (s, 2H); 3.98 (s, 3H); 4.21 (t, 2H); 4.60 (d, 1H); 6.95 (t, 1H); 7.26 (s, 1H); 7.36 (d, 2H); 7.40 (s, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.65 (s, 1H); 12.04 (brs, 1H).

Ejemplo 314. Preparación de Compuesto 491 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con N,N,N'-trimetiletilendiamina (337 mg, 3.3 mmol) produjo el compuesto 191 en Tabla 17 (54 mg, 42 %).

MS ES^+: 586 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.32 (m, 1H); 2.34 (m, 1H); 2.88 (s, 6H); 2.93 (s, 3H); 3.39 (m, 2H); 3.56 (m, 4H); 3.99 (s, 3H); 4.01 (s, 2H); 4.30 (t, 2H); 6.91 (m, 1H); 7.33 (s, 1H); 7.35 (dd, 2H); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 315. Preparación de Compuesto 492 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con piperidina (281 mg, 3.3 mmol) produjo el compuesto 192 en Tabla 17 (81 mg, 64 %).

MS ES^+: 569 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.38 (m, 2H); 1.50 (m, 4H); 2.34 (brs, 4H); 2.41 (t, 2H); 3.90 (s, 2H); 3.96 (s, 3H); 4.19 (t, 2H); 6.93 (t, 1H); 7.24 (s, 1H); 7.34 (d, 2H); 7.38 (s, 1H); 8.11 (brs, 1H); 8.67 (s, 1H); 10.63 (s, 1H); 11.98 (brs, 1H).

Ejemplo 316. Preparación de Compuesto 493 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con pirrolidina (235 mg, 3.3 mmol) produjo el compuesto 193 en Tabla 17 (66 mg, 54 %).

MS ES^+: 555 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): MS ES+: 555 (M+H)+

lHN1vfR (DMSO~, TFA): 1.90 (m, 2H); 2.06 (m, 2H); 2.28 (m, 2H); 3.09 (m,2H); 3.36 (m, 2H); 3.68 (m, 2H); 3.99 (s, 3H); 4.01 (s, 2H); 4.29 (t, 2H); 6.93 (m; 1H); 7.30 (s, 1H); 7.34 (dd, 2H); 7.65 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 317. Preparación de Compuesto 494 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con 2-amino-2-metil-1-propanol (294 mg, 3.3 mmol) produjo el compuesto 194 en Tabla 17 (28 mg, 22 Ola).

MS ES^+: 573 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.24 (s, 6H); 2.23 (m, 2H); 3.10 (t, 2H); 3.45 (s, 2H); 3.99 (s, 3H); 4.01 (s, 2H); 4.31 (t, 2H); 6.91 (m, 1H); 7.30 (s, 1H); 7.34 (dd, 2H); 7.64 (s, 1R); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 318. Preparación de Compuesto 495 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con

2- metilaminoetanol (248 mg. 3.3 mmol) produjo el compuesto 195 en Tabla 17 (33 mg. 27 %).

MS ES^+: 559 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$): 1.95 (m. 2H); 2.24 (s, 3H); 2.48 (m, 2H); 2.45 (m, 2H); 3.49 (m, 2H); 3.93 (s, 2H); 3.98 (s, 3H); 4.21 (t, 2H); 4.38 (m, 1H); 6.95 (m, 1H); 7.27 (s, 1H); 7.36 (dd. 2H); 7.40 (s, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.65 (s, 1H); 12.04 (brs, 1H).

Ejemplo 319. Preparación de Compuesto 496 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con N,N- dimetiletilendiamina (291 mg, 3.3 mmol) produjo el compuesto 196 en Tabla 17 (22 mg, 17

5 %).

MS ES^+: 572 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.23 (m, 2H); 2.89 (s, 6H); 3.22 (m, 2H); 3.41 (s, 4H); 3.96 (s, 3H); 4.01 (s, 2H); 4.31 (t, 2H); 6.92 (m, 1H); 7.31 (s, 1H); 7.35 (dd, 2H); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 320. Preparación de Compuesto 497 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con (S(-(+)-1-amino-2-propanol (248 mg, 3.3 mmol) produjo el compuesto 197 en Tabla 17 (32 Mg, 26 %).

MS ES^+: 559 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.15 (d, 3H); 2.24 (m, 2H); 2.83 (dd, 1H); 3.06 (dd, 1H); 3.15 (t, 2H); 3.95 (m, 1H); 3.99 (s, 3H); 4.01 (s, 3H); 4.29 (t, 1H); 6.92 (m, 1H); 7.28 (s, 1H); 7.34 (dd, 2H); 7.65 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 321. Preparación de Compuesto 498 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con (R)-(-)-1-amino-2-propanol (248 mg, 3.3 mmol) produjo el compuesto 198 en Tabla 17 (40 mg, 32 %).

MS ES$^+$: 559 $(M_+H)^+$

^{1}HNMR (DMSOd_6,TFA): 1.15 (d, 3H); 2.24 (m, 2H); 2.83 (dd, 1H); 3.06 (dd, 1H); 3.15 (t, 2H); 3.95 (m, 1H); 3.99 (s, 3H); 4.01 (s, 3H); 4.29 (t, 1H); 6.90 (m, 1H); 7.28 (s, 1H); 7.34 (dd, 2H); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 322. Preparación de Compuesto 499 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con tert-butil-1-piperazina carboxilato (615 mg, 3.3 mmol) y tratando la mezcla de la reacción cruda con ácido hidroclorhídrico en 1,4-dioxano (4M, 2 ml) produjo el compuesto 199 en Tabla 17 (66 mg, 45 %, 3 HCl).

MS ES$^+$: 570 $(M_+H)^+$

^{1}HNMR (DMSOd_6,TFA): 2.35 (m, 2H); 3.20-3.94 (m, 10H); 3.99 (s, 3H); 4.03 (s, 2H); 4.33 (t, 2H); 6.93 (m, 1H); 7.36 (s, 1H); 7.37 (dd, 2H); 7.65 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 323. Preparación de Compuesto 500 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con 5 N-alilpiperazina (416 mg, 3.3 mmol) produjo el compuesto 200 en Tabla 17 (33 mg, 25 %).

MS ES$^+$: 610 $(M_+H)^+$

^{1}HNMR (DMSOd_6): 1.96 (m, 2H); 2.30-2.50 (m, 10H); 2.93 (d, 2H); 3.92 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 5.12 (d, 1H); 5.18 (d, 1H); 5.82 (m, 1H); 6.95 (m, 1H); 7.25 (s, 1H); 7.35 (dd, 2H); 7.40 (s, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.64 (s, 1H); 11.99 (brs, 1H).

Ejemplo 324. Preparación de Compuesto 501 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con (R)-(-)-2-pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 201 en Tabla 17 (51 mg, 40 %).

MS ES$^+$: 585 $(M_+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.57 (m, 1H); 1.67 (m, 2H); 1.82 (m, 1H); 1.96

(m, 2H); 2.18 (q, 1H); 2.45 (m, 3H); 2.98 (m, 1H); 3.10 (m, 1H); 3.20 (m, 1H); 3.92 (s, 2H); 3.98 (s, 3H); 4.22 (t, 2H); 4.35 (brs, 1H); 6.95 (m, 1H); 7.27 (s, 1H); 7.36 (dd, 2H); 7.40 (s, 1H); 8.13 (s, 1H); 8.68 (s, 1H); 10.66 (s, 1H); 12.00 (brs, 1H).

Ejemplo 325. Preparación de Compuesto 502 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 132, pero comenzando con ciclopentilamina (281 mg, 3.3 mmol) produjo el compuesto 202 en Tabla 17 (28 mg, 22 %).

MS ES^+: 569 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.31 (m,2H); 1.47 (m,2H); 1.62 (m, 2H); 1.73 (m, 2H); 1.93 (m, 2H); 2.70 (t, 2H); 3.03 (m, 1H); 3.92 (s, 2H); 3.97 (s, 3H); 4.23 (t, 2H); 6.94 (m, 1H); 7.26 (s, 1H); 7.36 (dd, 2H); 7.39 (s, 1H); 8.11 (s, 1H); 8.67 (s, 1H); 10.66 (s, 1H).

Ejemplo 326. Preparación de Compuesto 503 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con 2- metilaminoetanol (248 mg, 3.3 mmol) produjo el compuesto 203 en Tabla 17 (31 mg, 24 %).

MS ES^+: 575 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.31 (m, 2H); 2.88 (s, 3H); 3.16-3.45 (m, 4H); 3.77 (t, 2H); 3.99 (s, 5H); 4.29 (t, 2H); 7.30 (s, 1H); 7.38 (t, 1H); 7.50 (m, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 7.97 (dd, 1H); 9.09 (s, 1H).

Ejemplo 327. Preparación de Compuesto 504 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con N,N,N'-trimetiletilendiamina (337 mg, 3.3 mmol) produjo el compuesto 204 en Tabla 17 (28 mg, 21 %).

MS ES^+: 602 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.32 (m, 2H); 2.89 (s, 6H); 2.93 (s, 3H); 3.38 (m,2H); 3.56 (brs, 4H); 3.99 (s, 5H); 4.30 (t, 2H); 7.35 (s, 1H); 7.39 (*l*, 1H); 7.50 (m, 1H); 7.65 (s, 1H); 7.91 (s, 1H); 7.97 (dd, 1H); 9.09 (s, 1H).

Ejemplo 328. Preparación de Compuesto 505 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con N-alilpiperazina (416 mg, 3.3 mmol) produjo el compuesto 205 en Tabla 17 (42 mg, 30 %).

MS ES^+: 626 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.33 (m, 2H); 3.20-3.80 (m, 10H); 3.91 (d, 2H); 3.99 (s, 5H); 20 4.32 (t, 2H); 5.60 (m, 2H); 5.94 (m, 1H); 7.33 (s, 1H); 7.39 (t, 1H); 7.50 (m, 1H); 7.65 (s, 1H); 7.91 (s, 1H); 7.97 (dd, 1H); 9.09 (s, 1H).

Ejemplo 329. Preparación de Compuesto 506 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con 4-hidroxipiperidina 25 (334 mg, 3.3 mmol) produjo el compuesto 206 en Tabla 17 (32 mg, 25 %).

MS ES^+: 601 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$): 1.41 (m, 2H); 1.73 (m, 2H); 1.96 (m, 2H); 2.03 (m, 2H); 2.45 (m, 2H); 2.74 (m, 2H); 3.46 (m, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4.21 (t, 2H); 4.55 (brs, 1H); 7.26 (s, 1H); 7.40 (s, 1H); 7.41 (t, 1H); 7.51 (m, 1H); 7.97 (dd, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.49 (s, 1H); 12.03 (brs, 1H).

Ejemplo 330. Preparación de Compuesto 507 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con 3-pirrolidinol (288 mg, 3.3 mmol) produjo el compuesto 207 en Tabla 17 (24 mg, 19 %).

MS ES^+: 587 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$): 1.57 (m, 1H); 1.98 (m, 3H); 2.30-2.81 (m, 6H); 3.38 (m, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4.22 (t, 2H); 4.74 (brs, 1H); 7.27 (s, 1H); 7.39 (s, 1H); 7.40 (t, 1H); 7.50 (m, 1H); 7.96 (dd, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.49 (s, 1H); 12.05 (brs, 1H).

588

Ejemplo 331. Preparación de Compuesto 508 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con 1-(2-aminoetil)pirrolidina (377 mg, 3.3 mmol) produjo el compuesto 208 en Tabla 17 (18 mg, 13 %).

MS ES^+: 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.91 (m, 2H); 2.06 (m, 2H); 2.23 (m, 2H); 3.11 (m, 2H); 3.22 (t, 2H); 3.41 (m, 2H); 3.47 (m, 2H); 3.67 (m, 2H); 3.98 (s, 5H); 4.30 (t, 2H); 7.30 (s, 1H); 7.36 (t, 1H); 7.49 (m, 1H); 7.63 (s, 1H); 7.91 (s, 1H). 7.95 (dd, 1H); 9.09 (s, 1H).

Ejemplo 332. Preparación de Compuesto 509 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con N-acetilpiperazina (423 mg, 3.3 mmol) produjo el compuesto 209 en Tabla 17 (113 mg, 82 %).

MS ES^+: 628 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.98 (m, 2H); 2.00 (s, 3H); 2.36 (t, 2H); 2.42 (t, 2H); 2.92 (t, 0.5H); 2.99 (t, 0.5H); 3.45 (m, 4H); 3.55 (t, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4:23 (t, 2H); 7.27 (s, 1H); 7.40 (s, 1H); 7.41 (t, 1H); 7.52 (m, 1H); 7.97 (dd, 1H); 8.13 (s, 1H); 8.69 (s, 1H); 10.51 (s, 1H).

Ejemplo 333. Preparación de Compuesto 510 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con 2-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 210 en Tabla 17 (34 mg, 24 %).

MS ES^+: 629 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.48-1.90 (m, 7H); 2.08 (m, 1H); 2.27 (m, 2H); 3.09-3.69 (m, 7H); 3.99 (s, 5H); 4.30 (m, 2H); 7.30 (d, 1H); 7.38 (t, 1H); 7.50 (m, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 7.97 (dd, 1H); 9.09 (s, 1H).

Ejemplo 334. Preparación de Compuesto 511 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con

2-(2-hidroxietil)piperazina (430 mg, 3.3 mmol) produjo el compuesto 211 en Tabla 17 (80 mg, 58 %).

MS ES^+: 630 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H); 2;42 (m, 12H); 3.49 (dd, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.37 (t, 1H); 7.25 (s, 1H); 7.39 (s, 1H); 7.40 (t, 1H); 7.51 (m, 1H); 7.97 (dd, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.42 (s, 1H); 12.02 (brs, 1H).

Ejemplo 335. Preparación de Compuesto 512 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con ciclopentilamina (281 mg, 3.3 mmol) produjo el compuesto 212 en Tabla 17 (12 mg, 9 %).

MS ES^+: 585 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.59 (m, 4H); 1.73 (m, 2H); 2.00 (m, 2H); 2.21 (m, 2H); 3.13 (t, 2H); 3.56 (m, 1H); 3.99 (s, 5H); 4.31 (t, 2H); 7.29 (s, 1H); 7.37 (t, 1H); 7.49 (m, 1H); 7.64 (s, 1H); 7.92 (s, 1H); 7.96 (dd, 1H); 9.09 (s, 1H).

Ejemplo 336. Preparación de Compuesto 513 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con 4-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 213 en Tabla 17 (54 mg, 39 %).

MS ES^+: 629 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H); 1.36 (m, 3H); 1.63 (d, 2H); 1.88 (t, 2H); 1.96 (m, 2H); 2.44 (t, 2H); 2.87 (d, 2H); 3.44 (m, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2HJ); 4.33 (t, 1H); 7.25 (s, 1H); 7.40 (s, 1H); 7.41 (t, 1H); 7.51 (m, 1H); 7.97 (dd, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.48 (s, 1H); 12.03 (brs, 1H).

Ejemplo 337. Preparación de Compuesto 514 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con 3-hidroxipiperidina (334 mg, 3.3 mmol) produjo el compuesto 214 en Tabla

17 (96 mg, 73 %).

MS ES^+: 601 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.09 (m, 1H); 1.43 (m, 1H); 1.63 (m, 1H); 1.78 (m, 2H); 1.87 (m, 1H); 1.96 (m,2H); 2.47 (m, 2H); 2.68 (m, 1H); 2.84 (brd, 1H); 3.50 (m, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4.20 (t, 2H); 4.59 (d, 1H); 7.26 (s, 1H); 7.40 (s, 1H); 7.41 (t, 1H); 7.51 (m, 1H); 7.97 (dd, 1H); 8.13 (brs, 1H); 8.68 (s, 1H); 10.48 (s, 1H); 12.03 (brs, 1H).

Ejemplo 338. Preparación de Compuesto 515 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con 4-hidroximetilpiperidina (380 mg, 3.3 mmol) produjo el compuesto 214 en Tabla 17 (18 mg, 13 %).

MS ES^+: 615 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H); 1.35 (m, 1H); 1.65 (d, 2H); 1.88 (m, 2H); 1.97 (m, 2H); 2.46 (m, 2H); 2.91 (m, 2H); 3.25 (t, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.21 (t, 2H); 4.41 (t, 1H); 7.26 (s, 1H); 7.40 (s, 1H); 7.41 (t, 1H); 7.50 (m, 1H); 7.97 (dd, 1H); 8.13 (brs, 1H); 8.68 (s, 1H); 10.49 (s, 1H); 12.03 (brs, 1H).

Ejemplo 339. Preparación de Compuesto 516 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con 1-amino-2-propanol (248 mg, 3.3 mmol) produjo el compuesto 216 en Tabla 17 (14mg, 11 %).

MS ES^+: 575 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H); 1.96 (m, 2H); 2.49 (m, 2H); 2.74 (t, 2H); 3.71 (m, 2H); 3.90 (s, 2H); 3.98 (s, 3H); 4.24 (t, 2H); 4.50 (brs, 1H); 7.27 (s, 1H); 7.39 (s, 1H); 7.41 (t, 1H); 7.51 (m, 1H); 7.97 (dd, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.49 (s, 1H).

Ejemplo 340. Preparación de Compuesto 517 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con tert-butil-1-piperazincarboxilato (615 mg, 3.3 mmol) y tratando la mezcla

de la reacción cruda con ácido clorhídrico en 1,4-dioxano (4.M, 2 ml) produjo el compuesto 217 en Tabla 17 (61 mg, 47 %).

MS ES^+: 586 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.31 (m, 2H); 3.00-3.95 (m, 10 H); 3.99 (s, 5H); 4.31 (t, 2H); 7.32 (s, 1H); 7.39 (t, 1H); 7.50 (m, 1H); 7.65 (s, 1H); 7.91 (s, 1H); 7.97 (dd, 1H); 9.10 (s, 1H).

Ejemplo 341. Preparación de Compuesto 518 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 133, pero comenzando con 1-(2-morfolinoetil)piperazina (519 mg, 3.3 mmol) produjo el compuesto 218 en Tabla 17 (69 mg, 48 %).

MS ES^+: 699 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.31 (m, 2H); 2.98 (m, 2H); 3.10-37.5 (m, 16H); 3.86 (m, 4H); 3.99 (s, 5H); 4.31 (t, 2H); 7.33 (s, 1H); 7.39 (t, 1H); 7.50 (m, 1H); 7.65 (s, 1H); 7.92 (s, 1H); 7.97 (dd, 1H); 9.10 (s, 1H).

Ejemplo 342. Preparación de Compuesto 519 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 131, pero comenzando con pirrolidina (235 mg, 3.3 mmol) produjo el compuesto 219 en Tabla 17 (55 mg, 44 %).

MS ES^+: 571 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.90 (m, 2H); 2.06 (m, 2H); 2.27 (m, 2H); 3.09 (m, 2H); 3.36 (t, 2H); 3.66 (m, 2H); 3.98 (s, 5H); 4.29 (t, 2H); 7.29 (s, 1H); 7.39 (t, 1H); 7.50 (m, 1H); 7.64 (s, 1H); 7.90 (s,1H); 7.96 (dd, 1H); 9.09 (s, 1H).

Ejemplo 343. Preparación de Compuesto 520 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con 2- metilaminoetanol (248 mg, 3.3 mmol) produjo el compuesto 220 en Tabla 17 (34 mg, 29 %).

MS ES^+: 541 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.30 (m, 2H); 3.57 (s, 3H); 3.16-3.45 (m, 4H);

3.75 (t, 2H); 3.98 (s, 3H); 3.99 (s, 2H); 4.29 (t, 2H); 6.89 (t, 1H); 7.29 (s, 1H); 7.30-7.40 (m, 2H); 7.62 (d, 1H); 7.63 (s, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 344. Preparación de Compuesto 521 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con 1,2-diamino-2-metilpropano (291 mg, 3.3 mmol) produjo el compuesto 221 en Tabla 17 (10 mg, 8 %).

MS ES^+: 554 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.39 (s, 6H); 2.27 (m, 2H); 3.22 (m, 4H); 3.97 (s, 3H); 3.98 (s, 2H); 4.32 (t, 2H); 6.89 (m, 1H); 7.29-7.39 (m, 3H); 7.62 (d, 1H); 7.63 (s, 1H); 7.92 (s, 1H); 9.08 (s, 1H).

Ejemplo 345. Preparación de Compuesto 522 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con N,N-dimetiletilendiamina (291 mg, 3.3 mmol) produjo el compuesto 222 en Tabla 17 (26 mg, 22 %).

MS ES^+: 554 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.95 (m, 2H); 2.15 (s, 6H); 2.33 (t, 2H); 2.63 (t, 2H); 2.73 (t, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.23 (t,2H); 6.91 (m, 1H); 7.26 (s, 1H); 7.31-7.42 (m, 2H); 7.39 (s, 1H); 7.64 (d, 1H); 8.11 (s, 1H); 8.68 (s, 1H); 10.48 (s, 1H).

Ejemplo 346. Preparación de Compuesto 523 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con N,N,N'-trimetiletilendiamina (337 mg, 3.3 mmol) produjo el compuesto 223 en Tabla 17 (37 mg, 30 %).

MS ES^+: 568 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.34 (m, 2H); 2.88 (s, 6H); 2.93 (s, 3H); 3.38 (m, 2H); 3.55 (m, 4H); 3.98 (s, 3H); 3.99 (s, 2H); 4.29 (t, 2H); 6.89 (m, 1H); 7.29-7.41 (m, 2H); 7.33 (s, 1H); 7.63 (d, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 347. Preparación de Compuesto 524 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con N-alilpiperazina (416 mg, 3.3 mmol) produjo el compuesto 224 en Tabla 17 (77 mg, 59 %).

MS ES^+: 592 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.34 (m, 2H); 3.00-3.08 (m, 8H); 2.86 (d, 2H); 3.92 (m, 2H); 3.98 (s, 3H); 3.99 (s, 2H); 4.31 (t, 2H); 5.53-5.66 (m, 2H); 5.60-5.87 (m, 1H); 6.89 (m, 1H); 7.31-7.40 (m, 3H); 7.62 (d, 1H); 7.63 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 348. Preparación de Compuesto 525 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con 4-hidroxiplperidina (334 mg, 3.3 mmol) produjo el compuesto 225 en Tabla 17 (21 mg, 17 %).

MS ES^+: 567 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.59 (m, 1H); 1.85 (m, 2H); 2.01 (d, 1H); 2.28 (m, 2H); 3.03 (t, 1H); 3.21 (m, 1H); 3.28 (m,2H); 3.40 (m, 1H); 3.57 (d, 1H); 3.68 (m, 1H); 3.98 (s, 3H); 3.99 (s, 2H); 4.28 (t, 2H) ,6.90 (t, 1H); 7.29 (s, 1H); 7.30-7.40 (m, 2H); 7.63 (d, 1H); 7.64 (s, 1H) , 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 349. Preparación de Compuesto 526 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con 3-pirrolidinol (288 mg, 3.3 mmol) produjo el compuesto 226 en Tabla 17 (18 mg, 15 %).

MS ES^+: 553 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.84-2.03 (m, 2H); 2.27 (m, 2H); 3.02-3.79 (m, 6H); 3.99 (s, 3H); 4.00 (s, 2H); 4.29 (m, 2H); 4.41-4.51 (m, 1H); 6.91 (m, 1H); 7.28 (d, 1H); 7.31-7.41 (m, 2H); 7.63 (d, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 350. Preparación de Compuesto 527 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con 1-(aminoetil)pirrolidina (377 mg, 3.3 mmol) produjo el compuesto 227 en Tabla 17 (34 mg, 27 25 %).

MS ES^+: 580 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.68 (m, 4H); 1.97 (m, 2H); 2.47 (m, 6H); 2.70 (t, 2H); 2.77 (t, 2H); 3.91 (s, 2H); 3.97 (s, 3H); 4.24 (t, 2H); 6.91 (m, 1H); 7.27 (s, 1H); 7.30-7.42 (m, 2H); 7.39 (s, 1H); 7.64 (d,1H) , 8.12 (s, 1H); 8.68 (s, 1H); 10.49 (s, 1H).

Ejemplo 351. Preparación de Compuesto 528 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con N-acetilpiperazina (423 mg, 3.3 mmol) produjo el compuesto 228 en Tabla 17 (93 mg, 71 %).

MS ES^+: 594 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.99 (m,2H); 2.00 (s, 3H); 2.35 (t, 2H); 2.41 (t, 2H); 2.49 (m, 2H); 3.45 (m, 4H); 3.91 (s, 2H); 3.97 (s, 3H); 4.23 (t, 2H); 6.92 (m, 1H); 7.27 (s, 1H); 7.32-7.42 (m, 2H); 7.40 (s, 1H); 7.63 (d, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.48 (s, 1H).

Ejemplo 352. Preparación de Compuesto 529 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con 1-(2-hidroxietil)piperazina (430 mg, 3.3 mmol) produjo el compuesto 229 en Tabla 17 (91 mg, 69 %).

MS ES^+: 596 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H); 2.41 (m, 12H); 3.50 (q, 2H); 3.91 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.37 (t, 1H); 6.91 (t, 1H); 7.25 (s, 1H); 7.32-7.42 (m, 2H); 7.39 (s, 1H); 7.65 (d, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.48 (s, 1H); 12.04 (brs, 1H).

Ejemplo 353. Preparación de Compuesto 530 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con

ciclopentilamina (281 mg, 3.3 mmol) produjo el compuesto 230 en Tabla 17 (47 mg, 39 %).

MS ES^+: 551 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.39 (m, 2H); 1.50 (m, 2H); 1.65 (m, 2H); 1.80 (m, 2H); 2.00 (m, 2H); 2.80 (t, 2H); 3.16 (m, 1H); 3.91 (s, 2H); 3.98 (s, 3H); 4.25 (t, 2H); 6.98 (t, 1H); 7.28 (s, 1H); 7.31-7.42 (m, 2H); 7.40 (s, 1H); 7.64 (d, 1H); 8.13 (s, 1H); 8.69 (s, 1H); 10.49 (s, 1H).

Ejemplo 354. Preparación de Compuesto 531 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con 4-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 231 en Tabla 17 (65 mg, 50 %).

MS ES^+: 595 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H); 1.36 (m, 3H); 1.63 (d, 2H); 1.88 (m, 2H); 1.96 (m, 2H); 2.44 (m, 2H); 2.87 (d, 2H); 3.44 (m, 2H); 3.91 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.33 (t, 1H); 6.91 (t, 1H); 7.25 (s, 1H); 7.32-7.42 (m, 2H); 7.40 (s, 1H); 7.63 (d, 1H); 8.12 (brs, 1H); 8.68 (s, 1H); 10.48 (s, 1H); 12.03 (s, 1H).

Ejemplo 355. Preparación de Compuesto 532 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con 3-hidroxipiperidina (334 mg, 3.3 mmol) produjo el compuesto 232 en Tabla 17 (72 mg, 58 %).

MS ES^+: 567 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.09 (m, 1H); 1.43 (m, 1H); 1.63 (m, 1H); 1.78 (m, 2H); 1.87 (m, 1H); 1.96 (t, 2H); 2.47 (m, 2H); 2.69 (m, 1H); 2.85 (brd, 1H); 3.49 (m, 1H); 3.91 (s, 2H); 3.98 (s, 3H); 4.20 (t, 2H); 4.60 (d, 1H), 6.91 (t, 1H); 7.26 (s, 1H); 7.31-7.42 (m,2H); 7.40 (s, 1H); 7.64 (d, 1H); 8.13 (brs, 1H); 8.68 (s, 1H); 10.48 (s, 1H); 12.02 (brs, 1H).

Ejemplo 356. Preparación de Compuesto 533 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con

4-hidroximetilpiperidina (380 mg, 3.3 mmol) produjo el compuesto 233 en Tabla 17 (56 mg, 44 %).

MS ES^+: 581 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H); 1.34 (m, 1H); 1.65 (d, 2H); 1.88 (t, 2H); 1.97 (m, 2H); 2.45 (t, 2H); 2.90 (d, 2H); 3.25 (t, 2H); 3.91 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.41 (t, 1H); 6;93 (t, 1H); 7.25 (s, 1H); 7.32-7.42 (m, 2H); 7.40 (s, 1H); 7.63 (d, 1H); 8.12 (brs, 1H); 8.68 (s, 1H); 10.48 (s, 1H); 12.03 (brs, 1H).

Ejemplo 357. Preparación de Compuesto 534 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con 1-amino-2-propanol 25 (248 mg, 3.3 mmol) produjo el compuesto 234 en Tabla 17 (36 mg, 30 %).

MS ES^+: 541 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H); 1.95 (m, 2H); 2.48 (m, 2H); 2.72 (t, 2H); 3.69 (m, 1H); 3.90 (s, 2H); 3.97 (s, 3H); 4.23 (t, 2H); 4.47 (brs, 1H); 6.91 (t, 1H); 7.26 (s, 1H); 7.32-7.41 (m,2H); 7.39 (s, 1H); 7.63 (d, 1H); 8.11 (s, 1H); 8.67 (s, 1H); 10.48 (s, 1H).

Ejemplo 358. Preparación de Compuesto 535 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con (R)-(-)-2-pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 235 en Tabla 17 (66 mg, 53 %).

MS ES^+: 567 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.57 (m, 1H); 1.67 (m, 2H); 2.82 (m, 1H); 1.96 (m, 2H); 2.18 (m, 1H); 2.45 (m, 2H); 2.98 (m, 1H); 3.10 (m, 1H); 3.20 (m, 1H); 3.41 (m, 1H); 3.91 (s, 2H); 3.98 (s, 3H); 4.22 (t, 2H); 4.35 (brs, 1H); 6.91 (t, 1H); 7.26 (s, 1H); 7.31-7.42 (m, 2H); 7.39 (s, 1H); 7.64 (d, 1H); 8.13 (s, 1H); 8.68 (s, 1H); 10.48 (s, 1H); 12.01 (brs, 1H).

Ejemplo 359. Preparación de Compuesto 536 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con

(S)-(+)-2-pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 236 en Tabla 17 (59 mg, 48 %).

MS ES^+: 567 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.78 (m, 1H); 1.90 (m, 1H); 2.03 (m, 1H); 2.13 (m, 1H); 2.31 (m,2H); 3.23 (m, 2H); 3.61 (m, 4H); 3.77 (q, 1H); 3.98 (s, 3H); 3.99 (s, 2H); 4.29 (t, 2H); 6.89 (t, 1H); 7.29 (s, 1H); 7.30-7.40 (m, 2H); 7.63 (d, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 360. Preparación de Compuesto 537 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con t-butil-1-piperazinecarboxilato (615 mg, 3.3 mmol) y tratando la mezcla de reacción cruda con ácido clorhídrico en 1,4-dioxano (4M, 2 ml) produjo el compuesto 237 en Tabla 17 (35 mg, 27 %).

MS ES^+: 552 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H); 2.33 (brs, 4H); 2.42 (t, 2H); 2.73 (t, 4H); 3.89 (s, 2H); 3.95 (s, 3H); 4.19 (t, 2H); 6.89 (t, 1H); 7.24 (s, 1H); 7.32-7.42 (m, 2H); 7.37 (s, 1H); 7.62 (d, 1H); 8.10 (s, 1H); 8.66 (s, 1H); 10.47 (s, 1H).

Ejemplo 361. Preparación de Compuesto 538 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con 1-(2-morfolinoetil)piperazina (519 mg, 3.3 mmol) produjo el compuesto 238 en Tabla 17 (50 mg, 37%).

MS ES^+: 665 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (m, 2H); 2.99 (t, 2H); 3.05-3.75 (m, 16H); 3.86 (brs, 4H); 3.99 (s, 3H); 4.00 (s, 2H); 4.29 (t, 2H); 6.90 (t, 1H); 7.32 (s, 1H); 7.41-7.31 (m, 2H); 7.62 (d, 1H); 7.64 (s, 1H); 7.92 (s, 1H); 9.09 (s, 1H).

Ejemplo 362. Preparación de Compuesto 539 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 134, pero comenzando con 2-amino-2-metil-1-propanol (294 mg, 3.3 mmol) produjo el compuesto 239 en Tabla 17 (40 mg, 33 %).

MS ES^+: 555 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 0.96 (s, 6H); 1.91 (m, 2H); 2.67 (t, 2H); 3.19 (s, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.24 (t, 2H); 4.53 (brs, 1H); 6.91 (m, 1H); 7.26 (s, 1H); 7.36 (m, 2H); 7.38 (s, 1H); 7.63 (d, 1H); 8.11 (s, 1H); 8.67 (s, 1H); 10.48 (s, 1H).

Ejemplo 363. Preparación de Compuesto 540 en Tabla 18

4-((2-amino-1,3-tiazol-5-il)acético ácido)-6-metoxi-7-(3-morfolinopropoxi)quinazolina (125 mg, 0.27 mmol) en DMF (2.5 ml) se hizo reaccionar con N-etilanilina (84.3 µl, 0.707 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (136 mg, 0.37 mmol) y DIEA (95 µl, 0.54 mmol) a 50°C durante 18 horas. La mezcla de la reacción se enfrió, se agregaron bicarbonato de sodio (sat., 1 ml) [y] 3 g de alúmina, la mezcla se evaporó a sequedad, y el residuo se purificó por cromatografía sobre alúmina, eluyente CH_2Cl_2, CH_2Cl_2/MeOH 99/1 a 95/5 para producir el compuesto del título (68 mg, 44 %).

MS ES^+: 563.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.05 (t, 3H); 2..31 (t, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.65 (m, 6H); 3.97 (s, 3H); 4.03 (d, 2H); 4.29 (t, 2H); 7.31 (s, 1H); 7.38 (s, 1H); 7.40 (m, 2H); 7.46 (m, 1H); 7.53 (m, 2H); 7.87 (s, 1H); 9.06 (s, 1H).

Ejemplo 364. Preparación de Compuesto 541 en Tabla 18

Una reacción análoga a la descrita en Ejemplo 240, pero comenzando con 3-cloro-4-fluoro-N-metilanilina (97 mg, 0.35 mmol) produjo el compuesto del título (98 mg, 60 %).

MS ES^+: 601.5, 603.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.31 (t, 2H); 3.15(t, 2H); 3.21 (s, 3H); 3.35 (t, 2H); 3.54 (d, 2H); 3.7 (m, 4H); 3.97 (s, 3H); 4.03 (d,2H); 4.29 (t, 2H); 7.31 (s, 1H); 7.41 (s, 1H); 7.50 (m, 2H); 7.80 (m, 1H); 7.87 (s, 1H); 9.06 (s, 1H).

N -(tert -butiloxicarbonil)- 3 -cloro-4- fluoroanilina.

3-cloro-4-fluoroanilina (2g, 13.7 mmol) en THF (12.5 ml) bajo argón, se

trató con NaHMDS (1 M, 27.5 ml, 27.5 mmol) a temperatura ambiente durante 15 minutos. Di-tert-butil dicarbonato en THF (10 ml) se agregó lentamente a la mezcla de la reacción, y la mezcla se agitó a temperatura ambiente durante 45 minutos. El solvente se evaporó, se diluyó HCl (0.1 N), y la mezcla se extrajo con acetato de etilo, se secó, se purificó por cromatografía de gel de sílice, éter/éter de petróleo 10-20/90-80 para producir el compuesto del título (2.77 g, 82 %).

^{1}HNMR ($CDCl_3$): 1.49 (s, 9H); 6.42 (s, 1H); 7.01 (t, 1H); 7.01 (m, 1H); 7.54 (m, 1H).

3 -cloro-4- fluoro-N –metilanilina.

A una solución de N-(tert-butiloxicarbonil)-3-cloro-4-fluoroanilina (250 mg, 1.02 mmol) en THF (4 ml) a O°C se agregó hidruro de sodio (60 %, 45 mg, 1.12 mmol), y la mezcla se agitó durante 20 minutos. Yoduro de metilo (70 µl, 1.12 mmol) se adicionó a la mezcla que se agitó a temperatura ambiente durante 4 horas. El solvente se evaporó, se adicionó una solución saturada de cloruro de sodio, y la mezcla se extrajo con CH_2Cl_2, se secó, y se purificó por cromatografía de gel de sílice, éter / éter de petróleo, 8/2 para producir un compuesto (235 mg). Este compuesto se disolvió en CH_2Cl_2 (2 ml) y TFA (2 ml), se añadió H_2O (200 µl), la mezcla se agitó durante 1 hora a temperatura ambiente, el solvente se evaporó, para producir el compuesto del título (256 mg, 89 %).

^{1}HNMR ($CDCl_3$): 2.98 (s, 3H); 7.3 (m, 3H).

Ejemplo 365. Preparación de Compuesto 542 en Tabla 18

Una reacción análoga a la descrita en Ejemplo 240, pero comenzando con etil-2-(3-cloro-4-fluoroanilin)acetato (151 mg, 0.65 mmol) produjo el compuesto del título (10 mg, 4.5 %).

MS ES$^+$: 673.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.18 (t, 3H); 2.30 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.83 (s, 1H); 3.97 (s, 3H); 4.03 (m, 4H); 4.13 (s, 2H); 4.29 (t, 2H); 4.41 (s, 1H); 7.30 (s, 1H); 7.44 (s, 1H); 7.55 (m, 2H); 7.78 (m, 1H); 7.87 (s, 1H); 9.06 (s, 1H).

Ejemplo 366. Preparación de Compuesto 543 en Tabla 18

Una reacción análoga a la descrita en Ejemplo 240, pero comenzando con 2-anilinoacetonitrilo (371 mg, 2.72 mmol) produjo el compuesto del título (110 mg, 18 %).

MS ES^+: 574.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.77 (s, 1H); 3.97 (s, 3H); 4.04 (d, 2H); 4.30 (t, 2H); 4.81 (s, 2H); 7.31 (s, 1H); 7.43 (s, 1H); 7.57 (m, 5H); 7.88 (s, 1H); 9.09 (s, 1H).

Ejemplo 367. Preparación de Compuesto 544 en Tabla 18

Una reacción análoga a la descrita en Ejemplo 240, pero comenzando con 3-anilinoacetonitrilo (335 mg, 2.18 mmol) produjo el compuesto del título (100 mg, 18 %).

MS ES^+: 588.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.29 (t, 2H); 2.75 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (m, 4H); 3.95 (t, 2H); 3.97 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 7.29 (s, 1H); 7.42 (s, 1H); 7,48 (m, 3H); 7.55 (m, 2H); 7.87 (s, 1H); 9.08 (s, 1H).

Ejemplo 368. Preparación de Compuesto 545 en Tabla 18

Una reacción análoga a la descrita en Ejemplo 240, pero comenzando con N-(2-tert-butiletil)-3-cloro-4-fluoroanilina (346 mg, 1.42 mmol) produjo el compuesto del título (147 mg, 30 %),

MS ES^+: 687.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.08 (s, 9H); 2.31 (t, 2H); 3.14 (t, 2H); 4.3-4.5 (m, 4H); 3.55 (d, 2H); 3.68 (m, 6H); 3.97 (s, 3H); 4.03 (d, 2H); 4.29 (t, 2H); 7.30 (s, 1H); 7.41 (s, 1H); 7.51 (m, 2H); 7.78 (m, 1H); 7.87 (s, 1H); 9.06 (s, 1H).

N -(2- hidroxietil)-3-cloro-4- fluoroanilina.

etil-2-(3-cloro-4-fluoroanilin)acetato (J. Med. Chem. 1965, 405-407) (2 g, 8.6 mmol) en THF (15 ml) éter (10 ml) se trató con Li Al H4 (460 mg, 12.1

mmol) a 40°C durante 4 horas. A continuación la mezcla se vertió en hielo, se trató con NaOH (2N, 10 ml),se extrajo con acetato de etilo, se secó, se evaporó para producir el compuesto del título (1.48 g, 90 %).

^{1}HNMR ($CDCl_3$): 1.67 (s, 1H); 3.24 (t, 2H); 3.84 (t, 2H); 3.92 (s, 1H); 6.47 (m, 1H); 6.64 (m, 1H); 6.95 (t, 1H).

N -(2-tert-butoxietil)- 3-chloro-4- fluoroanilina.

N-2-hidroxietil-3-chloro-4-fluoroanilina (1.48 g, 7.81 mmol) en CH_2Cl_2 (20 ml) se hizo reaccionar con N,N-diisopropil O-tert-butil-isourea (6.25 g, 31.2 mmol) a temperatura ambiente de un día para otro. El producto se purificó por cromatografía de gel de sílice, eluyente, éter / éter de petróleo 5/95, 10/90 para producir el compuesto del título (1.15 g, 60 %).

^{1}HNMR (CDCL3): 1.20 (s, 9H); 3.18 (t, 2H); 3.55 (t, 2H); 4.00 (s, 1H); 6.44 (m, 1H); 6.62 (m, 1H); 6.93 (t, 1H).

Ejemplo 369. Preparación de Compuesto 546 en Tabla 18

Una reacción análoga a la descrita en Ejemplo 240, pero comenzando con N-alilanilina (0.3 ml, 2.18 mmol) produjo el compuesto del título (252 mg, 50 %). MS ES^+: 575.7 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.31 (t,2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (m, 4H); 3.97 (s, 3H); 4.03 (d, 2H); 4.28 (m,4H); 5.12 (m, 2H); 5.82 (m, 1H); 7.30 (s, 1H); 7.38 (m, 3H); 7.40 (s, 1H); 7.51 (m, 2H); 7.87 (s, 1H); 9.07 (s, 1H).

Ejemplo 370. Preparación de Compuesto 547 en Tabla 18

Una reacción análoga a la descrita en Ejemplo 240, pero comenzando con N-etil-3,4-(metilendioxi)anilina (320 ~1, 2.18 mmol) produjo el compuesto del título (351 mg, 66 %).

MS ES^+: 607.7 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.04 (t, 3H); 2.31 (t, 2H); 3.16 (t, 2H); 3.34 (t, 2H); 3.54 (d, 2H); 3.68 (m, 6H); 3.97 (s, 3H); 4.09 (d, 2H); 4.29 (t, 2H); 6.12 (s, 2H); 6.83 (d, 1H); 7.02 (m, 2H); 7.30 (s, 1H); 7.42 (s, 1H); 7.86 (s, 1H); 9.06 (s, 1H).

Ejemplo 371. Preparación de Compuesto 548 en Tabla 18

Una reacción análoga a la descrita en Ejemplo 240, pero comenzando con etil-4-(N-butilamino)benzoato (482 mg, 2.18 mmol) produjo el compuesto del título (58 mg, 10 %).

MS ES^+: 663.7 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 0.85 (t, 3H); 1.32 (m, 7H); 2.31 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.70 (m, 6H); 3.97 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 4.35 (s, 2H); 7.30 (s, 1H); 7.41 (s, 1H); 7.54 (d, 2H); 7.87 (s, 1H); 8.07 (d, 2H); 9.07 (s, 1H).

Ejemplo 372. Preparación de Compuesto 549 en Tabla 18

Una reacción análoga a la descrita en Ejemplo 240, pero comenzando con N-etil-m-toluidina (294 mg, 2.18 mmol) produjo el compuesto del título (294 mg, 2.18 %).

MS ES^+: 577.7 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.05 (t, 9H); 2.31 (t, 2H); 2.38 (s, 3H); 3.16 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.67 (m, 6H); 3.97 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 7.18 (m, 2H); 7.28 (d, 1H); 7.30 (s, 1H); 7.39 (s, 1H); 7.42 (d, 1H); 7.86 (s, 1H); 9.07 (s, 1H).

Ejemplo 373. Preparación de Compuesto 550 en Tabla 18

Compuesto 245 (120 mg) en CH_2Cl_2 (2 ml) se trató con TFA (3 ml) y H_2O (200 µl) a temperatura ambiente durante 3 horas. El solvente se evaporó para producir el compuesto del título(45 mg, 41%).

MS ES^+: 631.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.29 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.51 (t, 2H); 3.54 (d, 2H); 3.70 (m, 6H); 3.97 (s, 3H); 4.03 (d, 2H); 4.30 (t, 2H); 7.30 (s, 1H); 7.42 (s, 1H); 7.54 (m, 2H); 7.78 (d, 1H); 7.87 (s, 1H); 9.06 (s, 1H).

Ejemplo 374. Preparación de Compuesto 551 en Tabla 19

Ácido 4-((2-amino-4-metil-1,3-tiazol-5-il)acético)-6-metoxi-7-(3-morfolinopropoxi)quinazolina (118 mg, 0.25 mmol) en DMF (1.5 ml) se hizo reaccionar con anilina (32 mg, 0.35 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (142 mg, 0.375 mmol) y DIEA (65 mg, 0.5 mmol) a 65° de un día para otro. Se enfrió la mezcla, se agregó bicarbonato de sodio, y la mezcla resultante se evaporó. El residuo se disolvió en CH_2Cl_2 / MeOH 92/8 y se purificó por cromatografía de gel de sílice sobre alúmina, eluyente CH_2Cl_2, CH_2Cl_2 / MeOH 98/2 a 95/5, se realizó una segunda purificación sobre gel de sílice, eluyente CH_2Cl_2 / MeOH 95/5 a 90/10 para producir el compuesto del título (86 mg, 62 %).

MS ES^+: 549.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.31 (t, 2H); 2.34 (s, 3H); 3.15 (t, 2H); 3.34 (t, 2H); 3.54 (d, 30 2H); 3.72 (t, 2H); 3.90 (s, 2H); 3.98 (s, 3H); (4.03); (d, 2H); 4.30 (t, 2H); 7.08 (t, 2H); 7.29 (s, 1H); 7.31 (t, 2H); 7.62 (d, 2H); 7.85 (s, 1H); 9.05 (s, 1H).

4-(etil(2-amino-4-metil-1,3-tiazol-5-il)acetato)-6-metoxi-7-(3-morflinopropoxi)quinazolina.

N'-(2-ciano-4-metoxi-5-(3-morfolinopropoxi)fenil)-N,N-dimetilimidoformamida (1.38 g, 4 mmol) en ácido acético se hizo reaccionar con etil-2-amino-4-metil-l,3-tiazol-5-il)acetato a reflujo durante 3.5 horas. La mezcla se enfrió, se evaporó, se agregó HCl (1N) y la mezcla se extrajo con acetato de etilo. Se agregó cuidadosamente bicarbonato de sodio a la fase acuosa, la cual se extrajo con acetato de etilo. Las fracciones orgánicas se secaron, se evaporaron, el residuo se purificó por cromatografía sobre alúmina, eluyente CH_2Cl_2, CH_2Cl_2 / AcOEt 1/1, CH_2Cl_2 / AcOEt / MeOH 50/45/5 para producir el material inicial como un sólido amarillo (1.12 g, 52 %).

MS ES^+: 502.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.24 (t, 3H); 2.28 (m, 5H); 3.15 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3;92 (s, 2H); 3.98 (s, 3H); 4.04 (d, 2H); 4.15

(q, 2H); 4.30 (t, 2H); 7.30 (s, 1H); 7.86 (8, 1H); 9.05 (s, 1H).

Ácido 4-((2-amino-4-metil-1,3-tiazol-5-il)acético)-6-metoxi-7-(3-morfolinopropoxi)quinazolina.

4-(etil(2-amino-4-metil-1,3-tiazol-5-il)acetato)-6-metoxi-7-(3-morfolinopropoxi)quinazolina (1.1 g, 2.2 mmol) en etanol (11 ml) trató con NaOH (2N, 5.5 ml, 11 mmol) a temperatura ambiente durante 1 hora. La mezcla se acidificó luego con HCl (2N) a pH 3. Se evaporó la solución, el sólido se suspendió en CH_2Cl_2 (8 ml) MeOH (6 ml), y se adicionó DIEA (852 mg, 6.6 mmol). La mezcla se agitó durante 10 minutos, se filtró. El filtrado se concentró, se agregó etanol y el sólido se recuperó para producir el compuesto del título (980 mg, 94 %).

MS ES^+: 474.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.28 (m, 5H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.70 (t, 2H); 3.83 (s, 2H); 3.98 (s, 3H); 4.04 (d, 2H); 4.30. (t, 2H); 7.30 (s, 1H); 7.86 (s, 1H); 9.05 (s, 1H).

Ejemplo 375. Preparación de Compuesto 552 en Tabla 19

Una reacción análoga a la descrita en Ejemplo 251, pero comenzando con 3-cloro-4-fluoroanilina (51 mg, 0.35 mmol) produjo el compuesto del título (60 mg, 40 %).

MS ES^+: 601.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.30 (t, 2H); 2.33 (s, 3H); 3.16 (t, 2H); 3.36 (t, 2H); (3.55) (d, 2H); 3.69 (t, 2H); 3.90 (s, 2H); 3.98 (s, 3H); 4.04 (d, 2H); 4.30 (t, 2H); 7.28 (s, 1H); 7.39 (t, 1H); 7.49 (m, 1H); 7.86 (s, 1H); 7.96 (m, 1H); 9.05 (s, 1H).

Ejemplo 376. Preparación de Compuesto 553 en Tabla 19

Una reacción análoga a la descrita en Ejemplo 251, pero comenzando con 2-aminopiridina (33 mg, 0.35 mmol) produjo el compuesto del título (45 mg, 32 %).

MS ES^+: 550.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.31 (t, 2H); 2.35 (s, 3H); 3.16 (t, 2H); 3.36 (t,

2H); 3.55 (d, 10 2H); 3.69 (t, 2H); 3.98 (s, 3H); 4.04 (m, 4H); 4.30 (t, 2H); 7.30 (m, 2H); 7.87 (s, 1H); 7.95 (d, 1H); 8.05 (m, 1H); 8.40 (d, 1H); 9.04 (s, 1H).

Ejemplo 377. Preparación de Compuesto 554 en Tabla 19

Una reacción análoga a la descrita en Ejemplo 251, pero comenzando con 3,4 difluoroanilina 15 (50 mg, 0.39 mmol) produjo el compuesto del título (120 mg, 74 %).

MS ES^+: 585.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.30 (t, 2H); 2.33 (s, 3H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.67 (t, 2H); 3.90 (s, 2H); 3.98 (s, 3H); 4.05 (d, 2H); 4.31 (t, 2H); 7.28 (s, 1H); 7.32 (m, 1H); 7.40 (q, 1H); 7.80 (m, 1H); 7.86 (s, 1H); 9.05 (s, 1H).

Ejemplo 378. Preparación de Compuesto 555 en Tabla 20

N'-(2-ciano-5-((2S)-2-hidroxi-3-piperidinilpropoxi)-4-metoxifenil)-N,N-dimetilimidoformamida (381 mg, 0.96 mmol) en ácido acético (6 ml) se irradió en un horno microondas en presencia de N-(4-fluoro-3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (275 mg, 0.96 mmol) a reflujo durante 0.5 hora. El solvente se evaporó, y el residuo se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH sat. NH_3 95/5 a 93/7 para producir el compuesto del título (230 mg, 40 %).

MS ES^+: 601.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.42 (m, 1H); 1.6-1.9 (m, 5H); 3.02 (m, 2H); 3.28 (m, 2H); 3.52 30 (m,2H); 3.99 (s, 5H); 4.19 (d, 2H); 4.43 (m, 1H); 7.35 (s, 1H); 7.40 (t, 1H); 7.48 (m, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 7.95 (m, 1H); 9.08 (s, 1H).

N'-(2-ciano-5-((2S)-2-hidroxi-3-piperidinilpropoxi)-4-metoxifenil)-N,N,-dimetilimidoformamida.

N'-(2-ciano-5-(2S)-oxiranilmetoxi-4-metoxifenil)-N,N-dimetilimidoformamida (850 mg, 3.09 mmol) en cloroformo (6 ml) y etanol (12 ml) se irradió con piperidina (0.46 ml, 4.6 mmol) en un horno

microondas a reflujo durante 10 minutos. El solvente se evaporó y el residuo se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH 90/10 para producir el compuesto del título (954 mg, 86 %).

MS ES^+: 361.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.43 (m, 6H); 2.4 (m, 6H); 2.97 (s, 3H); 3.06 (s, 3H); 3.75 (s, 3H); 3.95 (d, 2H); 4.03 (m, 1H); 4.83 (s, 1H); 6.75 (s, 1H); 7.10 (s, 1H); 7.90 (s, 1H).

N'-(2-ciano-5-(2S)-oxiranilmetoxi-4-metoxifenil)-N,N-dimetilimidoformamida.

N'-(2-ciano-4-metoxi-5-hidroxifenil)-N,N-dimetil-imidoformamida (1 g, 4.57 mmol) en DMF (25 ml) se hizo reaccionar con (2S) glicidil toxilato (1.15 g, 5.02 mmol) en presencia de carbonato de cesio (5.95 g, 18.3 mmol) a 60°C bajo argón durante 2 horas. El solvente se evaporó, se agregó agua, y la mezcla se extrajo con acetato de etilo, se secó, se concentró y purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / AcOEt 80/20 a 70/30 para producir el compuesto del título (1.18 g, 94 %).

MS ES^+: 276.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.70 (m, 1H); 2.86 (m, 1H); 2.95 (s, 3H); 3.01 (s, 3H); 3.35 (m, 1H); 3.75 (s, 3H); 3.90 (m, 1H); 4.37 (m, 1H); 6.75 (s, 1H); 7.11 (s, 1H); 7.89 (s, 1H).

Metil-(2-tritilamino-1,3-tiazol-5-il)acetato.

Metil-(2-amino-1,3-tiazol-5-il)acetato (1 g, 5.8 mmol) en CH_2Cl_2 (15 ml) se hizo reaccionar con cloruro de trifenilmetilo (1.73 g, 6.2 mmol) y trietilamina (0.89 ml, 6.4 mmol) a O°C durante 1.5 hora. Se agregó agua a la mezcla la cual se extrajo con acetato de etilo, se secó, se purificó por cromatografía de gel de sílice para producir el compuesto del título (2.21 g, 91 %).

^{1}HNMR ($DMSOd_6$): 3.58 (s, 3H); 3.59 (s, 2H); 6.57 (s, 1H); 7.23 (m, 15H); 8.40 (s, 1H).

Ácido (2-tritilamino-1,3-tiazol-5-il)acético

Metil(2-tritilamino-1,3-tiazol-5-il)acetato (2 g, 4.8 mmol) en THF (10 ml) y etanol (10 ml) se hizo reaccionar con hidróxido de sodio (1N, 7.2 ml, 7.2

mmol) a temperatura ambiente durante 1.5 hora. El solvente se evaporó, se añadió HCl (6N), el sólido se recuperó por filtración para producir el compuesto del título (1.96 g).

^{1}HNMR ($DMSOd_6$): 3.63 (s, 2H); 5.70 (s, 1H); 7.32 (m, 15H).

N-(4-fluoro-3-clorofenil)-2-tritilamino-1,3-tiazol-5-il)acetamida

Ácido (2-tritilamino-1,3-tiazol-5-il)acético (1.96 g, 4.9 mmol) en DMF (25 ml) se hizo reaccionar con 3-cloro-4-fluoroanilina (1.07 g, 7.3 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (2.42 g, 6.37 mmol) y DIEA (1.7 ml, 9.8 mmol) a 50°C durante 18 horas. Se evaporó DMF, el residuo se absorbió en CH_2Cl_2 / EtOAc, se lavó con una solución saturada de bicarbonato de sodio. Se recuperó el sólido que se precipitó en la fase orgánica, se evaporó la fase orgánica, se añadió MeOH al residuo para producir un sólido, se recuperó en consecuencia una segunda cosecha del compuesto del título para producir en conjunto (1.38 g, 53 %).

^{1}HNMR ($DMSOd_6$): 3.56 (s, 2H); 6.61 (s, 1H); 7.28 (m, 17H); 7.88 (m, 1H); 8.41 (s, 1H).

N-(4-fluoro-3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida.

N-(4-fluoro-3-clorofenil)-2-(2-tritilamino-1,3-tiazol-5-il)acetamida (12.28 g, 23 mmol) se disolvió en TFA (100 ml) y agua (10 ml). La mezcla se agitó a temperatura ambiente durante 45 minutos. Se agregó agua (300 ml) a la mezcla de la reacción, se recuperó un sólido pro filtración, se lavó con agua y éter. El sólido se disolvió en MeOH, y la solución se trató con amoníaco (pH 8), luego se evaporó parcialmente MeOH, se agregó agua (300 ml) y se recuperó un precipitado del compuesto del título, se secó (5.37 g, 81 %).

^{1}HNMR ($DMSOd_6$): 3.64 (s, 2H); 6.76 (m, 3H); 7.38 (t, 1H); 7.48 (m, 1H); 7.92 (m, 1H).

Ejemplo 379. Preparación de Compuesto 556 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con N'-(2-ciano-5-((2S)-2-hidroxi-3-pirrolidinilpropoxi)-4-metoxifenil)-N,N,-

dimetilimido- formamida (267 mg, 0.77 mmol) produjo el compuesto del título (213 mg, 52 %).

MS ES^+: 587.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.68 (m, 4H); 2.5 (m, 5H); 2.66 (m, 1H); 3.88 (s, 2H); 3.96 (s, 3H); 4.00 (m, 1H); 4..07 (m, 1H); 4.20 (m, 1H); 4.95 (m, 1H); 7.26 (s, 1H); 7.36 (s, 1H); 7.37 (m, 1H); 7.47 (m, 1H); 7.95 (m, 1H); 8.11 (s, 1H); 8.66 (s, 1H).

N'-(2-ciano-5-((2S)-2-hidroxi-3-pirrolinilpropoxi)-4-metoxifenil)-N,N-dimetilimidoformamida.

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con pirrolidina (1.4 ml, 30 16 mmol) produjo el compuesto del título (2.8 g, 74 %).

MS ES^+: 347.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.67 (m, 4H); 1.45 (m, 4H); 1.63 (m, 2H); 2.95 (8, 3H); 3.05 (8, 3H); 3.73 (8, 3H); 3.95 (m, 2H); 4.04 (m, 1H); 4.93 (m, 1H); 6.73 (8, 1H); 7.08 (s, 1H); 7.89 (s, 1H).

Ejemplo 380. Preparación de Compuesto 557 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con N'-(2-ciano-5-((2S)-2-hidroxi-3-(4-hidroxipiperidinil)propoxi)-4-metoxi-fenil)-N,N-dimetilimidoformamida (195 mg, 0.52 mmol) produjo el compuesto del título (88 mg, 30 %).

MS ES^+: 617.5, 619.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H); 1.70 (m, 2H); 2.13 (m, 2H); 2.43 (m, 2H); 2.77 (m, 2H); 3.43 (m, 1H); 3.88 (s, 2H); 3.96 (s, 3H); 4.03 (m, 2H); 4.19 (m, 1H); 4.52 (d, 1H); 4.87 (m, 1H); 7.27 (s, 1H); 7.39 (m, 2H); 7.49 (m, 1H); 7.99 (m, 1H); 8.67 (s, 1H).

N'-(2-ciano-5-((2S)-2-hidroxi-3-(4-hidroxipiperidinil)propoxi)-4-metoxifenil)-N,N- dimetilimidoformamida.

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con 4-hidroxipiperidina (131 mg, 1.27 mmol) produjo el compuesto del título (200 mg, 58 %).

MS ES^+: 377.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.39 (m, 2H); 1.68 (m, 2H); 2.10 (m, 2H); 2.40 (m, 2H); 2.75 (m,2H); 2.95 (s, 3H); 3.05 (s, 3H); 3.21 (s, 3H); 3.31 (m, 1H); 3.95 (m, 2H); 4.00 (m, 1H); 4.52 (m, 1H); 4.82 (m, 1H); 6.73 (s, 1H); 7.08 (s, 1H); 7.88 (s, 1H).

Ejemplo 381. Preparación de Compuesto 558 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 255a, pero comenzando con N'-(2-ciano-5-((2S)-2-hidroxi-3-(4-tert-butiloxicarbonilpiperazinil)propoxi)-4-metoxifenil)-N,N-dimetilimidoformamida (355 mg, 0.77 mmol) produjo el compuesto del título (70 mg, 17 %).

MS ES^+: 602.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.42 (m, 6H); 2.73 (d, 4H); 3.88 (s, 2H); 3.96 (s, 3H); 4.04 (m, 2H); 4.19 (m, 1H); 4.90 (m, 1H); 7.28 (s, 1H); 7.37 (m, 2H); 7.47 (m, 1H); 7.94 (m, 1H); 8.11 (s, 1H); 8.66 (s, 1H) .

N'-(2-ciano-5-((2S)-2-hidroxi-3-(4-tert-butiloxicarbonilpiperazinil)propoxi)-4-metoxifenil)- N,N -dimetilimidoformamida.

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con tert- butiloxicarbonilpiperazina (284 mg, 1.53 mmol) produjo el compuesto del título (444 mg, 88 %).

MS ES^+: 462.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.39 (s, 9H); 2.40 (m, 6H); 2.95 (s, 3H); 3.04 (s, 3H); 3.30 (m, 4H); 3.72 (s, 3H); 3.95 (m, 2H); 4.02 (m, 1H); 4.91 (d, 1H); 6.74 (s, 1H); 7.09 (s, 1H); 7.88 (s, 1H).

Ejemplo 382. Preparación de Compuesto 559 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con N'-(2-ciano-5-((2S)-2-hidroxi-3-ciclopentilaminopropoxi)-4-metoxifenil)-N,N- dimetilimidoformamida (290 mg, 0.77 mmol) produjo el compuesto del título (226 mg, 54 %).

MS ES$^+$: 601.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.32 (m, 2H), 1.48 (m, 2H); 1.62 (m, 2H); 1.73 (m, 2H); 2.63 (m, 1H); 2.71 (m, 1H); 3.05 (m, 1H); 3.89 (s, 2H); 3.98 (m, 4H); 4.09 (m, 1H); 4.17 (m, 1H); 5.03 15 (m, 1H); 7.27 (s, 1H); 7.40 (m, 2H); 7.51 (m, 1H); 7.97 (m, 1H); 8.12 (s, 1H); 8.67 (s, 1H).

N'-(2-ciano-5 -((2S)-2-hidroxi-3-ciclopentiaminopropoxi)-4-metoxifenil)-N,N- dimetlimidoformamida.

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con ciclopentilamina 20 (2.7 ml, 27 mmol) produjo el compuesto del título (1.6 g, 82 %).

MS ES$^+$: 361.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.30 (m, 2H); 1.48 (m, 2H); 1.60 (m, 2H); 1.72 (m, 2H); 2.56 (m, 1H); 2.67 (m, 1H); 2.97 (s, 3H); 3.01 (m, 1H); 3.07 (s, 3H); 3.75 (s, 3H); 3.89 (m, 1H); 4.00 (m, 2H); 5.01 (m, 1H); 6.75 (s, 1H); 7.10 (s, 1H); 7.91 (s, 1H).

Ejemplo 383. Preparación de Compuesto 560 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con N'-(2-ciano-5-((2S)-2-hidroxi-3-((2-hidroxi-1,1-dimetiletil)amino)propoxi-4-metoxifenil)-N,N-dimetilimidoformamida (350 mg, 0.77 mmol) produjo el compuesto del título (147 mg, 34 %).

MS ES$^+$: 305.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 0.97 (s, 3H); 0.98 (s, 3H); 2.63 (m, 2H); 3.19 (dd, 2H); 3.89 (m, 3H); 3.98 (s, 3H); 4.10 (m, 1H); 4.18 (m, 1H); 4.56 (m, 1H); 7.29 (s, 1H); 7.39 (m, 2H); 7.50 (m, 1H); 7.97 (m, 1H); 8.13 (s, 1H); 8.68 (s, 1H).

N'-(2-ciano-5-((2S)-2-hidroxi-3-((2-hidroxi-1,1-dimetiletil)amino)propoxi)-4- metoxifenil)-N,N-dimetilimidoformamida.

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con 2-amino-2-metil-1-propanol (1.8 ml, 18.2 mmol) produjo el compuesto del título (1.25 g, 93 Ola).

^{1}HNMR ($DMSOd_6$): 0.93 (s, 3H); 0.94 (s, 3H); 2.58 (m, 2H); 3.19 (m, 2H);

3.73 (s, 3H); 3.80 (m, 1H); 3.97 (m, 1H); 4.03 (m, 1H); 4.50 (m, 1H); 4.95 (m, 1H); 6.75 (s, 1H); 7.10 (s, 1H); 7.91 (s, 1H).

Ejemplo 384. Preparación de Compuesto 561 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con N-(3,4-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) y ácido acético (3 ml) produjo el compuesto del título (263 mg, 60 %).

MS ES^+: 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.37 (m, 2H); 1.50 (m, 4H); 2.41 (m, 6H); 3.88 (s, 2H); 3.96 (s, 3H); 4.03 (m, 2H); 4.18 (d, 1H); 4.88 (m, 1H); 7.28 (s, 1H); 7.40 (s, 1H); 7.40 (m, 2H); 7.80 (m, 1H); 8.11 (s, 1H); 8.66 (s, 1H).

N -(3, 4-difluorofenil)-2-(2-amino-1 ,3-tiazol-5- il)acetamida.

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con N-(3,4-difluorofenil)-2-(2-tritilamino-1,3-tiazol-5-il)acetamida (1,75 g, 3.42 mmol) produjo el compuesto del título (642 mg, 70 %).

^{1}HNMR ($DMSOd_6$): 3.62 (s, 2H); 6.73 (s, 1H); 6.74 (s, 2H); 7.28 (m, 1H); 7.37 (q, 1H); 7.77 (m, 1H).

N -(3 ,4-difluorofenil)-2-(2-tritilamino-1 ,3-tiazol-5-il)acetamida.

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con 3,4-difluoroanilina (0.97 ml, 9.75 mmol) produjo el compuesto del título (1.75 g, 46 %).

MS ES^+: 512.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 3.54 (s, 2H); 6.58 (s, 1H); 7.25 (m, 17H); 7.71 (m, 1H); 8.39 (s, 1H).

Ejemplo 385. Preparación de Compuesto 562 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 256, pero comenzando con N-(3,4-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (226 mg, 53 %).

MS ES^+: 571.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.70 (m, 4H); 2.52 (m, 5H); 2.68 (m, 1H); 3.89 (s,

2H); 3.98 (s, 3H); 4.06 (m, 2H); 4.21 (m, 1H); 4.95 (m, 1H); 7.28 (*s*, 1H); 7.33 (m, 1H); 7.39 (*s*, 1H); 7.40 (m, 1H); 7.81 (m, 1H); 8.12 (*s*, 1H); 8.68 (*s*, 1H).

Ejemplo 386. Preparación de Compuesto 563 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 257, pero comenzando con N-(3,4-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (220 mg, 49 %).

MS ES^+: 601.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H); 1.70 (m, 2H); 2.12 (m, 2H); 2.40 (m, 2H); 2.78 (m, 2H); 3.43 (m, 1H); 3.88 (s, 2H); 3.96 (s, 3H); 4.03 (m, 2H); 4.18 (m, 1H); 4.51 (d, 1H); 4.87 (m, 1H); 7.27 (s, 1H); 7.32 (m, 1H); 7.38 (s, 1H); 7.40 (m, 1H); 7.80 (m, 1H); 8.11 (s, 1H); 8.67 (*s*, 1H).

Ejemplo 387. Preparación de Compuesto 565 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 259, pero comenzando con N-(3,4-difluorofenil)-2-(2(amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (233 mg, 53 %).

MS ES^+: 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.32 (m, 2H); 1.47 (m, 2H); 1.61 (m, 2H); 1.72 (m, 2H); 2.63 (m, 1H); 2.72 (m, 1H); 3.05 (m, 1H); 3.89 (s, 2H); 3.97 (m, 4H); 4.09 (m, 1H); 4.16 (m, 1H); 5.05 (m, 1H); 7.27 (s, 1H); 7.34 (m, 1H); 7.38 (s, 1H); 7.42 (m, 1H); 7.82 (m, 1H); 8.12 (s, 1H); 8.67 (s, 1H).

Ejemplo 388. Preparación de Compuesto 566 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 256, pero comenzando con N-(3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (238 mg, 56 %).

MS ES^+: 569.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.70 (s, 1H); 2.52 (m, 5H); 2.68 (m, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4.06 (m, 2H); 4.21 (m, 1H); 4.97 (m, 1H); 7.14 (d, 1H); 7.27 (s, 1H); 7.37 (m, 2H); 7.48 (d, 1H); 7.85 (m, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

N -(3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida.

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con N-(3-clorofenil)-2-(2-tritilamino-1,3-tiazol-5-il)acetamida (3.62 g, 7.1 mmol) produjo el compuesto del título (1.6 g, 84%).

^{1}HNMR ($DMSOd_6$): 3.63 (s, 2H); 6.74 (m, 3H); 7.11 (m, 1H); 7.33 (t, 1H); 7.42 (d, 1H); 7.79 (m, 1H).

N -(3-clorofenil)- 2-(2-tritilamino-1,3-tiazol-5 -il)acetamida.

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con 3-cloroanilina (1.4 ml, 13 mmol) produjo el compuesto del título (3.62 g, 71 %).

^{1}HNMR ($DMSOd_6$): 3.55 (s, 2H); 6.59 (s, 1H); 7.21 (m, 18H); 7.76 (m, 1H); 8.39 (s, 1H).

Ejemplo 389. Preparación de Compuesto 567 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 257, pero comenzando con N-(3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.75 mmol) produjo el compuesto del título (156 mg, 35 %).

MS ES^+: 599.4, 601.4 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H); 1.70 (m, 2H); 2.12 (m, 2H); 2.42 (m, 2H); 2.77 (m, 2H); 3.42 (m, 1H); 3.89 (s, 2H); 3.96 (s, 3H); 4.02 (m, 2H); 4.18 (m, 1H); 4.52 (d, 1H); 4.89 (m, 1tl); 7.12 (d, 1H); 7.26 (s, 1tl); 7.35 (t, 1tl); 7.38 (s, 1H); 7.46 (d, 1H); 7.84 (m, 1H); 8.11 (s, 1H); 8.67 (s, 1H).

Ejemplo 390. Preparación de Compuesto 568 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 259, pero comenzando con N-(3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.75 mmol) produjo el compuesto del título (255 mg, 58 %).

MS ES^+: 583.5, 585.5 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$): 1.32 (m, 2H); 1.48 (m, 2H); 1.62 (m, 2H); 1.73 (m, 2H); 2.63 (m, 1H); 2.72 (m, 1H); 3.04 (m, 1H); 3.90 (s, 2H); 3.97 (m, 4H); 4.09 (m, 1H); 4.16 (m, 1H); 5.05 (m, 1H); 7.12 (d, 1H); 7.27 (s, 1H); 7.37 (t, 1H); 7.39 (s, 1H); 7.48 (m, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

Ejemplo 391. Preparación de Compuesto 569 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 260, pero comenzando con N-(3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida *(200* mg, 0.74 mmol) produjo el compuesto del título (130 mg, 30 %).

MS ES^+: 587.5, 589.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 0.97 (s, 6H); 2.63 (m,2H); 3.19 (m, 2H); 3.90 (m, 3H); 3.98 (s, 3H); 4.10 (m, 1H); 4.18 (m, 1H); 4.55 (m, 1H); 5.03 (m, 1H); 7.13 (d, 1H); 7.29 (s, 1H); 7.37 (t, 1H); 7.39 (s, 1H); 7.48 (d, 1H); 7.86 (m, 1H); 8.13 (s, 1H); 8.68 (s, 1H).

Ejemplo 392. Preparación de Compuesto 570 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 258, pero comenzando con N-(3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.75 mmol) produjo el compuesto del título (211 mg,48%).

MS ES^+: 584.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.37 (m, 6H); 2.70 (m, 4H); 3.89 (s, 2H); 3.96 (s, 3H); 4.05 (m,2H); 4.19 (m, 1H); 4.90 (m, 1H); 7.12 (d, 1H); 7.27 (s, 1H); 7.35 (t, 1H); 7.37 (s, 1H); 7.47 (d, 1H); 7.84 (m, 1H); 8.10 (s, 1H); 8.66 (s, 1H).

Ejemplo 393. Preparación de Compuesto 571 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 266, pero comenzando con N'-(2-ciano-5-((2S)-2-hidroxi-3-metoxi)propoxi-4-metoxifenil)-N,N-dimetil imidoformamida (252 mg, 0.82 mmol) produjo el compuesto del título (200 mg, 50 %).

MS ES^+: 530.4, 532.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 3.22 (s, 3H); 3.42 (m, 2H); 3.91 (s, 2H); 3.98 (s, 2H); 4.10 (m, 3H); 5.21 (d, 1H); 7.13 (d, 1H); 7.26 (s, 1H); 7.37 (t, 1H); 7.39 (s, 1H); 7.48 (d, 1H); 7.85 (m, 1H); 8.13 (m, 1H); 8.69 (s, 1H).

N'-(2-ciano-5 -((2S)-2-hidroxi-3-metoxi)propoxi-4-metoxi-fenil)-N,N-dimetilimidoformamida.

N'-(2-ciano-5-(2S)-oxiranILmetoxi-4-metoxifenil)-N,N-

dimetilimidofomamida (1 g, 3.6 mmol) en metanol (80 ml) se trató con metóxido de sodio (10 g, 218 mmol) a reflujo en un horno microondas durante 0.5 horas. El solvente se evaporó y la mezcla se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH 95/5 para producir el compuesto del título (896 mg, 80 %).

^{1}HNMR ($DMSOd_6$): 2.97 (s, 1H); 3.07 (s, 1H); 3.29 (s, 1H); 3.38 (m, 2H); 3.75 (s, 3H); 3.98 (m, 3H); 5.16 (d, 1H); 6.75 (s, 1H); 7.10 (s, 1H); 7.93 (s, 1H).

Ejemplo 394. Preparación de Compuesto 572 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con N-(3-clorofenil)-2-(2-amino-13-tiazol-5-il)acetamida (200 mg, 0.75 mmol) produjo el compuesto del título (268 mg, 61 %).

MS ES$^+$: 583.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.38 (m, 2H); 1.50 (m, 4H); 2.43 (m, 6H); 3.91 (s, 2H); 3.98 (s, 3H); 4.05 (m, 2H); 4.21 (m, 1H); 4.88 (m, 1H); 7.14 (d, 1H); 7.29 (s, 1H); 7.37 (t, 1H); 7.39 (s, 1H); 7.48 (d, 1H); 7.85 (m, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

Ejemplo 395. Preparación de Compuesto 573 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con N-(3,5-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título(157 mg, 36 %).

MS ES$^+$: 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.37 (m, 2H); 1.50 (m, 4H); 2.40 (m, 6H); 3.90 (s, 2H); 3.96 (s, 3H); 4.05 (m, 2H); 4.19 (m, 1H); 4.88 (m, 1H); 6.92 (m, 1H); 7.28 (s, 1H); 7.34 (m, 2H); 7.38 (s, 1H); 8.11 (s, 1H); 8.67 (s, 1H).

N-(3 ,5-difluorofenil)-2-(2-amino-1 ,3-tiazol-5-il) acetamida.

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con N-(3,5-difluorofenil)-2-(2-tritilamino-1,3-tiazol-5-il)acetamida (11.4 g, 28.5 mmol) produjo el compuesto del título (4.75 g, 62 %).

^{1}HNMR ($DMSOd_6$): 3.64 (s, 2H); 6.74 (s, 1H); 6.76 (s, 2H); 6.89 (m, 1H);

7.29 (m, 2H).

N -(3,5 -difluorofenil)-2-(2-tritilamino-1,3-tiazol-5-il)acetamida.

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con 3,5-difluoroanilina (1.68 g, 13 mmol) produjo el compuesto del título (3.53 g, 69 %).

^{1}HNMR ($DMSOd_6$): 3.56 (s, 2H); 6.59 (s, 1H); 6.90 (m, 1H); 7.28 (m, 17H); 8.40 (s, 1H). 15

Ejemplo 396. Preparación de Compuesto 574 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 256, pero comenzando con N-(3,5-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (200 mg, 47 %).

MS ES$^+$: 571.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.65 (m, 4H); 2.50 (m, 5H); 2.65 (m, 1H); 3.91 (s, 1H); 3.96 (s, 3H); 4.04 (m, 2H); 4.20 (m, 1H); 4.95 (m, 1H); 6.92 (m, 1H); 7.26 (s, 1H); 7.34 (m, 2H); 7.38 (s, 1H); 8.11 (s, 1H); 8.66 (s, 1H).

Ejemplo 397. Preparación de Compuesto 575 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 260, pero comenzando con N-(3,5-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (177 mg, 40 %).

MS ES$^+$: 589.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 0.96 (s, 3H); 0.97 (s, 3H); 2.64 (m, 2H); 3.19 (dd, 2H); 3.92 (m, 3H); 3.98 (s, 3H); 4.09 (m, 1H); 4.20 (m, 1H); 4.56 (m, 1H); 5.05 (m, 1H); 6.94 (m, 1H); 7.29 (s, 1H); 7.35 (m, 2H); 7.39 (s, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

Ejemplo 398. Preparación de Compuesto 576 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 258, pero comenzando con N-(3,5-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (40 mg, 9 %).

MS ES$^+$: 628.5 $(M+H)^+$

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^{1}HNMR ($DMSOd_6$): 2.05 (s, 3H); 2.40 (m, 4H); 2.57 (m, 2H); 2.69 (m, 4H); 3.91 (s, 2H); 3.97 (s, 3H); 4.35 (m, 2H); 5.31 (m, 1H); 6.93 (m, 1H); 7.33 (s, 1H); 7.35 (m, 2H); 7.39 (s, 1H); 8.13 (s, 1H); 8.68 (s, 1H).

Ejemplo 399. Preparación de Compuesto 577 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 258, pero comenzando con N-(3,5-ditluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (192 mg, 44 %).

MS ES^+: 586.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.42 (m, 6H); 2.74 (m, 4H); 3.92 (s, 2H); 3.98 (s, 3H); 4.09 (m, 2H); 4.20 (m, 1H); 4.92 (m, 1H); 6.93 (m, 1H); 7.29 (s, 1H); 7.35 (m, 2H); 7.39 (s, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

Ejemplo 400. Preparación de Compuesto 578 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 256, pero comenzando con N-(3-fluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.8 mmol) produjo el compuesto del título (156 mg, 35 %).

MS ES^+: 553.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.70 (m, 4H); 2.5 (m, 5H); 2.67 (m, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4.06 (m, 2H); 4.20 (m, 1H); 4.97 (m, 1H); 6.92 (m, 1H); 7.28 (m, 1H); 7.35 (m, 2H); 7.39 (s, 1H); 7.63 (m, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

N -(3- fuorofenil)-2-(2-amino-1,3-tiazol- 5-il)acetamida.

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con N-(3-fuorofenil)-2-(2-tritilamino-1,3-tiazol-5-il)acetamida (14.6 g, 38.4 mmol) produjo el compuesto del título (6.21 g, 65 %).

^{1}HNMR ($DMSOd_6$): 3.65 (s, 2H); 6.76 (m, 3H); 6.89 (t, 1H); 7.35 (m, 2H); 7.59 (d, 1H).

N -(3- fluorofenil)-2-(2-tritilamino-1,3 -tiazol-5-il)acetamida.

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con 3-fluoroanilina produjo el compuesto del título (14.6 g, 79 %).

^{1}HNMR ($DMSOd_6$): 3.56 (s, 2H); 6.61 (s, 1H); 6.89 (t, 1H); 7,25 (m, 17H);

7.56 (d, 1H); 8.41 (s, 1H).

Ejemplo 401. Preparación de Compuesto 579 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con N-(3-fluororfenil)-2-(2-amino-1,3-tiazol-5-il)acetamide (200 mg, 0.8 mmol) produjo el compuesto del título (214 mg, 47 %).

MS ES^+: 567.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.38 (m, 2H); 1.52 (m, 4H); 2.42 (m, 6H); 3.91 (s, 2H); 3.98 (s, 3H); 4.04 (m, 2H); 4.20 (m, 1H); 4.89 (m, 1H); 6.91 (m, 1H); 7.29 (s, 1H); 7.37 (m, 2H); 7.39 (s, 1H); 7.63 (m, 1H); 8.13 (s, 1H); 8.68 (s, 1H).

Ejemplo 402. Preparación de Compuesto 580 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 258, pero comenzando con N-(3-fluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.8 mmol) produjo el compuesto del título (210 mg, 46%).

MS ES^+: 568.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.38 (m, 6H); 2.70 (m, 4H); 3.89 (s, 2H); 3.96 (s, 3H); 4.02 (m, 2H); 4.19 (m, 1H); 4.98 (m, 1H); 6.89 (m, 1H); 7.27 (s, 1H); 7.32 (m, 2H); 7.37 (s, 1H); 7.61 (m, 1H); 8.10 (s, 1H); 8.66 (s, 1H).

Ejemplo 403. Preparación de Compuesto 581 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 258, pero comenzando con N-(3-fluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.8 mmol) produjo el compuesto del título (35 mg, 7 %).

MS ES^+: 610.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.03 (s, 3H); 2.38 (m, 4H); 2.57 (m, 2H); 2.69 (m, 4H); 3.88 (s, 2H); 3.95 (s, 3H); 4.34 (m, 2H); 5.30 (m, 1H); 6.89 (m, 1H); 7.31 (s, 1H); 7.34 (m, 2H); 7.37 (s, 1H); 7.62 (m, 1H); 8.11 (s, 1H); 8.66 (s, 1H).

Ejemplo 404. Preparación de Compuesto 582 en Tabla 20

Una reacción análoga a la descrita en Ejemplo 259, pero comenzando con N-(3-fluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.8 mmol) produjo el compuesto del título (196 mg, 43 %).

MS ES^+: 567.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.30 (m, 2H); 1.47 (m, 2H); 1.61 (m,2H); 1.73 (m, 3H); 2.62 (m, 1H); 2.71 (m,1H); 3.0 (m, 1H); 3.89 (m, 1H); 3.97 (s, 3H); 4.07 (m, 1H); 4.13 (m, 1H); 5.03 (m, 1H); 6.90 (m, 1H); 7.25 (s, 1H); 7.35 (m, 2H); 7.37 (s, 1H); 7.62 (m, 1H); 8.10 (s, 1H); 8.66 (s, 1H).

Ejemplo 405. Preparación de Compuesto 583 en Tabla 21

Ácido 4-((2-amino-1,3-tiazol-5-il)acético)-6,7-dimetoxiquinazolina (173 mg, 0.5 mmol) en NMP (2 ml) se hizo reaccionar con 3,5-difluoroanilina (98 mg, 0.75 mmol) en la presencia de hexafluorofosfato de 0-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (285 mg, 0.75 mmol) y DIEA (130 µl, 0.75 mmol) a 50°C durante 20 horas. La mezcla se enfrió, se agregó dimetilamina (2M MeOH, 2 ml), y la solución resultante se agitó a temperatura ambiente durante 15 horas, se evaporó MeOH, y se adicionó agua (20 ml) a la mezcla, se recuperó el precipitado, se lavó con agua, y se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH 50/40/10 para producir el compuesto del título (22 mg, 10 %).

^{1}HNMR ($DMSOd_6$): 3.90 (s, 2H); 3.95 (s, 6H); 6.93 (t, .1H); 7.26 (s, 1H); 7.34 (d, 2H); 7.39 (s, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

Ácido 4-((2-amino-1,3-tiazol-5-il)acético)-6,7-dimetoxiquinazolina.

4-(metil(2-amino-1,3-tiazol-5-il)acetato)-6,7-dimetoxiquinazolina (3.92 g, 10.9 mmol) en etanol 50 ml se trató con hidróxido de sodio (2N, 27 ml, 54.5 mmol) durante 45 minutos. El solvente se evaporó, el residuo se disolvió en CH_2Cl_2 / MeOH trietilamina (3 eq.) se añadió, se retiró el sólido por filtración, el filtrado se evaporó y trituró con etanol para producir el compuesto del título como un sólido (1.88 g, 50 %).

^{1}HNMR ($DMSOd_6$): 3.83 (s, 2H); 3.96 (s, 6H); 7.27 (s, 1H); 7.35 (s, 1H); 8.13 (s, 1H); 8.69 (s, 1H).

4-(metil(2-amino-1,3-tiazol-5-il)acetato)-6,7-dimetoxiquinazolina.

N'-(2-ciano-4,5-dimetoxifenil)-N,N-dimetilimidoformamida (3.5 g, 15 mmol) en ácido acético (35 ml) se hizo reaccionar con metil(2-amino-1,3-tiazol-5-il)acetato (3.22 g, 18.7 mmol)

a reflujo durante 4 horas. El solvente se evaporó y el residuo se purificó por cromatografía de gel de sílice, eluyente CR_2Cl_2 / MeOH 95/5 para producir el compuesto del título (3.92 g, 73 %).

^{1}HNMR ($DMSOd_6$): 3.69 (s, 3H); 3.95 (s, 2H); 3.96 (s, 6H); 7.27 (s, 1H); 7.38 (s, 1H); 8.12 (s, 1H); 8.69 (s, 1H).

Ejemplo 406. Preparación de Compuesto 584 en Tabla 21

Una reacción análoga a la descrita en Ejemplo 283, pero comenzando con 3-cloroanilina (80 µl, 0.75 mmol) produjo el compuesto del título (81 mg, 26 %). MS ES$^+$: 456.4, 458.4 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$): 3.9.1 (s, 2H); 3.96 (s, 6H); 7.14 (d, 1H); 7.28 (s, 1H); 7.37 (t, 1H); 7.48 (d, 1H); 7.85 (m, 1H); 8.13 (s, 1H); 8.69 (s, 1H).

Ejemplo 407. Preparación de Compuesto 585 en Tabla 21

Una reacción análoga a la descrita en Ejemplo 283, pero comenzando con 3-cloro-4-fluoroanilina 15 (110 mg, 0.75 mmol) produjo el compuesto del título (93.7 mg, 40 %).

MS ES$^+$: 474.4, 476.4 $(M_+H)^+$

^{1}HNMR: 3.90 (s, 2H); 3.97 (s, 3H); 7.28 (s, 1H); 7.40 (m, 1H); 7.40 (s, 1H); 7.50 (m, 1H); 7.96 (m, 1H); 8.14 (s, 1H); 8.70 (s, 1H).

Ejemplo 408. Preparación de Compuesto 586 en Tabla 21

Una reacción análoga a la descrita en Ejemplo 283, pero comenzando con 3,4-difluoroanilina (75 mg, 0.75 mmol) produjo el compuesto del título (130 mg, 60 %).

MS ES$^+$: 458.5 $(M_+H)^+$

^{1}HNMR: 3.89 (s, 2H); 3.97 (s, 6H); 7.28 (s, 1H); 7.33 (m, 1H); 7.40 (s, 1H); 7.41 (m, 1H); 7.82 (m, 1H); 8.14 (s, 1H); 8.69 (s, 1H).

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Ejemplo 409. Preparación de Compuesto 587 en Tabla 22

Ácido 4-((2-amino-1,3-tiazol-5-il)(hidroxi)acético)-6-metoxi-7-(3-morfolinopropoxi)quinazolina (143 mg, 0.3 mmol) en DMF (4 ml) se hizo reaccionar con anilina (36 mg, 0.39 mmol), 1-(3-dimetilaminopropil)-3-etilcarbodiimida clorhidrato (63 mg, 0.33 mmol), 2-hidroxipiridina N-óxido (33 mg, 0.3 mmol) y DIEA (36 mg, 0.3 mmol) a 90°C durante 1 hora. Se enfrió la mezcla, se diluyó CH_2Cl_2 (8 ml) y se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2/ MeOH 90/10 a 85/15. Las fracciones combinadas que contenían el producto se evaporaron, el residuo se disolvió en MeOH, se agregó agua y se recuperó el precipitado, se disolvió en MeOR / CH_2Cl_2, se secó, se concentró para producir el compuesto del título (145 mg, 88 %).

MS ES^+: 551.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H); 3.15 (t, 2H); 3.34 (t, 2H); 3.55 (d, 2H); 3.71 (t, 2H); 3.98 (s, 3H); 4.03 (d, 2H); 4.31 (t, 2H); 5.47 (s, 1H); 7.11 (t, 1H); 7.31 (s, 1H); 7.33 (t, 2H); 7.70 (s, 1H); 7.73 (d, 2H); 7.92 (s, 1H); 9.12 (s, 1H).

4-(2-amino-1,3-tiazol-5- il)-6- metoxi-7-(3-morfolinopropoxi)quinazolina.

N'-(2-ciano-4-metoxi-5-(3-morfolinopropoxi)fenil)-N,N-dimetilimidoformamida

(692 mg, 2 mmol) se hizo reaccionar con amino-1,3-tiazol (240 mg, 2.4 mmol) en ácido acético (6.9 ml) a reflujo durante 4 horas. La mezcla se concentró, el residuo se disolvió en AcOEt, se lavó con bicarbonato de sodio acuoso, se secó la fase orgánica, se concentró, el aceite residual se trituró en éter para producir un sólido (560 mg, 70 %).

MS ES^+: 402.6 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.29 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 3.99 (s, 3H); 4.04 (d, 2H); 4.31 (t, 2H); 7.32 (s, 1H); 7.47 (d, 1H); 7.75((d, 1H); 7.95 (s, 1H); 9.11 (s, 1H).

Ácido 4-((2-amino-1,3-tiazol-5-il)(hidroxi)acético)-6-metoxi-7-(3-morfolinopropoxi)quinazolina.

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20 4-(2-amino-1,3-tiazol-5-il)-6-metoxi-7-(3-morfolinopropoxi)quinazolina (1.6 g, 4 mmol) en agua (16 ml), MeOH (16 ml), se hizo reaccionar con ácido glioxílico (740 mg, 8 mmol) a pH 11.5 (NaOH 6N) y 45-50°C durante 6 horas. Se evaporó metanol, y el pH de la fase acuosa se ajustó a 3 (HCl 6N), y la solución se vertió en una columna (isolute®) de intercambiador fuerte de cationes, se lavó con agua (120 ml), metanol (120 ml) y se eluyó con CH_2Cl_2 / MeOH, NH_3 (3N) 1/1 200 ml para producir el compuesto del título (1.58 g, 83 %).

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.98 (s, 3H); 4.03 (d, 2H); 4.30 (t, 2H); 5.38 (s, 1H); 7.32 (s, 1H); 7.68 (s, 1H); 7.91 (8, 1H); 9.12 (s, 1H).

Ejemplo 410. Preparación de Compuesto 588 en Tabla 22

Una reacción análoga a la descrita en Ejemplo 287, pero comenzando con 3,4-difluoroanilina (34 mg, 0.26 mmol) produjo el compuesto del título (30 mg, 26%).

MS ES$^+$: 587.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.69 (t,2H); 3.98 (s, 3H); 4.04 (d, 2H); 4.30 (t, 2H); 5.48 (s, 1H); 7.32 (s, 1H); 7.40 (q, 1H); 7.57 (m, 5 1H); 7.70 (s, 1H); 7.92 (m, 2H); 9.12 (s, 1H).

Ejemplo 411. Preparación de Compuesto 589 en Tabla 22

N'-(2-ciano-4-metoxi-5-(3-N-metilpiperazinilpropoxi)-4-metoxifenil)-N,N-dimetilimidoformamida (144 mg, 0.4 mmol) se hizo reaccionar con N-(3,4-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)-2-hidroxiacetamida (137 mg, 0.4 mmol) en ácido acético (350 µl) a reflujo durante 40 minutos. El solvente se retiro, y el residuo se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH / Et3N, 90.10.1 para producir el compuesto del título (180 mg, 37 %).

MS ES$^+$: 600.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.30 (t, 2H); 2.94 (s, 3H); 3.1-4.1 (m, 8H); 3.44

(t, 2H); 3.99 (s, 3H); 4.30 (t, 2H); 5.48 (s, 1H); 7.32 (s, 1H); 7.40 (q, 1H); 7.57 (m, 1H); 7.70 (s, 1H); 7.92 (m, 2H); 9.12 (s, 1H).

Metil(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)acetato.

Metil(2-amino-1,3-tiazol-5-il)acetato (4.3 g, 25 mmol) se hizo reaccionar con di-tert-butil dicarbonato (10.9 g, 50 mmol) limpio, a 100°C durante 2 horas. La mezcla fría se trituró en éter para producir el compuesto del título como un sólido (4.3 g, 63 %).

^{1}HNMR ($DMSOd_6$): 1.48 (s, 9H); 3.66 (s, 3H); 3.86 (s, 2H); 7.17 (s, 1H).

Metil(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)(oxo)acetato.

Metil(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)acetato (4.08 g, 15 mmol) en dioxano (60 ml) se hizo reaccionar con dióxido de selenio (4 g, 36 mmol) a reflujo durante 45 minutos. La mezcla se enfrió, se añadió CH_2Cl_2 / MeOH 8/2 (150 ml), el material insoluble se filtró, la fase orgánica se lavó con una solución saturada de bicarbonato de sodio, y se extrajo con CH_2Cl_2, se secó, se purificó por cromatografía sobre alúmina, eluyente: CH_2Cl_2 / MeOH 9/1 para producir el compuesto del título (1 g, 23 %).

^{1}HNMR ($DMSOd_6$): 1.57 (s, 9H); 3.94 (s, 3H); 8.48 (s, 1H).

Ácido (2-tert-butoxicarbonilamino-1,3-tiazol-5-il)(oxo)acético.

Metil(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)(oxo)acetato (1.14 g, 4 mmol) en

etanol (10 ml) se trató con hidróxido de sodio (2N, 4 ml, 8 mmol) durante 3M o minutos a temperatura ambiente. Se retiró etanol, la solución acuosa se acidificó (pH 3). El sólido se recuperó, se secó para producir el producto del título (900 mg, 82 %).

^{1}HNMR ($DMSOd_6$): 1.53 (s, 9H); 8.41 (s, 1H).

N-(3,4-difluorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)(oxo)acetamida. Ácido 2-tert-butoxicarbonilamino-1,3-tiazol-5-il)(oxo)acético (136 mg, 0.5 mmol) en DMF (2 ml) se hizo reaccionar con 3,4-difluoroanilina (77 mg, 0.6 mmol) en presencia de hexafluorofosfato de 0-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluroni (203 mg, 0.55 mmol) y DIEA (77 mg, 0.6 mmol) durante 15 minutos. La mezcla se diluyó con agua, el sólido se filtró, se lavó con agua, se secó, para producir el

compuesto del título (162 mg, 84 %).

^{1}HNMR ($DMSOd_6$): 1.53 (s, 9H); 7.48 (q, 1H); 7.68 (m, 1H); 7.98 (m, 1H); 8.61 (s, 1H).

N-(3,4-difluorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)-2-hidroxiacetamida.

N-(3,4-difluorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)(oxo) acetamida (938 mg, 2.4 mmol) en THF (50 ml) y MeOH (10 ml) se trató con borohidruro de sodio (93 mg, 2.4 mmol) durante 30 minutos. La mezcla se evaporó, el residuo se disolvió en etanol (3 ml), se añadió agua (25 ml), y el pH se ajustó a 6, se agregó más agua, se recuperó un sólido, se secó, se recristalizó en éter / éter de petróleo para producir el compuesto del título (850 mg, 90 %).

^{1}HNMR ($DMSOd_6$): 1.48 (s, 9H); 5.34 (d, 1H); 6.78 (d, 1H); 7.33 (s, 1H); 7.40 (s, 1H); 7.56 (m, 1H); 7.90 (m, 1H).

N-(3,4-difluorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)-2-hidroxiacetamida (847 mg, 2.2 mmol) en CH_2Cl_2 (12 ml) y TFA (4 ml) se agitó a temperatura ambiente durante 3 horas. El solvente se evaporó, el residuo se disolvió en MeOH / H_20, el pH se ajustó a 7 y la mezcla se extrajo con acetato de etilo. La capa orgánica se secó, se evaporó, el residuo se trituró en éter, el sólido se filtró para producir el compuesto del título (515 mg, 82 %).

^{1}HNMR ($DMSOd_6$): 5.17(d, 1H); 6.51 (d, 1H); 6.91 (m, 3H); 7.39 (s, 1H); 7.52 (m, 1H); 7.87 (m, 1H).

Ejemplo 412. Preparación de Compuesto 590 en Tabla 22

N'-(2-ciano-4-metoxi-5-(3-piperidinilpropoxi)-4-metoxifenil)-N,N-dimetilimidofonnamida (100 mg, 0.29 mmol) se hizo reaccionar con N-(3-fluorofenil)-2-(2-amino-1,3-tiazol-5-il)-2-hidroxiacetamida (82 mg, 0.3 mmol) en ácido acético (260 mg) a 105°C durante 40 minutos. La mezcla se evaporó y purificó por cromatografía de gel de sílice, eluyenye CH_2Cl_2 / MeOH (NH3 3N) 9/1 para producir el compuesto del título (42 mg, 26 %).

MS ES^+: 567.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.4 (m, 2H); 1.51 (m, 4H); 1.95 (t, 2H); 2.40 (m, 6H); 3.95 (s, 3H); 4.19 (t, 2H); 5.41 (d, 1H); 6.78 (d, 1H); 6.91 (m, 1H); 7.25 (s, 1H); 7.35 (q, 1H); 7.50 (s, 1H); 7.55 (d, 1H); 7.71 (m, 1H); 8.10 (s, 1H); 8.68 (s, 1H).

N'-(2-ciano-4-metoxi-5-(3-piperidinilpropoxi)-4-metoxifenil)-N,N-dimetetilimidoformamida.

N'-(2-ciano-4-metoxi-5-(3-cloropropoxi)-4-metoxifenil)-N,N-dimetilimidoformamida (3 g, 10 mmol) en acetonitrilo (50 ml) se hizo reaccionar con piperidina (10 ml, 100 mmol) en presencia de KI (300 mg, 1.8 mmol) y K_2CO_3 (2.1 g, 0.015 mmol) a 75° C bajo argón durante 3 horas. El solvente se evaporó, y el residuo se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH, NH_3 3N 95/5 para producir el compuesto del título (3.48 g, 100 %).

MS ES^+: 345.6 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$): 1.4 (m, 2H); 1.50 (m, 4H); 1.88 (m, 2H); 2.35 (m, 6H); 2.95 (s, 3H); 3.05 (s, 3H); 3.72 (s, 3H); 4.05 (t, 2H); 6.72 (s, 1H); 7.07 (s, 1H); 7.89 (s, 1H).

N -(3-fluorofenil)-2-(2-amino-1,3-tiazol-5'-il)-2-hidroxiacetomida.

Una reacción análoga a la descrita en Ejemplo 289, pero comenzando con N-(3-fluorobenzil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)-2-hidroxiacetamida (2.55 g, 0.69 mmol) produjo el compuesto del título (1.37 g, 75 %).

MS ES^+: 268.5 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$): 5.16 (d, 1H); 6.45 (d, 1H); 6.90 (m, 4H); 7.34 (q, 1H); 7.49 (d, 1H); 25 7.70 (m, 1H).

N-(3-fluorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)-2-hidroxiacetamida.

Una reacción análoga a la descrita en Ejemplo 289, pero comenzando con N-(3-fluorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)- (oxo)-acetamida (2.92 g, 8 mmol) produjo el compuesto del título (2.59 g, 88 %).

^{1}HNMR ($DMSOd_6$): 1.48 (s, 9H); 5.34 (d, 1H); 6.74 (d, 1H); 6.90 (m, 1H); 7.33 (m, 2H); 7.54 (d, 1H); 7.70 (m, 1H).

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N-(3-fluorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)(oxo) acetamida.

Una reacción análoga a la descrita en Ejemplo 289, pero comenzando con 3-fluoroanilina (1.6 g, 14.4 mmol) produjo el compuesto del título (4.06 g, 93 %).

^{1}HNMR ($DMSOd_6$): 1.54 (s, 9H); 7.01 (m, 1H); 7.42 (m, 1H); 7.69 (m, 1H); 7.80 (m, 1H); 5 8.6 (s, 1H).

Ejemplo 413. Preparación de Compuesto 591 en Tabla 22

Una reacción análoga a la descrita en Ejemplo 290, pero comenzando con N-(3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)-2-hidroxiacetamida (99 mg, 0.35 mmol) produjo el compuesto del título (47 mg, 23 %).

MS ES^+: 583.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.38 (m, 2H); 1.51 (m, 4H); 1.95 (m, 2H); 2.38 (m, 6H); 3.95 (s, 3H); 4.19 (t, 2H); 5.40 (d, 1H); 6.79 (d, 1H); 7.14 (d, 1H); 7.24 (s, 1H); 7.35 (t, 1H); 7.50 (s, 1H); 7.67 (d, 1H); 7.95 (s; 1H); 8.10 (s, 1H); 8.68 (s, 1H).

N -(3-clorofenil)-2-(2-amino-1,3-tiazol-5- il)- 2-hidroxiacetamida.

Una reacción análoga a la descrita en Ejemplo 290, pero comenzando con N-(3-clorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)-2-hidroxiacetamida (2.13 g, 5.5 mmol) produjo el compuesto del título (1.02 g, 65 %).

^{1}HNMR ($DMSOd_6$): 5.15 (d, 1H); 6.45 (d, 1H); 6.90 (m, 3H); 7.12 (dd, 1H); 7.33 (t, 1H); 20 7.62 (d, 1H); 7.89 (m, 1H).

N-(3-clorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)-2-hidroxiacetamida.

Una reacción análoga a la descrita en Ejemplo 290, pero comenzando con N-(3-clorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)(oxo)acetamida (2.5 g, 6.5 mmol) produjo el compuesto del título (2.23 g, 89 %).

^{1}HNMR ($DMSOd_6$): 1.48 (s, 9H); 5.34 (d, 1H); 6.74 (d, 1H); 7.14 (m, 1H); 7.34 (m, 2H); 7.65 (m, 1H); 7.92 (m, 1H).

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N-(3-clorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il) (oxo) acetamida.

Una reacción análoga a la descrita en Ejemplo 290, pero comenzando con 3-cloroanilina (1.84 g, 14 mmol) produjo el compuesto del título (3.6 g, 79 %).

^{1}HNMR ($DMSOd_6$): 1.54 (s, 9H); 7.24 (d, 1H); 7.43 (t, 1H); 7.79 (d, 1H); 8.03 (s, 1H); 8.61 (s, 1H).

Ejemplo 414. Preparación de Compuesto 592 en Tabla 22

N'-(2(ciano-4-metoxi-5-(N-metil-3-piperazinilpropoxifenil)-N,N-dimetilimidoformamida (140 mg, 0.39 mmol) en ácido acético (0.5 ml) en presencia de N-(3,4-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)-2-(hidroxiimino) acetamida (116 mg, 0.39 mmol) se calentó a 110 °C durante 16 horas. La mezcla se concentró y purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH, HN_3 3N 95/5 a 90/10, para producir el compuesto del título (23 mg, 10 %).

MS ES$^+$: 613.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.0 (m, 2H); 2.22 (s, 3H); 2.47 (m, 10H); 4.0 (s, 3H); 4.22 (t, 2H); 7.29 (m, 1H); 7.47 (m, 1H); 7.57 (m, 1H); 7.97 (m, 1H); 8.2 (s, 1H); 8.38 (s, 1H); 8.80 (s, 1H).

N-(3,4-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)-2-(hidroxiimino)acetamida.

N-(3,4-difluorofenil)-2-(2-tert-butoxicarbonil-amino-1,3-tiazol-5-il)-2-(hidroxiimino)acetamida (600 mg, 1.5 mmol) en CH_2Cl_2 (12 ml) y TFA (4 ml) se agitó a temperatura ambiente durante 2 horas. La mezcla se evaporó, se disolvió en metanol, el pH se ajustó a 6 con bicarbonato de sodio, se agregó agua, el precipitado se recuperó, se secó para producir el compuesto del título (388 mg, 86 %).

MS ES$^+$: 299.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): mezcla de isómeros: 7.05,7.8 (2s, 1H); 7.43 (m, 4H); 7.88 (m, 1H).

N-(3,4-difluorofenil)-2-(2-tert-butoxicarbonil-amino-1,3-tiazol-5-il)-2-

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(hidroxiimino)acetamida.

N-(3,4-difluorofenil)-2-(2-tert-butoxicarbonil-amino-1,3-tiazol-5-il)(oxo) acetamida (100 mg, 0.26 mmol) en piridina (8 ml) se hizo reaccionar con hidroxilamina clorhidrato (27 mg, 0.39 mmol) a 70°C durante 15 horas. El solvente se evaporó, se agregó agua al residuo, el sólido se filtró, se lavó con agua, se secó para producir el compuesto del título (84 mg, 81 %).

^{1}HNMR ($DMSOd_6$): mezcla de isómeros: 7.41, 8.18 (2s, 1H); 7.50 (m, 2H); 7.90 (m, 1H).

Ejemplo 415. Preparación de Compuesto 593 en Tabla 23

Ácido 5-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)amino)tiofen-2-carboxílico (80 mg, 0.18 mmol) en DMF (2 ml) se hizo reaccionar con 2-aminopiridina (17 mg, 0.18 mmol) en presencia de hexafluorofosfato de 0-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (70 mg, 0.18 mmol) y DIEA (80 µl, 0.46 mmol), a 50° C durante 6 horas. Se añadió una solución saturada de bicarbonato de sodio (2 ml) y la mezcla se agitó durante 0.5 hora Se recuperó un sólido por filtración, se lavó con agua, se secó para producir el compuesto del título (15 mg, 16 %).

MS ES^+: 521 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (m, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d,2H); 3.69 (t, 2H); 4.03 (d, 2H); 4.05 (s, 3H); 4.32 (t, 2H); 7.43 (m,2H); 7.53 (t, 1H); 7.94 (d, 1H); 8.21 (m, 2H); 8.35 (t, 1H); 8.49 (d, 1H); 9.30 (s, 1H).

Ejemplo 416. Preparación de Compuesto 594 en Tabla 23

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con 4-metilanilina (19 mg, 0.18 mmol) produjo el compuesto del título (69 mg, 72 %).

MS ES^+: 535 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.34 (s, 3H); 2.40 (t, 2H); 3.11 (t, 2H); 3.38 (t, 2H); 3.60 (d, 2H); 3.90 (t, 2H); 4.03 (d, 2H); 4.05 (s, 3H); 4.35 (t, 2H); 7.15 (d, 2H); 7.27 (d, 1H); 7.52 (s, 1H); 7.62 (d, 2H); 7.85 (d, 1H); 8.15 (s, 1H);

8.87 (s, 1H).

Ejemplo 417. Preparación de Compuesto 595 en Tabla 23

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con 2-metilanilina (19 mg, 0.18 mmol) produjo el compuesto del título (28 mg, 29 %). MS ES^+: 535 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2/28 (s, 3H); 2.32 (t, 2H); 3.18 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 4.05 (d, 2H); 4.07 (s, 3H); 7.30 (m, 4H); 7.35 (d, 1H); 7.41 (s, 1H); 7.96 (d, 1H); 8.22 (s, 1H); 9.26 (s, 1H).

Ejemplo 418. Preparación de Compuesto 596 en Tabla 23

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con 3-metoxianilina (22 mg, 0.18 mmol) produjo el compuesto del título (14 mg, 14 %).

MS ES^+: 550.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.17 (t,2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 3.78 (s, 3H); 4.04 (d, 2H); 4.06 (s, 3H); 4.33 (t, 2H); 6.7 (d, 1H); 7.28 (s, 1H); 7.35 (s, 30 1H); 7.36 (d, 1H); 7.41 (s, 1H); 7.45 (s, 1H); 8.01 (d, 1H); 8.22 (s, 1H); 9.27 (s, 1H).

Ejemplo 419. Preparación de Compuesto 597 en Tabla 23

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con 2-hidroximetil-anilina (22 mg, 0.18 mmol) produjo el compuesto del título (7 mg, 7 %).

MS ES^+: 550.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (m, 2H); 3.18 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.06 (m, 5H); 4.32 (t, 2H); 4.65 (s, 2H); 7.22 (t, 1H); 7.32 (t, 1H); 7.37 (d, 1H); 7.40 (s, 1H); 7.46 (d, 1H); 7.72 (d, 1H); 7.81 (d, 1H); 8.22 (s, 1H); 9.27 (s, 1H).

Ejemplo 420. Preparación de Compuesto 598 en Tabla 23

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con

3-nitroanilina (25 mg, 0.18 mmol) produjo el compuesto del título (6 mg, 6 %).

MS ES^+: 565.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.18 (t, 2H); 3.38 (t, 2H); 3.58 (d, 2H); 3.70 (t, 2H); 4.05 (d, 2H); 4.07 (s, 3H); 4.33 (t, 2H); 7.39 (d, 1H); 7.42 (s, 1H); 7.68 (t, 1H); 7.98 (d, 1H); 8.08 (d, 1H); 8.20 (m, 1H); 8.23 (s, 1H); 8.77 (s, 1H); 9.3 (s, 1H).

Ejemplo 421. Preparación de Compuesto 599 en Tabla 23

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con 4-trifluoromethiloaniline (29 mg, 0.18 mmol) produjo el compuesto del título (8 mg; 8 %).

MS ES^+: 588.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (m, 2H); 3.19 (t, 2H); 3.41 (t, 2H); 3.61 (d, 2H); 3.75 (t, 2H); 4.05 (d, 2H); 4.08 (s, 1H); 4.37 (t, 2H); 7.39 (d, 1h); 7.43 (s, 1H); 7.72 (d, 2H); 8.03 (d, 2H); 8.10 (d, 1H); 8.23 (s, 1H); 9.29 (s, 1H).

Ejemplo 422. Preparación de Compuesto 600 en Tabla 23

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con 3-cloroanilina (23 mg, 0.18 mmol) produjo el compuesto del título (21 mg, 21 %).

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (m, 2H); 3.19 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 4.03 (d, 2H); 4.07 (s, 3H); 4.34 (t, 2H); 7.17 (d, 1H); 7.37 (t, 1H); 7.40 (m, 2H); 7.70 (d, 1H); 7.95 (m, 1H); 8.02 (d, 1H); 8.22 (s, 1H); 9.29 (s, 1H).

Ejemplo 423. Preparación de Compuesto 601 en Tabla 23

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con 2-metoxianilina (22 mg, 0.18 mmol) produjo el compuesto del título (32 mg, 32 %).

^{1}HNMR ($DMSOd_6$, TFA): 2.35 (t, 2H); 3.18 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 3.87 (s, 3H); 4.05 (d, 2H); 4.06 (s, 3H); 4.34 (t, 2H); 6.99

(t, 1H); 7.11 (d, 1H); 7.20 (s, 1H); 7.33 (d, 1H); 7.40 (s, 1H); 7.73 (dd, 1H); 7.97 (d, 1H); 8.22 (s, 1H); 9.27 (s, 1H).

Ejemplo 424. Preparación de Compuesto 602 en Tabla 23

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con 3-(2-hidroxietil) anilina (25 mg, 0.18 mmol) produjo el compuesto del título (27 mg, 26 %).

MS ES^+: 564.7 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.37 (d, 3H); 2.32 (t, 2H); 3.19 (t, 2H); 3.38 (t, 2H); 3.58 (d, 2H); 3.62 (t, 2H); 4.06 (d, 2H); 4.08 (s, 3H); 4.36 (t, 2H); 4.76 (q, 1H); 7.08 (d, 1H); 7.29 (t, 1H); 7.35 (d, 1H); 7.42 (s, 1H); 7.70 (d, 1H); 7.76 (s, 1H); 8.05 (d, 1H); 8.23 (s, 1H); 9.28 (s, 1H).

Ejemplo 425. Preparación de Compuesto 603 en Tabla 23

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con 3-fluoro-4-metoxianilina (25 mg, 0.18 mmol) produjo el compuesto del título (14 mg, 14 %).

MS ES^+: 568.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.19 (t, 2H); 3.38 (t, 2H); 3.57 (d, 2H); 3.72 (t, 2H); 3.85 (s, 3H); 4.04 (d, 2H); 4.07 (s, 3H); 4.35 (t, 2H); 7.17 (t, 1H); 7.36 (d, 1H); 7.42 (s, 1H); 7.47 (dd, 1H); 7.73 (dd, 1H); 7.98 (d, 1H); 8.24 (s, 1H); 9.27 (s, 1H).

Ejemplo 426. Preparación de Compuesto 604 en Tabla 23

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con 2-metil-4-fluoroanilina (23 mg, 0.18 mmol) produjo el compuesto del título (27 mg, 27 %).

MS ES^+: 552.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.28 (s, 3H); 2.31 (t,2H); 3.18 (t, 2H); 3.38 (t, 2H); 3.57 (d, 2H); 3.71 (t, 2H); 4.05 (d, 2H); 4.07 (s, 3H); 7.07 (dt, 1H); 7.15 (dd, 1H); 7.35 (d, 1H); 7.36 (m, 1H); 7.41 (s, 1H); 7.95 (d, 1H); 8.23 (s, 1H); 9.26 (s, 1H).

Ejemplo 427. Preparación de Compuesto 605 en Tabla 23

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con 2-fluoro-5-metilanilina (23 mg, 0.18 mmol) produjo el compuesto del título (9 mg, 9 %).

MS ES^+: 552.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (m, 5H); 3.19 (t, 2H); 3.38 (t, 2H); 3.56 (d, 2H); 3.71 (t, 2H); 4.04 (d, 2H); 4.07 (s, 3H); 4.35 (t, 2H); 7.09 (m, 1H); 7.18 (m, 1H); 7.35 (d, 1H); 7.40 (s, 1H); 7.41 (m, 1H); 8.0 (d, 1H); 8.23 (s, 1H); 9.27 (s, 1H).

Ejemplo 428. Preparación de Compuesto 606 en Tabla 23

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con 10 3-cianoanilina (21 mg, 0.18 mmol) produjo el compuesto del título (9 mg, 9 %). MS ES^+: 545.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (t,2H); 3.21 (t, 2H); 3.39 (t, 2H); 3.60 (d, 2H); 3.72 (t, 2H); 4.07 (d, 2H); 4.10 (s, 3H); 4.37 (t, 2H); 7.40 (d, 1H); 7.44 (s, 1H); 7.62 (s, 1H); 7.63 (m, 1H); 8.06 (m, 1H); 8.06 (d, 1H); 8.26 (s, 1H); 8.30 (s, 1H); 9.32 (s, 1H).

Ejemplo 429. Preparación de Compuesto 607 en Tabla 23

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con isoamilamina (16 mg, 0.18 mmol) produjo el compuesto del título (15 mg, 17 %).

MS ES^+: 514.7 $(M+H)^+$

^{1}HNMR ($CDCl_3$): 0.96 (d, 6H); 1.77 (m, 5H); 2.11 (m, 2H); 2.5 (m, 4H); 2.56 (t, 2H); 3.73 (m, 4H); 4.03 (s, 3H); 4.22 (t, 2H); 6.05 (t, 1H); 6.88 (d, 1H); 7.24 (s, 1H); 7.39 (d, 1H); 7.58 (s, 1H); 8.70 (s, 1H).

Ejemplo 430. Preparación de Compuesto 608 en Tabla 23

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con 2-cloroanilina (23 mg, 0.18 mmol) produjo el compuesto del título (5 mg, 5

%).

MS ES^+: 554.5, 556.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.19 (t, 2H); 3.39 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 4.04 (d, 2H); 4.07 (s, 3H); 4.34 (t, 2H); 7.32 (t, 1H); 7.36 (d, 1H); 7.41 (s, 1H); 7.41 (t, 1H); 7.57 (d, 1H); 7.63 (d, 1H); 8.0 (d, 1H); 8.23 (s, 1H); 9.27 (s, 1H).

Ejemplo 431. Preparación de Compuesto 609 en Tabla 24

Una reacción análoga a la descrita en Ejemplo 293, pero comenzando con ácido 5-((6-metox-7-(3-morfolinopropoxi)quinazolin-4-il)amino)tiofen-3-carboxílico (80 mg, 0.18 mmol) y anilina (20 µl, 0.22 mmol)) produjo el compuesto del título (28 mg, 30 %).

MS ES^+: 520 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.18 (t, 2H); 3.38 (t,2H); 3.56 (d, 2H); 3.71 (t, 2H); 4.05 (d, 2H); 4.06 (s, 3H); 4.34 (t, 2H); 7.12 (t, 1H); 7.37 (t, 2H); 7.40 (s, 1H); 7.76 (d, 1H); 7.79 (d, 2H); 8.18 (s, 1H); 8.21 (d, 1H); 9.17 (s, 1H).

Ácido 5-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)amino)tiofen-3-carboxílico.

Etil-5-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)amino tiofen-3-carboxilato (1.05 g, 2.2 mmol) en metanol (10 ml) se trató con hidróxido de sodio (2N, 10 ml) a 75°C durante 1.5 hora. Metanol se evaporó, HCl (2N) se agregó (pH 3), se filtró el sólido, se volvió a disolver en CH_2Cl_2 / MeOH 1/1, se añadió DIEA (1.5 ml, 8.8 mmol), el sólido se retiró por filtración, el filtrado se concentró, y el residuo se disolvió en etanol, se obtuvo el material del título como un sólido (0.7 g, 71 %).

MS ES^+: 445 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.36 (t,2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.79 (t, 2H); 4.03 (d, 2H); 4.08 (s, 3H); 4.35 (t, 2H); 7.45 (s, 1H); 7.81 (s, 1H); 8.03 (s, 1H); 8.50 (s, 1H); 9.15 (s, 1H).

Etil-5-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)aminotiofen-3-carboxilato.

4-cloro-6-metoxi-7-(3-morfolinopropoxi)quinazolina (1 g, 3 mmol) en isopropanol (25 ml) e isopropanol HCl (0.5 ml) se hizo reaccionar con etil 5-aminotiofen-3-carboxilato (0.6 g, 3.3 mmol) a 110°C durante 1 hora. La mezcla se enfrió, se diluyó con EtOAc, se filtró para producir el compuesto del título (1.58 g, 99 %).

MS ES^+: 473 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.33 (t, 3H); 2.33 (t,2H); 3.17 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.75 (t, 2H); 4.03 (d, 2H); 4.06 (s, 3H); 4.30 (q, 2H); 4.33 (t,2H); 7.42 (s, 1H); 7.73 (s, 1H); 8.09 (s, 1H); 8.35 (s, 1H); 9.15 (s, 1H).

Ejemplo 432. Preparación de Compuesto 610 en Tabla 24

Una reacción análoga a la descrita en Ejemplo 309, pero comenzando con 4-fluoroanilina (24 mg, 0.18 mmol) produjo el compuesto del título (20 mg, 22 %).

MS ES^+: 538.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.20 (t, 2H); 3.40 (t, 2H); 3.60 (d, 2H); 3.72 (t, 2H); 4.04 (d, 2H); 4.07 (s, 3H); 4.34 (t, 2H); 7.9 (s, 1H); 7.20 (m, 2H); 7.41 (s, 1H); 7.76 (d, 1H); 7.82 (m, 1H); 8.19 (s, 1H); 8.21 (d, 1H); 9.17 (s, 1H).

Ejemplo 433. Preparación de Compuesto 611 en Tabla 24

Una reacción análoga a la descrita en Ejemplo 309, pero comenzando con 3-hidroxianilina (24 mg, 0.18 mmol) produjo el compuesto del título (15 mg, 17 %).

MS ES^+: 536.6 $(M+H)^+$

Ejemplo 434. Preparación de Compuesto 612 en Tabla 24

Una reacción análoga a la descrita en Ejemplo 309, pero comenzando con 3-(metiltio)anilina (30 mg, 0.18 mmol) produjo el compuesto del título (23 mg, 24 %).

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.56 (d,

2H); 3.69 (t, 2H); 4.04 (m, 5H); 4.33 (t, 2H); 7.24 (t, 1H); 7.32 (t, 1H); 7.41 (s, 1H); 7.43 (m, 2H); 7.72 (d, 2H); 8.16 (m, 2H); 9.17 (s, 1H).

Ejemplo 435. Preparación de Compuesto 613 en Tabla 24

Una reacción análoga a la descrita en Ejemplo 309, pero con 4-fluoro-3-cloroanilina (32 mg, 0.18 mmol) produjo el compuesto del título (21 mg, 21 %). MS ES^+: 577 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.19 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.71 (t, 2H); 4.06 (m, 5H); 4.34 (t, 2H); 7.41 (m, 2H); 7.75 (m, 2H); 8.11 (m, 1H); 8.18 (s, 1H); 8.21 B(s, 1H); 9.18 (s, 1H).

Ejemplo 436. Preparación de Compuesto 614 en Tabla 24

Una reacción análoga a la descrita en Ejemplo 309, pero comenzando con 2,4-difluorobencilamina (31 mg, 0.18 mmol) produjo el compuesto del título (22 rng, 22 %).

MS ES^+: 570.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.34 (t, 2H); 3.19 (t, 2H); 3.39 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 4.06 (m, 5H); 4.34 (t, 2H); 4.51 (s, 2H); 7.06 (t, 1H); 7.15 (t, 1H); 7.40 (s, 1H); 7.48 (m, 1H); 7.69 (d, 1H); 8.03 (d, 1H); 8.17 (s, 1H); 9.14 (s, 1H).

Ejemplo 437. Preparación de Compuesto 615 en Tabla 24

Una reacción análoga a la descrita en Ejemplo 309, pero comenzando con 3-fluoroanilina (24 5 mg, 0.18 mmol) produjo el compuesto del título (27 mg, 29 %).

MS ES^+: 538.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (t, 2H); 3.18 (t, 2H); 3.38 (t, 2H); 3.58 (d, 2H); 3.72 (d, 2H); 4.04 (d, 2H); 4.07 (s, 3H); 4.35 (t, 2H); 6.91 (m, 1H); 7.42 (m, 2H); 7.59 (d, 1H); 7.78 (d, 1H); 7.79 (m, 1H); 8.19 (s, 1H); 8.24 (d, 1H); 9.18 (s, 1H).

Ejemplo 438. Preparación de Compuesto 616 en Tabla 24

Ácido 2-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)amino)imidazol-5-carboxílico (200 mg, 0.47 mmol) en DMF (3 ml) se hizo reaccionar con anilina (43 µl, 0.47 mmol) en presencia de hexafluorofosfato de 0-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (178 mg, 0.47 mmol) y DIEA (120 µl, 0.7 mmol) a 40°C durante 3 horas. Se agregó una solución de dimetilamina en metanol (2M, 1 ml) y se practicó agitación durante 3 horas. El solvente se evaporó, y la mezcla se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2/ MeOH NH_3 (sat.) 95/5 para producir el compuesto del título (80 mg, 34 %).

MS ES^+: 504.1 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.29 (t, 2H); 3.18 (t, 2H); 3.35 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 3.96 (s, 3H); 4.04 (d, 2H); 4.27 (t, 2H); 7.15 (t, 1H); 7.25 (s, 1H); 7.40 (t, 2H); 7.74 (d, 2H); 7.81 (s, 1H); 8.09 (s, 1H); 8.75 (s, 1H).

Ejemplo 439. Preparación de Compuesto 617 en Tabla 25

Una reacción análoga a la descrita en Ejemplo 316, pero comenzando con 4-fluoroanilina (60 µl, 0.58 mmol) produjo el compuesto del título (120 mg, 39 %). MS ES^+: 522.1 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.29 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.55 (d, 1H); 3.69 (t, 2H); 3.96 (s, 3H); 4.04 (d, 2H); 4.27 (t, 2H); 7.22 (m, 3H); 7.74 (m, 2H); 7.82 (s, 1H); 8.07 (s, 1H); 8.76 (s, 1H).

Ejemplo 440. Preparación de Compuesto 618 en Tabla 25

Una reacción análoga a la descrita en Ejemplo 316, pero comenzando con alilamina 50 µl, 0.7 mmol) produjo el compuesto del título (133 mg, 40 %).

MS ES^+: 468.1 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.28 (t, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.94 (m, 5H); 4.04 (d, 2H); 4.26 (t, 2H); 5.14 (dd, 1H); 5.23 (dd, 1H); 5.88 (m, 1H); 7.23 (s, 1H); 7.77 (s, 1H); 7.86 (s, 1H); 8.71 (s, 1H).

Ácido 2-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)amino)imidazol-

5-carboxílico.

Etil-2((4-imino-6-metoxi-7-(3-morfolinoropoxi)quinazolin-3-(4H)-il)imidazol-5-carboxilato (650 mg, 1.42 mmol) en metanol (14 ml) se trató con hidróxido de sodio (2N, 14 ml) a 80°C durante 1.5 hora. Metanol se evaporó, se agregó ácido clorhídrico (6N) (pH 2.5), el precipitado se recuperó por filtración, se secó para producir el compuesto del título (650 mg, 100 %).

^{1}HNMR ($DMSOd_6$, TFA): 2.35 (t, 2H); 3.13 (t, 2H); 3.32 (t, 2H); 3.5 (d, 2H); 3.95 (m, 7H); 4.28 (t, 2H); 7.42 (s, 1H); 7.8 (s, 1H); 7.86 (s, 1H); 8.72 (s, 1H).

Ejemplo 441. Preparación de Compuesto 619 en Tabla 26

4-cloro-6-metoxi-7-(3-morfolinopropoxi)quinazolina (265 mg, 0.79 mmol) en 2-propanol (14 ml) se hizo reaccionar con clorhidrato de 4-amino-N-feniltiofen-3-carboxamida (210 mg, 0.82 mmol) a 100°C durante 2 horas. El solvente se evaporó y el residuo se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH, NH_3 sat. 95/5 para producir el compuesto del título (330 mg, 81 %).

MS ES^+: 520.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.30 (t, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 4.03 (s, 3H); 4.04 (d, 2H); 4.32 (t, 2H); 7.13 (t, 1H); 7.35 (t, 2H); 7.39 (s, 1H); 7.69 (d, 2H); 7.79 (s, 1H); 8.13 (d, 1H); 8.58 (d, 1H); 8.95 (s, 1H).

4-(tert-butoxicarbonilamino-N-feniltiofen-3-carboxamida.

Ácido 4-(tert-butoxicarbonilamino)tiofen-3-carboxílico obtenido por un procedimiento de la literatura, Tetrahedron Letters 1997, 2637, (385 mg, 1.58 mmol) en DMF (5 ml) se hizo reaccionar con anilina (140 µl, 1.58 mmol) en presencia de hexafluorofosfato de 0-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (602 mg, 1.58 mmol) a 40°C durante 7 horas. El solvente se evaporó, y el residuo se purificó por cromatografía de gel de sílice, eluyente éter de petróleo / AcOEt: 80/20 para producir el compuesto del título (348 mg, 70 %).

^{1}HNMR ($CDCl_3$): 1.50 (s, 9H); 7.19 (t, 1H); 7.39 (t, 2H); 7.54 (d, 2H); 7.69 (s, 2H); 7.71 (s, 1H); 9.45 (s, 1H).

4-amino-N-feniltiofen-3-carboxamida.

4-(tert-butoxicarbonilamino)-N-feniltiofen-3-carboxamida (300 mg, 0.94 mmol) en CH_2Cl_2 (3 ml) se trató con TFA (0.36 ml, 4.71 mmol) a temperatura ambiente durante 2.5 horas. El solvente se evaporó, el residuo se disolvió en metanol / HCl, se agregó a la solución, el precipitado se recuperó para producir el compuesto del título (210 mg, 87 %) el cual se empleó en el siguiente paso.

Ejemplo 442. Preparación de Compuesto 620 en Tabla 26

Una reacción análoga a la descrita en Ejemplo 319, pero comenzando con 4-amino-N-aliltiofen-3-carboxamida (218 mg, 1.06 mmol) produjo el compuesto del título (366 mg, 75 %).

MS ES^+: 484.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.28 (t,2H); 3.15 (t,2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.95 (d, 2H); 4.03 (m, 5H); 4.32 (t, 2H); 5.14 (dd, 1H); 5.24 (dd, 1H); 5.91 (m, 1H); 7.41 (s, 1H); 7.59 (s, 1H); 8.28 (d, 1H); 8.51 (d, 1H); 9.04 (s, 1H). 4-tert-butoxicarbonilamino)- N-aliltiofen-3-carboxamida.

Una reacción análoga a la descrita en Ejemplo 319, pero comenzando con alilamina (150 µl, 2.06 mmol) produjo el compuesto del título (385 mg, 66 %).

^{1}HNMR ($CDCl_3$): 1.51 (s, 9H); 4.04 (m, 2H); 5.21 (dd, 1H); 5.29 (dd, 1H); 5.92 (m, 1H); 6.1 (m, 1H); 7.54 (d, 1H); 7.64 (m, 1H); 9.64 (s, 1H).

4-amino-N-aliltiofen-3-carboxamida.

Una reacción análoga a la descrita en Ejemplo 319, pero comenzando con 4-tert-butoxicarboxilamino-N-aliltiofen-3-carboxamida (320 mg, 1.13 mmol) produjo el compuesto del título (218 mg, 94 %) el cual se usó en el estado actual en el siguiente paso.

Ejemplo 443. Preparación de Compuesto 621 en Tabla 27

4-cloro-6-metoxi-7-(3-morfolinopropoxi)quinazaolina (100 mg, 0.29 mmol) en isopropanol (5 ml). se hizo reaccionar con metil-4-amino-tiofen-4-carboxilato clorhidrato (63.6 mg, 0.33 mmol) a reflujo durante 1 hora. Se agregó acetato de etilo a la mezcla de reacción, se recuperó el sólido por filtración, se secó, para producir el compuesto del título (140 mg, 89, %).

MS ES^+: 459.1 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.39 (t, 2H); 3.19 (t, 2H); 3.40 (t, 2H); 3.58 (d, 2H); 3.77 (m, 5H); 4.06 (m, 5H); 4.37 (t, 2H); 7.42 (s, 1H); 7.95 (s, 1H); 8.01 (d, 1H); 8.49 (d, 1H); 8.93 (s, 1H).

Ejemplo 444. Preparación de Compuesto 624 en Tabla 28

4-cloro-6-metoxi-7-(3-morfolinopropoxi)quinazolina (110 mg, 0.3 mmol) en 2-pentanol (5 ml) e isopropanol / HCl (55 µl) se hizo reaccionar con 2-amino-5-isopropiltiofen-3-carboxamida (60 mg, 0.33 mmol) a 100°C durante 1 hora, éter y acetato de etilo se agregaron a la mezcla, el precipitado se filtró para producir el compuesto del título (155 mg, 93 %).

MS ES^+: 486.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.38 (d, 6H); 2.38 (t, 2H); 3.20 (m, 3H); 3.38 (t, 2H); 3.57 (d, 2H); 3.82 (t, 2H); 4.05 (d, 2H); 4.08 (s, 3H); 4.39 (t, 2H); 7.40 (s, 1H); 7.47 (s, 1H); 7.52 (s, 1H); 9.23 (s, 1H).

Ejemplo 445. Preparación de Compuesto 623 en Tabla 28

Una reacción análoga a la descrita en Ejemplo 322, pero comenzando con alil-5-aminotiofen-2-carboxilato (67 mg, 0.33 mmol) a 100° C durante 2 horas produjo el compuesto del título (151 mg, 85 %).

MS ES^+: 485.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.38 (t,2H); 3.18 (t, 2H); 3.38 (t, 2H); 3.57 (d, 2H); 3.80 (t, 2H); 4.06 (d, 2H); 4.12 (s, 3H); 4.38 (t, 2H); 4.84 (d, 2H); 5.33 (d, 1H); 5.45 (d, 1H); 6.10 (m, 1H); 7.48 (s, 1H); 7.65 (d, 1H); 7.84 (d, 1H); 8.64 (s, 1H); 9.30 (s, 1H).

Ejemplo 446. Preparación de Compuesto 624 en Tabla 28

Una reacción análoga a la descrita en Ejemplo 322, pero comenzando con 2-aminotiofen-3-carboxamida (46 mg, 0.33 mmol) produjo el compuesto del título (154 mg, 99 %).

MS ES^+: 444.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.34 (t, 2H); 3.15 (t, 2H);.3.36 (t, 2H); 3.54 (d, 2H); 3.76 (t, 2H); 4.02 (d, 2H); 4.05 (s, 3H); 4.36 (t, 2H); 7.32 (d, 1H); 7.41 (s, 1H); 7.48 (s, 1H); 7.66 (d, 1H); 9.23 (s, 1H).

Ejemplo 447. Preparación de Compuesto 625 en Tabla 28

Una reacción análoga a la descrita en Ejemplo 322, pero comenzando con 2-amino-5-etiltiofen-3-carboxamida (55 mg, 0.33 mmol) produjo el compuesto del título (147 mg, 90 %).

MS ES^+: 472.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.34 (t, 3H); 2.38 (t, 2H); 2.86 (q, 2H); 3.18 (t,2H); 3.38 (t,2H); 3.57 (d, 2H); 3.80 (t, 2H); 4.05 (d,2H); 4.07 (s, 3H); 4.38 (t, 2H); 7.40 (s, 1H); 7.43 (s, 1H); 7.52 (s, 1H); 9.21 (s, 1H).

Ejemplo 448. Preparación de Compuesto 626 en Tabla 29

Metil-2-ciano-4-metoxi-5-(3-morfolinopropoxi)fenilimidoformato (100 mg; 0.3 mmol) en DMF (1.5 ml) se hizo reaccionar con 2-amino-4-fenil-1,3-tiazol (58 mg; 0.33 mmol) en presencia de hidruro de sodio (13.2 mg; 0.33 mmol) a 75°C durante 1.5 horas. Se agregó ácido acético (1.5 eq.) y el solvente se.evaporó para producir 6-metoxi-7-(3-momorfolinopropoxi)-3-(4-fenil-1,3-tiazol-2-il)quinazolin-4(3H)-imina como un intermedio que se volvió a disolver en DMF (1.5 ml) y se agregó acetato de amonio (95 mg; 0.9 mmol). La mezcla se agitó a 75°C durante 1 hora, el solvente se evaporó y el residuo se purificó por cromatografía de gel de sílice, CH_2Cl_2/MeOH 95/5 → 90/10 para producir el compuesto del título (44 mg, 31 %).

^{1}HNMR ($DMSOd_6$, TFA): 2.30 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H) 20; 4.05 (m, 5H); 4.33 (t, 2H); 7.42 (m, 2H); 7.51 (t, 2H);

7.90 (s, 1H); 8.00 (d, 2H); 8.35 (s, 1H); 9.27 (s, 1H).

Ejemplo 449. Preparación de Compuesto 627 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con 2-amino-4-metil-5-acetil-1,3-tiazol (103 mg, 0.66 mmol), calentando a 75°C durante 1 hora en el primer paso, y agitando el intermedio en las condiciones anteriores a temperatura ambiente durante 1 hora, produjo el compuesto (71 mg, 52 %).

MS ES^+: 458 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 2.55 (s, 3H); 2.67 (s, 3H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.0 (*s*, 3H); 4.03 (d, 2H); 4.32 (t, 2H); 7.37 (s, 1H); 7.99 (s, 1H); 9.26 (*s*, 1H).

Ejemplo 450. Preparación de Compuesto 628 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con etil-2-amino-4-trifluorometil-1,3-tiazol-5-carboxilato (79 mg, 0.33 mmol) produjo el compuesto del título (81 mg, 50 %).

MS ES^+: 542 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.34 (t, 3H); 2.32 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.03 (s, 3H); 4.04 (d, 2H); 4.36 (m, 4H); 7.47 (s, 1H); 8.41 (s, 1H); 9.34 (s, 1H).

Ejemplo 451. Preparación de Compuesto 629 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con etil-2-amino-4-fenil-1,3-tiazol-5-carboxilato (82 mg, 0.33 mmol) produjo el compuesto del título (133 mg, 81 %).

MS ES^+: 550 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.25 (t, 2H); 2.32 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.02 (s, 1H); 4.04 (d, 2H); 4.26 (q, 2H); 4.35 (t, 2H); 7.45 (s, 1H); 7.50 (m, 3H); 7.79 (m, 2H); 8.33 (s, 1H); 9.37 (s, 1H).

Ejemplo 452. Preparación de Compuesto 630 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con 4,5,6,7-tetrahydro-1,3-benzotiazol-2-amina (51 mg, 0.33 mmol) produjo el compuesto del título (97 mg, 71 %).

MS ES^+: 456 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.83 (m, 4H); 2.29 (t, 2H); 2.61 (m, 2H); 2.67 (m, 2H); 3.15 (t, 25 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.97 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 7.28 (s, 1H); 7.84 (s, 1H); 9.0 (s, 1H).

Ejemplo 453. Preparación de Compuesto 631 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con N-(4-(2-amino-1,3-tiazol-4-il)fenil)acetamida (77 mg, 0.33 mmol) produjo el compuesto del título (58 mg, 36 %).

MS ES^+: 535 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.09 (s, 3H); 2.32 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 4.05 (s, 3H); 4.06 (d, 2H); 4.35 (t, 2H); 7.40 (s, 1H); 7.72 (d, 2H); 7.77 (s, 1H); 7.92 (d, 2H); 8.33 (s, 1H); 9.25 (s, 1H).

Ejemplo 454. Preparación de Compuesto 632 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con 5-fenil-4-(trifluorometil)-1,3-tiazol-2-amina (81 mg, 0.33 mmol) produjo el compuesto del título (144 mg, 88 %).

MS ES^+: 546 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.04 (d, 2H); 4.05 (s, 3H); 4.36 (t, 2H); 7.49 (s, 1H); 7.54 (s, 5H); 8.46 (s, 1H); 9.30 (s, 1H).

Ejemplo 455. Preparación de Compuesto 633 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con 4-(trifluorometil)-1,3-tiazol-2-amina (55 mg, 0.33 mmol) produjo el compuesto del título (62 mg, 44 %).

MS ES^+: 470 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.04 (s, 3H); 4.05 (d, 2H); 4.36 (t, 2H); 7.49 (s, 1H); 8.23 (s, 1H); 8.44 (s, 1H); 9.34 (s, 1H).

Ejemplo 456. Preparación de Compuesto 634 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con 4-tert-butil-1,3- tiazol-2-amina (52 mg, 0.33 mmol) produjo el compuesto del título (90 mg, 65 %).

MS ES^+: 458 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.46 (s, 9H); 2.32 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.00 (s, 3H); 4.03 (d, 2H); 4.32 (d, 2H); 7.38 (s, 1H); 7.95 (s, 1H); 9.18 (s, 1H).

Ejemplo 457. Preparación de Compuesto 635 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con 4,5-dimetil-1,3-tiazol-2-amina (42 mg, 0.33 mmol) produjo el compuesto del título (61 mg,47 %).

MS ES^+: 430 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.25 (s, 3H); 2.30 (m, 5H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.96 (s, 3H); 4.04 (d, 2H); 4.28 (t, 1H); 7.28 (s, 1H); 7.82 (s, 1H); 8.98 (s, 1H).

Ejemplo 458. Preparación de Compuesto 636 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con 4-metil-1,3-tiazol-2-amina (38 mg, 0.33 mmol) produjo el compuesto del título (40 mg, 32 %).

MS ES^+: 415 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H); 2.34 (s, 3H); 3.15 (t, 2H); 3.37 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3.99 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 7.03 (s, 1H); 7.29 (s, 1H); 7.87 (s, 1H); 9.05 (s, 1H).

Ejemplo 459. Preparación de Compuesto 637 en Tabla 29

1-(2-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)amino)-4-metil-1,3-tiazol-5- il)etanona (50 mg, 0.11 mmol) en etanol (4 ml) y piridina (1 ml) se hizo reaccionar con hidroxilamina clorhidrato (19.5 mg, 0.27 mmol) a reflujo durante 3 horas. El solvente se evaporó, se agregó agua al residuo y se recuperó un sólido, se lavó con agua para producir el compuesto del título (14 mg, 27 %)

MS ES^+: 473 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.25 (s, 3H); 2.30 (t, 2H); 2.53 (s, 3H); 3.17 (t, 2H); 3.38 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 3.99 (s, 3H); 4.05 (d, 2H); 4.32 (t, 2H); 7.32 (s, 1H); 7.88 (s, 1H); 9.12 (s, 1H).

Ejemplo 460. Preparación de Compuesto 638 en Tabla 29

Ácido 2-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)amino)-1,3-tiazol-5-carboxílico (89 mg, 0.2 mmol) en DMF (1.5 ml) se trató con difenilfosforil azida (66 mg, 0.24 mmol) y trietilamina (26 mg, 0.26 mmol). La solución se agitó a temperatura ambiente durante 1 hora y a 45°C durante 1 hora. Se adicionó tert-butanol (1 ml), y la mezcla se calentó a 90°C durante 2 horas. Se diluyó la mezcla con acetato de etilo, bicarbonato de sodio acuoso, se recuperó la fase orgánica, se secó sobre $MgSO_4$, se filtró, concentró y purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH 95/5 a 85/15 para producir el compuesto del título cómo un sólido amarillo (25 mg, 24 %).

MS ES^+: 517 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.50 (s, 9H); 2.31 (t, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.69 (t,2H); 3.97 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 7.13 (s, 1H); 7.26 (s, 1H); 7.94 (5, 1H); 9.11 (s, 1H).

Ejemplo 461. Preparación de Compuesto 639 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 337, pero comenzando con 0- metilhidroxilamina clorhidrato (18 mg, 0.22 mmol) y calentando a reflujo durante 72 horas produjo el compuesto del título (39 mg, 63 %).

MS ES$^+$: 487 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.26 *(s,* 3H); 2.31 (t, 2H); 3.53 (s, 3H); 3.16 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.76 (s, 2H); 3.94 *(s,* 3H); 3.99 (s,3H); 4.02 (d, 2H); 4.33 (t, 2H); 7.35 (s, 1H); 7.89 *(s,* 1H); 9.11 (s, 1H).

Ejemplo 462. Preparación de Compuesto 640 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 339, pero comenzando con 0-fenilhidroxilamina clorhidrato (32 mg, 0.22 mmol) produjo el compuesto del título (8 mg, 12 %).

MS ES$^+$: 549 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.28 (t, 2H); 3.12 (t, 2H); 3.32 (t, 2H); 3.52 (d, 2H); 3.65 (t, 2H); 3.96 (s, 3H); 4.0 (d, 2H); 4.27 (t, 2H); 7.06 (t, 1H); 7.20 (d, 2H); 7.28 (s, 1H); 7.34 (t, 2H); 7.91 *(s,* 1H); 9.17 *(s,* 1H).

Ejemplo 463. Preparación de Compuesto 641 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con 2-amino-5-(4-metoxifenil)-1,3-tiazol, HBr (86 mg, 0.33 mmol) produjo el compuesto del título (105 mg, 77 %).

MS ES$^+$: 508.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (t, 2H); 3.20 (t, 2H); 3.40 (t, 2H); 3.60 (d, 2H); 3.73 (t,2H); 3.86 (s, 3H); 4.08 (s, 3H); 4.09 (d, 2H); 4.36 (t, 2H); 7.10 (d, 2H); 7.44 (s, 1H); 7.76 (s, 1H); 7.96 (d, 2H); 8.33 (s, 1H); 9.26 (s, 1H).

Ejemplo 464. Preparación de Compuesto 642 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con 2-amino-5-FenIL)-1,3-tiazol (58 mg, 0.33 mmol) produjo el compuesto del título (120 mg, 84 %).

MS ES$^+$: 478.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 4.01 (s, 3H); 4.05 (d, 2H); 4.32 (t, 2H); 7.34 (s, 1H); 7.41 (t, 1H); 7.51 (t,2H); 7.72 (d, 2H); 7.97 (s, 1H); 8.24 (s, 1H); 9.16 (s, 1H).

Ejemplo 465. Preparación de Compuesto 643 en Tabla 29

Metil-2-ciano-4-metoxi-5-(3-morfolinopropoxi)fenil-imidoformato (300 mg, 0.9 mmol) en DMF (4.5 ml) se hizo reaccionar con 2-amino-5-etil-1,3-tiazol (127 mg, 0.99 mmol) en presencia de hidruro de sodio (39.6 mg, 0.99 mmol) a 75°C durante 2 horas. Se añadió ácido acético (77 µl, 1.35 mmol) a la mezcla a temperatura ambiente, seguido por MeOH/Me_2NH (2M) (90 µl, 0.18 mmol) y la mezcla se agitó a 75°C durante 1 hora. El solvente se evaporó y la mezcla se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2/MeOH 95/5 → 90/10 para producir el compuesto del título (193 mg, 50 %).

MS ES^+: 430.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.29 (t, 3H); 2.32 (t, 2H); 2.81 (q, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 3.98 (s, 3H); 4.05 (d, 2H); 4.30 (t, 2H); 7.30 (s, 1H); 7.50 (s, 1H); 7.87 (s, 1H); 9.04 (s, 1H).

Ejemplo 466. Preparación de Compuesto 644 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 343, pero comenzando con 2-amino-5-isopropil)-1,3-tiazol (141 mg, 0.99 mmol) produjo el compuesto del título (107 mg, 26 %).

MS ES^+: 444.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.33 (d, 6H); 2.32 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3.98 (s, 3H); 4.04 (d, 2H); 4.30 (t, 2H); 7.29 (s, 1H); 7.49 (s, 1H); 7.87 (s, 1H); 9.05 (s, 1H).

Ejemplo 467. Preparación de Compuesto 645 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 343, pero comenzando con 2-amino-5-bencil)-51,3-tiazol (188 mg, 0.99 mmol) produjo el compuesto del título (370 mg, 84 %).

MS ES^+: 492.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t,2H); 3.16 (t, 2H); 3.35,(t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3.98 (s, 3H); 4.04 (d, 2H); 4.18 (s, 2H); 4.29 (t, 2H); 7.27 (s, 1H); 7.28 (m, 1H); 7.35 (m, 4H); 7.61 (s, 1H); 7.88 (s, 1H); 9.02 (s, 1H).

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Ejemplo 468. Preparación de Compuesto 646 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 343, pero comenzando con 2-amino-5-metil)-1,3-tiazol (113 mg, 0.99 mmol) produjo el compuesto del título (300 mg, 80 %).

MS ES^+: 416.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H); 2.42 (s, 3H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.97 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 1.30 (s, 1H); 7.48 (s, 1H); 7.86 (s, 1H); 9.03 (s, 1H).

Ejemplo 469. Preparación de Compuesto 647 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 343, pero comenzando con 2-amino-5-butil)-1,3-tiazol (155 mg, 0.99 mmol) produjo el compuesto del título (385 mg, 93 %).

MS ES^+: 458.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 0.93 (t, 3H); 1.36 (m, 2H); 1.64 (m, 2H); 2.29 (t, 2H); 2.79 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.97 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 7.29 (s, 1H); 7.51 (s, 1H); 7.86 (s, 1H); 9.03 (s, 1H).

Ejemplo 470. Preparación de Compuesto 648 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 343, pero comenzando con 2-amino-5-formil-1,3-tiazol (499.4 mg, 3.9 mmol) produjo el compuesto del título (244 mg, 39 %).

MS ES^+: 430.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 4.03 (s, 3H); 4.06 (d, 2H); 4.35 (t, 2H); 7.45 (s,1H); 8.12 (s, 1H); 8.71 (s, 1H); 9.32 (s, 1H).

Ejemplo 471. Preparación de Compuesto 649 en Tabla 29

Una reacción análoga a la descrita en Ejemplo 337, pero comenzando con 2-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)amino-1,3-tiazol-5-carbaldehído (100 mg, 0.23 mmol) y calentando a 80°C durante 4 horas,

produjo el compuesto del título (21 mg, 20 %).

MS ES^+: 445.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H) 4.00 (s, 3H); 4.05 (d, 2H); 4.32 (t, 2H); 7.36 (s, 1H); 7.92 (s, 1H); 7.98 (s, 1H); 8.33 (s, 1H); 9.20 (s, 1H).

Ejemplo 472. Preparación de Compuesto 650 en Tabla 30

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con 2-amino-5-tert-butil-1,3,4-tiadiazol (52 mg, 0.33 mmol) produjo el compuesto del título (80 mg, 58 %).

MS ES^+: 458 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.45 (s, 9H); 2.32 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.00 (s, 3H); 4.03 (d, 2H); 4.32 (t, 2H); 7.38 (s, 1H); 7.95 (s, 1H); 9.18 (s, 1H).

Ejemplo 473. Preparación de Compuesto 651 en Tabla 30

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con 20 2-amino-5- cyclopropyl-l,3,4-tiadiazol (47 mg, 0.33 mmol) produjo el compuesto del título (105 mg, 83 %).

MS ES^+: 443 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.08 (m, 2H); 1.23 (m, 3H); 2.32 (t, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.99 (s, 3H); 4.04 (d, 2H); 4.32 (t, 2H); 7.38 (s, 1H); 7.93 (s, 1H); 9.14 (s, 1H).

Ejemplo 474. Preparación de Compuesto 652 en Tabla 30

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con 2-amino-5-etiltio-1,3,4-tiadiazol (53 mg, 0.33 mmol) produjo el compuesto del título (103 mg, 75 %).

MS ES^+: 463 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.41 (t, 3H); 2.31 (t, 2H); 3.15 (t, 2H); 3.31 (q, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.00 (s, 3H); 4.04 (d, 2H); 4.33 (t, 2H); 7.41 (s, 1H); 8.08 (s, 1H); 9.19 (s, 1H).

Ejemplo 475. Preparación de Compuesto 653 en Tabla 30

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con 2-amino-5-fenil-1,3,4-tiadiazol (91 mg, 0.33 mmol) produjo el compuesto del título (110 mg, 76 %).

MS ES^+: 479 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.16 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.69 (t, 2H); 4.03 (s, 3H); 4.05 (d, 2H); 4.34 (t, 2H); 7.42 (s, 1H); 7.61 (m, 3H); 7.99 (m, 2H); 8.06 (s, 1H); 9.25 (s, 1H).

Ejemplo 476. Preparación de Compuesto 654 en Tabla 30

Una reacción análoga a la descrita en Ejemplo 326, pero comenzando con N-fenil-4H-1,2,4- triazol-3,5-diamina (58 mg, 0.33 mmol) produjo el compuesto del título (70 mg, 49 %).

MS ES^+: 477 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.16 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 4.02 (s, 3H); 4.05 (d, 2H); 4.34 (t, 2H); 6.92 (t, 1H); 7.30 (t, 1H); 7.42 (s, 1H); 7.58 (d, 2H); 8.19 (s, 1H); 8.95 (s, 1H).

Biological Data

Los compuestos de la invención inhiben la actividad serina/treonina cinasa de la cinasa aurora2 y, en consecuencia, inhiben el ciclo celular y la proliferación de la célula. Estas propiedades pueden evaluarse por ejemplo, empleando uno o más de los procedimientos expuestos a continuación:

a) **Prueba de inhibición de cinasa aurora2**

Este ensayo determina la capacidad de un compuesto de prueba para inhibir actividad serina/treonina cinasa. El ADN que codifica aurora2 puede obtenerse por síntesis genética total o por clonado. Este ADN puede expresarse entonces en un sistema apropiado de expresión para obtener polipéptido con actividad serina/treonina cinasa. En el caso de aurora2, la secuencia codificadora se aisló de cADN mediante reacción en cadena la

polimerasa (PCH) y se clonó en los sitios de endonucleasa de restricción BamHl y Notl del vector de expresión del baculovirus pFastBac HTc (GibcoBRL/Life technologies). El cebador PCR 5' contenía una secuencia de reconocimiento para la endonucleasa de restricción BamHI 5' a la secuencia codificadora de aurora2. Esto permitió la inserción del gen aurora2 en un marco con los 6 residuos de histidina, región espaciadora y el sitio de escisión de proteasa rTEV codificado por el vector pFastBac HTc. El cebador PCR 3' reemplazó el codón de terminación de aurora2 con secuencia codificadora adicional seguida por un codón de terminación y una secuencia de reconocimiento para la endonucleasa de reastricción Notl. Esta secuencia codificadora adicional (5' TAC CCA TAC GAT GTT CCA GAT TAC GCT TCT TAA 3') codificó la secuencia polipeptídica YPYDVPDYAS. Esta secuencia, derivada de la proteína hemaglutina de la influenza, se emplea con frecuencia como una secuencia identificadora de epítopos que puede identificarse empleando anticuerpos monoclonales específicos. El vector pFastBac de recombinante codificó en consecuencia una proteína aurora2 marcada terminalmente C de epítopos de hemaglutina de influenza, marcada terminalmennte N. Detalles de los métodos para el ensamble de moléculas AND recombinante pueden encontrarse en textos estándar, por ejemplo Sambrook y colaboradores, 1989, Molecular Cloning - A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory press y Ausubel y colaboradores, 1999, Current Protocols in Molecular Biology, John Wiley and Sons Inc.

Producción de virus recombinante puede efectuarse siguiendo el protocolo del fabricante de GibcoBRL. Brevemente, el vector pFastBac-l que porta el gen aurora2 se transformó en células DH10Bac de E. coli que contienen el genoma del baculovirus (ADN bacmid) y mediante un evento de transposición en las células, una región del vector pFastBac que contiene gen de resistencia a la gentamicina y el gen aurora2 que incluye el promotor de polihedrina se transpuso directamente en el ADN bacmid. Mediante selección de en gentamicina, kanamicina, tetraciclina y X-gal, las colonias blancas resultantes deben contener AND bacmid recombinante que codifica

aurora2. AND bacmid se extrajo de un cultivo a pequeña escala de varias colonias blancas BH10Bac y se transfectaron en células de Spodoptera frugiperda Sf21 cultivadas en medio TC100 (GibcoBRL) que contenía 10% de suero empleando reactivo CellFECTIN (GibcoBRL) siguiendo las instrucciones del fabricante. Se cosecharon partículas de virus recogiendo el medio de cultivo de las células 72 horas después de la transfección. Se emplearon 0.5 ml de medio para infectar 100 ml de cultivo en suspensión de Sf21s que contenía 1 x 10^7 células/ml. El medio de cultivo de las células se cosechó 48 horas después de la infección y se determinó el título del virus utilizando en procedimiento de ensayo de placas estándar. Se emplearon stocks virales para infectar células Sf9 y "High 5" con una multiplicidad de infección (MOI) de 3 para determinar expresión de proteína aurora2 recombinante. Para la expresión a gran escala de actividad aurora2 cinasa, se cultivaron células de insecto a 28°C en medio TC100 suplementado con 10% de suero de ternero fetal (Viralex) y 0.2% F68 Pluronic (Sigma) en un aparejo de rodillos Wheaton [roller rig] a 3 r.p.m. Cuando la densidad de las células alcanzó 1.2x10^6 células ml^{-1} se infectaron con virus recombinante aurora2 puro de placas en una multiplicidad de infección de 1 y se cosecharon 48 horas después. Todos los pasos de purificación subsiguientes se realizaron a 4°C. Comprimidos de células de insecto que contenían un total de 2.0 x 10^8 células se descongelaron y diluyeron con una solución amortiguadora de lisis (25 mM HEPES ácido (N-[2-hidroxietil]piperazin-N'-[2-etanosulfónico]) pH 7.4 a 4°C, 100 mM KCl, 25 mMNaF, 1 mMNa_3VO_4, 1 mM PMSF (fenilmetilsulfonil fluoruro), 2 mM 2-mercaptoetanol, 2 mM imidazol, 1 µg/ml aprotinina, 1 µg /ml pepstatina, 1 µg/ml leupeptina), empleando 1.0 ml por 3 x 10^7 células. La lisis se logró utilizando un homogenizador Dounce, luego de lo cual el lisado se centrífugo a 41,000g durante 35 minutos. El sobrenadante aspirado se bombeó en una columna de cromatografía de 5 mm diámetro que contenía 500 µg Ni NTA (ácido nitrilo-triacético) agarosa (Qiagen, producto No. 30250) que había sido equilibrado en solución amortiguadora de lisis. Un nivel de línea base de absorbancia UV para el eluyente se alcanzó luego de

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lavar la columna con 12 ml de solución amortiguadora de lisis seguida por 7 ml de solución amortiguadora de lavado (25 mM HEPES pH 7.4 a 4°C, 100 mM KCl, 20 mM imidazol, 2 mM 2-mercaptoetanol). La proteína aurora2 enlazada se eluyó de la columna utilizando solución amortiguadora de elución (25 mM HEPES pH 7.4 a 4°C, 100 mM KCl, 400 mM imidazol, 2 mM 2-mercaptoetanol). Se recogió la fracción de elución (2.5 ml) correspondiente al pico en absorbancia UV. La fracción de elución que contenía la cinasa aurora2 activa se dializó exhaustivamente contra la solución amortiguadora de diálisis (25 mM HEPES pH 7.4 a 4°C, 45% glicerol (v/v), 100 mM KCl, 0.25% Nonidet P40 (v/v), 1 mM ditiotreitol).
Cada nuevo lote de enzima aurora2 se tituló en el ensayo mediante dilución con diluyente enzimático (25mM Tris-HCl p H7.5, 12.5 mM KCl, 0.6mM DTT). Para un lote típico, la enzima stock se diluye 1 en 666 con diluyente enzimático y 20 µl de enzima diluto se emplea para cada pozo de ensayo. Los compuestos de prueba (a 10mM en dimetilsulfóxido (DMSO)) se diluyeron con agua y 10 µl de compuesto diluido se transfirieron a pozos en las placas de ensayo. Pozos de control "Totales" & "blancos" contenían 2.5% DMSO en vez de compuesto. Se agregaron veinte microlitros de enzima recién diluida a todos los pozos, aparte de los pozos "blancos". Veinte microlitros de diluyente enzimático se agregaron a los pozos "blancos". Veitne microlitros de mezcla de reacción (25mM Tris-HCl, 78.4 mM KCl, 2.5 mM NaF, 0.6 mM ditiotreitol, 6.25 mM $MnCl_2$, 6.25 mM ATP, 7.5 µM de sustrato peptídico [biotina-LRRWSLGLRRWSLGLRRWSLGLRRWSLG]) que contenía 0.2µCi [γ^{33}]ATP (Amersham Pharmacia, actividad específica ≥2S00Ci/mmol) se añadió entonces a todos los pozoz de prueba para iniciar la reacción. Las placas se incubaron a temperatura ambiente durante 60 minutos. Para detener la la reacción se añadieron 100 µl 20% v/v de ácido ortofosfórico a todos los pozos. El sustrato peptídico se capturó en nitrocelulosa cargada positivamente P30 filtermat (Whatman) usando un cosechador de placas de 96 pozos (TomTek) & luego se ensayaron para detectar incorporación de ^{33}P con un contador de placa Beta. Se utilizaron valores de control

"Blanco" (sin enzima) y "total" (sin compuesto) para determinar el rango de dilución del compuesto de prueba los cuales arrojaron 50% de inhibición de la actividad enzimática. En esta prueba, el compuesto 52 en Tabla 2 produjo 50% de inhibición de actividad enzimática con una concentración de 0.167μM, y compuesto 253 en Tabla 21 arrojó 50% de inhibición de actividad enzimática at 0.089μM.

(a) **Ensayo de proliferación de células In Vitro**

Este ensayo determina la capacidad de un compuesto de prueba para inhibir el crecimiento de líneas de células mamíferas adherentes, por ejemplo, la línea de células tumorales humanos MCF7.

MCF-7 (ATCC HTB-22) u otras células adherentes se sembraron típicamente a 1 x 10^3 células por pozo (excluyendo los pozos periféricos) en DMEM (Sigma Aldrich) sin rojo fenol, más 10% de suero de ternero fetal, 1% L-glutamina y 1 % penicilina/estreptomicina en placas transparentes de 96 pozos tratadas con cultivo de tejido (Costar). Al día siguiente (día 1), el medio se retiró de un placa de control sin tratamiento y la placa se almacenó a -80°C. Las placas restantes se dosificaron con compuesto (diluido de 10mM de stock en DMSO usando DMEM (sin rojo fenol, 10% FCS, 1 % L-glutamina, 1 % penicilina/estreptomicina). Pozos de control no tratados se incluyeron en cada placa. Después de 3 días en la presencia / ausencia de compuesto (día 4) el medio se retiró y las placas se almacenaron a -80°C. Veinticuatro horas después, las placas se descongelaron a temperatura ambiente y se determinó la densidad de las células usando el estuche de ensayo de proliferación de c{elulas CyQUANT (c-7026/c-7027 Molecular Probes Inc.) de acuerdo con las indicaciones del fabricante. Brevemente, 200μl de una lisis de células / mezcla de tinte (10μl de solución amortiguadora de lisis de células 20X B, 190μl de agua esterilizada, 0.25μl de tinte CYQUANT GR) se agregaron a cada pozo y las placas se incubaron a temperatura ambiente durante 5 minutos en la oscuridad. La fluorescencia de los pozos se midió entonces usando un lector de microplaca de fluorescencia (ganancia 70, 2 lecturas por pozo, 1 ciclo con

excitación 485nm y emisión 530nm usando un lector de placa CytoFluor (perSeptive Biosystems Inc.)). Los valores del día 1 y el día 4 (compuesto tratado) junto con los valores de las células no tratadas se emplearon para determinar el rango de dilución de un compuesto de prueba que arrojó 50% de inhibición de la proliferación de las células. El Compuesto 52 en Tabla 2 fue efectivo en esta prueba a 0.616 μM y el Compuesto 253 en Tabla 20 fue efectivo a 5.9μM.

Estos valores podrían usarse también para calcular el rango de dilución de un compuesto de prueba al cual la densidad de las células cayó por debajo del valor de control del día 1. Esto indica la citotoxicidad del compuesto.

(a) <u>Ensayo de análisis del ciclo cellular In Vitro</u>

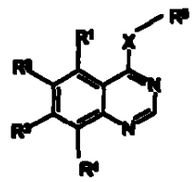
Este ensayo determina la capacidad de un compuesto de prueba para detener células en fases específicas del ciclo celular. En este ensayo podrían emplearse muchas líneas diferentes de células de mamífero y en este caso se incluyen células MCF7 a manera de ejemplo. Células MCF-7 se sembraron a 3 x 10^5 células por botella T25 tlask (Costar) e 5 ml DMEM (no rojo fenol 10% FCS, 1% L-glutamina 1% penicilina / estreptomicina). Seguidamente las botellas se incubaron de un día para otro en un incubador humidificado a 37°C con 5% CO_2. Al día siguiente se añadió a la botella 1ml de DMEM (no rojo fenol 10% FCS, 1% L-glutamina 1% penicilina / estreptomicina) que llevaba la concentración apropiada del compuesto de prueba solubilizado en DMSO. También se incluyeron tratamientos de control sin compuesto (0.5% DMSO). Las células se incubaron a continuación durante un tiempo definido (usualmente 24 horas) con compuesto. Pasado este tiempo, el medio se aspiró de las células y éstas se lavaron con 5ml de PBSA estéril precalentado (37°C), luego se aislaron de la botella mediante breve incubación con tripsina y seguida por resuspensión en 10ml de 1% de Albúmina de Suero Bovino 1 % (BSA, Sigma-Aldrich Co.) en PBSA estéril. Luego se centrifugaron las muestras a 2200 rpm durante 10 minutos. El sobrenadante se aspiró y el comprimido

de células se resuspendió en 200 µl de 0.1 % (w/v) Tris citrato de sodio, 0.0564% (w/v) NaCl, 0.03% (v/v) Nonidet NP40, [pH 7.6]. Se agregó yoduro de propridio (Sigma Aldrich Co.) a 40 µg/ml y RNAasa A (Sigma Aldrich Co.) a 100 µg/ml. A continuación las células se incubaron a 37°C durante 30 minutos. Las muestras se centrifugaron a 2200 rpm durante 10 minutos, se retiró el sobrenadante y el comprimido restante (nuclei) resuspendido en 200 µl de PBSA estéril. Cada muestra se inyectó luego 10 veces empleando una aguja caliber 21. Las muestras se transfirieron después a tubos LPS y el contenido de AND se analizó mediante separación celular activada por fluorescencia (FACS) usando un citómetro de flujo FACScan (Becton Dickinson). Típicamente se contaron y registraron 25.000 eventos usando software CellQuest vl.1 (Verity Software). La distribución del ciclo cellular de la población se calculó utilizando software Modfit (Verity Software) y se expresaron como porcentaje de células en fases GO/G1, S y G2/M del ciclo celular. Tratando célulasMCF7 con 11 µM Compuesto 52 en Tabla 2 durante 24 horas se produjeron los siguientes cambios en la distribución del ciclo celular:

Tratamiento	% células en G2/M
DMSO (control)	9.25%
10 µM Compuesto 52	> 50%

REIVINDICACIONES

1. El uso de un compuesto de formula (I)



(I)

o una sal, éster o amida de la misma;

en donde X es O, o S, S(O), o $S(O)_2$, o NR^6 en donde R^6 es hidrógeno o C_{1-6}alquilo;

R^5 es un anillo heteroaromático de 5 miembros opcionalmente sustituido,

R^1, R^2, R^3, R^4 se seleccionan independientemente de, halo, ciano, nitro, trifluorometilo, C_{1-3}alquilo, $-NR^7R^8$ (en donde R^7 y R^8, que pueden ser los mismos o diferentes, representa cada uno hidrógeno o C_{1-3}alquilo), o $-X^1R^9$ (en donde X^1 representa un enlace directo, -O-,$-CH_2$, -OCO-, carbonilo, -S-, -SO-, $-SO_2$-, $-NR^{10}CO$-, $-CONR^{11}$-, $-SO_2NR^{12}$-, $-NR^{13}SO_2$- o $-NR^{14}$- (en donde R^{10}, R^{11}, R^{12}, R^{13} y R^{14}, cada uno independientemente, representa hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxiC_{2-3}alquilo), y R^9 se selecciona de uno de los siguientes grupos:

1) hidrógeno o C_{1-5}alquilo que pueden ser no sustituidos o que pueden ser sustituidos con uno o más grupos seleccionados de hidroxi, fluoro o amino,

2) C_{1-5}alquilX^2COR^{15} (en donde X^2 representa -O-, o $-NR^{16}$- (en el cual R^{15} representa hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxiC_{2-3}alquilo) y R^{16} representa C_{1-3}alquilo, $-NR^{17}R^{18}$ o $-OR^{19}$ (en donde R^{17}, R^{18} y R^{19}, que pueden ser los mismos o diferentes, representan cada uno hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxi C_{2-3}alquilo));

3) C_{1-5}alquilX^3R^{20} (en donde X^3 representa -O-, -S-, -SO-, $-SO_2$-, -OCO-, $-NR^{21}CO$-, $-CONR^{22}$, $-SO_2NR^{23}$-, $-NR^{24}SO_2$- o $-NR^{25}$- (en donde R^{21}, R^{22}, R^{23}, R^{24} y R^{25}, cada uno independientemente, representa hidrógeno, C_{1-}

$_3$alquilo o C_{1-3}alcoxiC_{2-3}alquilo) y R^{20} representa hidrógeno, C_{1-3}alquilo, ciclopentilo, ciclohexilo o un grupo heterocíclico saturado de 5-6 miembros con 1-2 heteroátomos, seleccionados independientemente de O, S, y N, el cual grupo C_{1-3}alquilo puede llevar 1 ó 2 sustituyentes seleccionados de oxo, hidroxi, halógeno y C_{1-4}alcoxi y el cual grupo cíclico puede llevar 1 ó 2 sustituyentes seleccionados de oxo, hidroxi, halógeno, C_{1-4}alquilo, C_{1-4}hidroxialquilo y C_{1-4}alcoxi;

4) C_{1-5}alquilX^4C_{1-5}alquilX^5R^{26} (en donde X^4 y X^5 que pueden ser los mismos o diferentes son cada uno -O-, -S-, -SO-, -SO_2-, -NR^{27}CO-, -$CONR^{28}$-, -SO_2NR^{29}, -$NR^{30}SO_2$-, ó –NR^{31} (en donde R^{27}, R^{28}, R^{29}, R^{30} y R^{31}, cada uno independientemente, representa hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxiC_{2-3}alquilo) y R^{26} representa hidrógeno o C_{1-3}alquilo);

5) R^{32} (en donde R^{32} es un grupo heterocíclico saturado de 5-6 miembros (enlazado mediante carbono o nitrógeno) con 1-2 heteroátomos, seleccionados independientemente de O, S y N, el cual grupo hetrocíclico puede llevar 1 o 2 sustituyentes seleccionados de oxo, hidroxi, halógeno, C_{1-4}alquilo, C_{1-4}hidroxialquilo, C_{1-4}alcoxi, C_{1-4}alcoxiC_{1-4}alquilo y C_{1-4}alquilsulfonilC_{1-4}alquilo);

6) C_{1-5}alquilR^{32} (en donde R^{32} es como se define más arriba);

7) C_{2-5}alquenilR^{32} (en donde R^{32} es como se define más arriba);

8) C_{2-5}alquinilR^{32} (en donde R^{32} es como se define más arriba);

9) R^{33} (en donde R^{33} representa un grupo piridona, un grupo fenilo o un grupo heterocíclico aromático de 5-6 miembros (enlazado mediante carbono o nitrógeno) con 1-3 heteroátomos seleccionados de O, N y S, el cual grupo piridona, fenilo o grupo heterocíclico aromático puede llevar hasta 5 sustituyentes en un átomo de carbono disponible; seleccionado de hidroxi, halógeno, amino, C_{1-4}alquilo, C_{1-4}hidroxialquilo, C_{1-4}aminoalquilo, C_{1-4}alquilamino, C_{1-4}hidroxialcoxi, carboxi, trifluorometilo, ciano, -$CONR^{34}R^{35}$ y –$NR^{36}COR^{37}$ (en donde R^{34}, R^{35}, R^{36} y R^{37}, los cuales pueden ser los mismos o diferentes, representa cada uno hidrógeno, C_{1-4}alquilo o C_{1-3}alcoxiC_{2-3}alquilo));

10) C_{1-5}alquilR^{33}, (en donde R^{33} es como se define más arriba);

11) C_{2-5}alquenilR^{33}, (en donde R^{33} es como se define más arriba);

12) C_{2-5}alquinilR^{33}, (en donde R^{33} es como se define más arriba);

13) C_{1-5}alquilX^6R^{33} (en donde X^6 representa -O-, -S-, -SO-, $-SO_2$-, -NR^{38}CO-, -$CONR^{39}$-, -SO_2NR^{40}, -$NR^{41}SO_2$-, ó -NR^{42} (en donde R^{38}, R^{39}, R^{40}, R^{41} y R^{42}, cada uno independientemente, representa hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxiC_{2-3}alquilo) y R^{33} es como se define más arriba);

14) C_{2-5}alquenilX^7R^{33} (en donde X^7 representa -O-, -S-, -SO-, $-SO_2$-, -NR^{43}CO-, -$CONR^{44}$-, -SO_2NR^{45}, -$NR^{46}SO_2$-, ó -NR^{47} (en donde R^{43}, R^{44}, R^{45}, R^{46} y R^{47}, cada uno independientemente, representa hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxiC_{2-3}alquilo) y R^{33} es como se define más arriba);

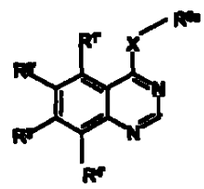
15) C_{2-5}alquinilX^8R^{33} (en donde X^8 representa -O-, -S-, -SO-, $-SO_2$-, -NR^{48}CO-, -$CONR^{49}$-, -SO_2NR^{50}, -$NR^{51}SO_2$-, ó -NR^{52} (en donde R^{48}, R^{49}, R^{50}, R^{51} y R^{52}, cada uno independientemente, representa hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxiC_{2-3}alquilo) y R^{33} es como se define más arriba);

16) C_{1-3}alquilX^9C_{1-3}alquilR^{33} (en donde X^9 representa -O-, -S-, -SO-, $-SO_2$-, -NR^{53}CO-, -$CONR^{54}$-, -SO_2NR^{55}, -$NR^{56}SO_2$-, ó -NR^{57} (en donde R^{53}, R^{54}, R^{55}, R^{56} y R^{57}, cada uno independientemente, representa hidrógeno, C_{1-3}alquilo o C_{1-3}alcoxiC_{2-3}alquilo) y R^{33} es como se define más arriba);

17) C_{1-3}alquilX^9C_{1-3}alquilR^{32} (en donde X^9 y R^{28} son como se define más arriba) en la preparación de un medicamento para uso en la inhibición de aurora2 cinasa.

2. Un método para inhibir aurora 2 cinasa en un animal de sangre caliente, tal como el hombre, necesitado de tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), como se define en la reivindicación 1 o una sal farmacéuticamente aceptable, o su éster hidrolizable *in vivo*.

3. Un compuesto de la fórmula (IA)



(IA)

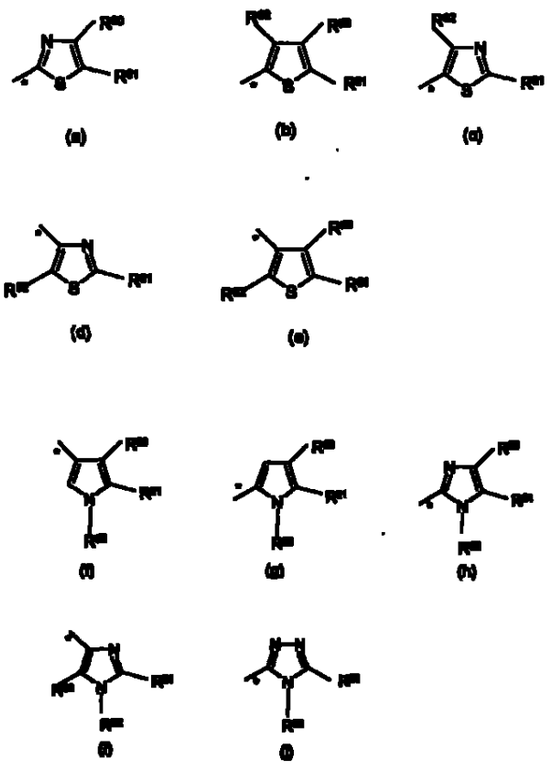
o una sal, éster o amida de la misma;
donde X es como se define en relación con fórmula (I);
$R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$ son equivalentes a R^1, R^2, R^3, R^4 como se definen en relación con fórmula (I) y R^{5a} es un anillo heteroaromático opcionalmente sustituido de 5 miembros, con sujeción a las siguientes condiciones: (i) que donde R^{5a} es un grupo pirazol, lleva un sustituyente de fórmula (k), (II) de (VI) arriba,
(ii) que donde X es NH y R^{5a} es un grupo tetrazoilo o pirazolana sustituido, por lo menos uno de $R^{1'}$, $R^{2'}$, $R^{3'}$ y $R^{4'}$ es distinto de hidrógeno; o
(iii) que donde X es O y R^{5a} es 1-metil-4-nitro-1H-imidazol-5-ilo, por lo menos uno de $R^{1'}$, $R^{2'}$, $R^{3'}$ y $R^{4'}$ es distinto de hidrógeno;
una sal farmacéuticamente aceptable, o su éster hidrolizable *in vivo*.

4. Un método para inhibir aurora 2 cinasa en un animal de sangre caliente, tal como el hombre, necesitado de tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de fórmula (I), como se define en la reivindicación 3 o una sal farmacéuticamente aceptable, o su éster hidrolizable *in vivo*.

5. Un compuesto de acuerdo con la reivindicación 1 ó 3 para uso en el método de tratamiento del organismo humano o animal por terapia.

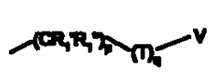
6. Una composición farmacéutica que comprende un compuesto de acuerdo con la reivindicación 1 ó 3, en combinación con un portador farmacéuticamente aceptable.

7. La composición tal como se cita en la reivindicación 3 en donde R^{5a} se selecciona del grupo conformado por:



en donde R^{60}, R^{61} y R^{62} se seleccionan independientemente de hidrógeno o un grupo sustituyente y * indica el punto de unión al grupo X en fórmula (IA).

8. La composición tal como se cita en la reivindicación 7 en donde R^{60}, R^{61} o R^{62} es un grupo de la sub-fórmula (k):

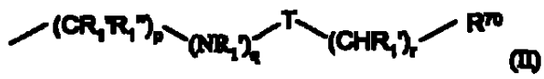


(k)

en donde p y q son independientemente 0 ó 1 y R_1' y R_1'' son independientemente hidrógeno, hidroxi, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, halógeno, ciano, alquilo opcionalmente sustituido, o alquienilo opcionalmente sustituido en donde R_1' puede formar con R_1'' un anillo de 3 a 6 miembros; en donde T es C=O, SO_n, C(=NOR)CO, C(O)C(O), C=NCN, o CV=NO o en donde n = 0, 1 ó 2 y V es independientemente R^{63} o $N(R^{63})R^{64}$ en donde R^{63} y R^{64} se

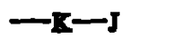
seleccionan independientemente de hidrógeno, hidrocarbilo opcionalmente sustituido o heterociclilo opcionalmente sustituido, o R^{63} y R^{64} juntos con el átomo de nitrógeno al cual se unen forman un anillo heterocíclico opcionalmente sustituido.

9. La composición tal como se cita en la reivindicación 7 en donde R^{60}, R^{61} o R^{62} es un grupo de sub-fórmula:



(II)

en donde p y q son independientemente 0 ó 1 y r es 0, 1, 2, 3 ó 4 y en donde R_1' y R_1'' son independientemente hidrógeno, hidroxi, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, halógeno, ciano, alquilo opcionalmente sustituido, alquienilo opcionalmente sustituido en donde R puede formar con R' un anillo de 3 a 6 miembros; en donde T es C=O, SO_n, C(=NOR)CO, C(O)C(O), C=NCN, o CV=NO o en donde n = 0, 1 ó 2 y V es independientemente R^{63} o $N(R^{63})R^{64}$ en donde R^{63} y R^{64} se seleccionan independientemente de hidrógeno, hidrocarbilo opcionalmente sustituido o heterociclilo opcionalmente sustituido, o R^{63} y R^{64} juntos con el átomo de nitrógeno al cual se unen forman un anillo heterocíclico opcionalmente sustituido; en donde R^{70} es hidrógeno, hidroxi (distinto de donde q es 0), C_{1-6}alquilo, C_{1-6}alcoxi, amino, *N*-C_{1-6}alquilamino, *N,N*-(C_{1-6}alquil)$_2$amino, hidroxiC_{2-6}alcoxi, C_{1-6}alcoxiC_{2-6}alcoxi, aminoC_{2-6}alcoxi, *N*-C_{1-6}alquilaminoC_{2-6}alcoxi, *N,N*-(C_{1-6}alquil)$_2$aminoC_{2-6}alcoxi o C_{3-7}cicloalquilo, o R^{70} es de la fórmula (III):

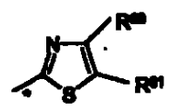


(III)

en donde J es arilo, heteroarilo o heterociclilo y K es un enlace, oxi, imino, *N*-(C_{1-6}alquil)imino, oxiC_{1-6}alquileno, iminoC_{1-6}alquileno, *N*-(C_{1-6}alkil)iminoC_{1-6}alquileno, -NHC(O)-, -SO_2NH-, -$NHSO_2$- o -NHC(O)-C_{1-6}alquileno.

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10. La composición como se cita en la Reivindicación 1, en donde R^{5a} está representado por:



(a)

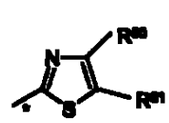
y en donde R^{60} es halógeno, CN, o $CONR^{63}R^{64}$, y en donde R^{61} es sub-fórmula (k):



(k)

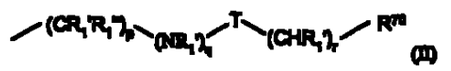
en donde p y q son independientemente 0 ó 1 y R_1' y R_1'' son independientemente hidrógeno, hidroxi, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, halógeno, ciano, alquilo opcionalmente sustituido, alquienilo opcionalmente sustituido, R_1' puede formar con R_1'' un anillo de 3 a 6 miembros; en donde T es C=O, SO_n, C(=NOR)CO, C(O)C(O)), C=NCN, o V=NO o en donde n=0, 1 ó 2 y V es independientemente R^{63} o $N(R^{63})R^{64}$ en donde R^{63} y R^{64} se seleccionan independientemente de hidrógeno, hidrocarbilo opcionalmente sustituido o heterociclicIo opcionalmente sustituido, o R^{63} y R^{64} junto con el átomo de nitrógeno al cual se unen forman un anillo heterocíclico opcionalmente sustituido.

11. La composición como se cita en la Reivindicación 7 en donde R^{5a} está representado por:



(a)

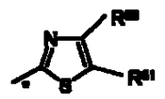
y en donde R^{60} es halógeno, CN, o $CONR^{63}R^{64}$, y en donde R^{61} es sub-fórmula (k):



(k)

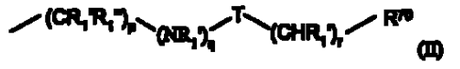
en donde p y q son independientemente 0 o 1, r es 0, 1, 2, 3 o 4 y R y R' son independientemente hidrógeno, hidroxi, alquilo opcionalmente sustituido, cicloalquilo opcionalmente sustituido, halógeno, ciano, alquilo opcionalmente sustituido, alquienilo opcionalmente sustituido, R puede formar con el otro grupo R un anillo de 3 a 6 miembros; en donde T es C=O, SO_n, C(=NOR)CO, C(O)C(O)), C=NCN, o V=NO o donde n = 0, 1 ó 2 y V es independientemente R^{63} o $N(R^{63})R^{64}$ en donde R^{63} y R^{64} se seleccionan independientemente de hidrógeno, hidrocarbilo opcionalmente sustituido o heterociclilo opcionalmente sustituido, o R^{63} y R^{64} juntos con el átomo de nitrógeno al cual se unen forman un anillo heterocíclico opcionalmente sustituido; en donde R^{70} es hidrógeno, hidroxi (distinto de donde q is 0), C_{1-6}alquilo C_{1-6}alcoxi, amino, *N*-C_{1-6}alquilamino, *N,N*-(C_{1-6}alquil)$_2$amino, hidroxiC_{2-6}alcoxi, C_{1-6}alcoxiC_{2-6}alcoxi, aminoC_{2-6}alcoxi, *N*-C_{1-6}alquilaminoC_{2-6}alcoxi, *N,N*-(C_{1-6}alquil)$_2$aminoC_{2-6}alcoxi o C_{3-7}cicloalquilo.

12. La composición como se cita en la Reivindicación 7 en donde R^{5a} está representado por:



(a)

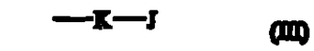
y en donde R^{60} es halógeno, CN, o $CONR^{63}R^{64}$, y en donde R^{61} es sub-fórmula (k):



(k)

en donde p y q son independientemente 0 ó 1, r es 0, 1, 2, 3 ó 4 y R y R' son independientemente hidrógeno, hidroxi, alquilo opcionalmente sustituido,

cicloalquilo opcionalmente sustituido, halógeno, ciano, alquilo opcionalmente sustituido, alquienilo opcionalmente sustituido, R puede formar con el otro grupo R un anillo de 3 a 6 miembros; en donde T es C=O, SOn, C(=NOH)CO, C(O)C(O)), C=NCN, o V=NO o en donde n= 0, 1 ó 2 y V es independientemente R^{63} oN(R^{63})R^{64} en donde R^{63} y R^{64} se seleccionan independientemente de hidrógeno, hidrocarbilo opcionalmente sustituido o heterociclilo opcionalmente sustituido, o R63 y R64 junto con el átomo de nitrógeno al cual se unen oara formar una anillo heterocíclico opcionalmente sustituido; en donde R^{70} es de la fórmula (III):

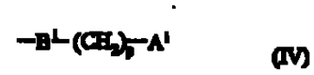


(III)

en donde J es arilo, heteroarilo o heterociclilo y K es un enlace, oxi, imino, *N*-(C_{1-6}alquil)imino, oxiC_{1-6}alquileno, iminoC_{1-6}alquileno, *N*-(C_{1-6}alquil)iminoC_{1-6}alquileno, -NHC(O)-, -SO_2NH-, -$NHSO_2$- o -NHC(O)-C_{1-6}alquileno-,

y cualquier grupo arilo, heteroarilo o heterociclilo en un grupo R^{70} puede sustituirse opcionalmente por uno o más grupos seleccionados de hidroxi, halo, trifluorometilo, ciano, mercapto, nitro,amino, carboxi, carbamoilo, formilo, sulfamoilo, C_{1-6}alquilo C_{2-6}alquenilo, C_{2-6}alquinilo, C_{1-6}alcoxi, -O-(C_{1-3}alquil)-O-, C_{1-6}alquil$S(O)_n$-(en donde n es 0-2), *N*-C_{1-6}alquilamino, *N,N*-(C_{1-6}alquil)$_2$amino, C_{1-6}alcoxicarbonilo, *N*-C_{1-6}alquilcarbamoilo, *N,N*-(C_{1-6}alquil)$_2$carbamoilo, C_{2-6}alcanoilo, C_{1-6}alcanoiloxi, C_{1-6}alcanoilamino, *N*-C_{1-6}alquilsulfamoilo, *N,N*-(C_{1-6}alquil)$_2$sulfamoilo, C_{1-6}alquilsulfonilamino y C_{1-6}alquilsulfonil-*N*-(C_{1-6}alquil)amino,

o cualquier grupo arilo, heteroarilo o heterociclilo en un grupo R^{70} puede sustituirse opcionalmente con uno o más grupos de la Fórmula (IV):



(IV)

en donde A^1 es halo, hidroxi, C_{1-6}alcoxi, ciano, amino, *N*-C_{1-6}alquilamino, *N,N*-(C_{1-6}alquil)$_2$amino, carboxi, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-C_{1-}

$_6$alquilcarbamoilo o *N,N*-(C_{1-6}alquil)$_2$carbamoilo, p es 1-6, y B^1 es un enlace, oxi, imino, *N*-(C_{1-6}alquil)imino o -NHC(O)-, con la condición que p es 2 o más, a menos que B^1 sea un enlace o -NHC(O)-;
o cualquier grupo arilo, heteroarilo o heterociclilo en un grupo R^{70} puede sustituirse opcionalmente con uno o más grupos de la Fórmula (V):

$$—E^1—D^1 \qquad (V)$$

en donde D^1 es arilo, heteroarilo o heterociclilo y E^1 es un enlace, C_{1-6}alquileno, oxiC_{1-6}alquileno, oxi, imino, *N*-(C_{1-6}alquil)imino, iminoC_{1-6}alquileno, *N*-(C_{1-6}alquil)-iminoC_{1-6}alquileno, C_{1-6}alquilen-oxiC_{1-6}alquileno, C_{1-6}alquilen-iminoC_{1-6}alquileno, C_{1-6}alquilen-*N*-(C_{1-6}alquil)-iminoC_{1-6}alquileno, -NHC(O)-, -$NHSO_2$-, -SO_2NH- o -NHC(O)-C_{1-6}alquilen-, y cualquier grupo arilo, heteroarilo o heterociclilo en un sustituyente en D^1 puede sustituirse opcionalmente con uno o más grupos seleccionados de hidroxi, halo, C_{1-6}alquilo, C_{1-6}alcoxi, carboxi, C_{1-6}alcoxicarbonilo, carbamoilo, *N*-C_{1-6}alquilcarbamoilo, *N*-(C_{1-6}alquil)$_2$carbamoilo, C_{2-6}alcanoilo, amino, *N*-C_{1-6}alquilamino y *N,N*-(C_{1-6}alquil)$_2$amino, y cualquier grupo C_{3-7}cicloalquilo o heterociclilo en un grupo R^{70} puede sustituirse opcionalmente con uno o dos sustituyentes oxo o tioxo, y cualquiera de los grupos R^{70} definidos aquí más arriba que comprende un grupo CH_2 que se une a 2 átomos de carbono o un grupo CH_3 que se une a un átomo de carbono, pueden llevar opcionalmente en cada uno de dicho grupo CH_2 o grupo CH_3 un sustituyente seleccionado de hidroxi, amino, C_{1-6}alcoxi, *N*-C_{1-6}alquilamino, *N,N*-(C_{1-6}alquil)$_2$amino y heterociclilo.

13. Un método para inhibir aurora2 cinasa en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento, que comprende administrar a dicho animal una cantidad efectiva de un compuesto de Fórmula (I), como se define en una cualquiera de las Reivindicaciones 7-12 o una sal farmacéuticamente aceptable, o un éster hidrolizable *in vivo* de la misma.

14. Un compuesto como en una cualquiera de las Reivindicaciones 7-12, para uso en un método de tratamiento del organismo humano o animal mediante terapia.

15. Una composición farmacéutica que comprende un compuesto de acuerdo con las Reivindicaciones 7-12 en combinación con un portador farmacéuticamente aceptable.

16. Un método para inhibir aurora2 cinasa en un animal de sangre caliente, tal como el hombre, necesitado de dicho tratamiento que comprende administrar a dicho animal una cantidad efectiva de un compuesto de una cualquiera de las reivindicaciones 7-12 o una sal farmacéuticamente, o un éster hidrolizable *in vivo* de la misma.

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INFORME INTERNACIONAL DE BÚSQUEDA

Solicitud Internacional No.
PCT/SE 01/01450

A. CLASIFICACIÓN DEL OBJETO DE LA SOLICITUD

IPC 7: C07D 403/12, C07D 409/12, C07D 413/12, A61K 31/505, A61P 35/00

De acuerdo con la Clasificación Internacional de Patentes (IPC) o con ambas, la Clasificación Nacional e IPC

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido y símbolos de clasificación)

IPC7: C07D, A61K

Documentación buscada distinta de la documentación mínima siempre que dichos documentos se incluyan en los campos buscados

SE, DK, FI, NO, clases como se indicó anteriormente

Base electrónica de datos consultada durante la búsqueda internacional (nombre de la base de datos y, eventualmente, términos de búsqueda empleados)

CHEM. ABS. DATA

C. DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría [1]	Designación del documento, con indicación, si se considera apropiado, de los pasajes relevantes	Relevante para la Reivindicación No.
X	WO 9935132 A1 (GLAXO GROUP LIMITED), 15 Julio de 1999 (15.07.99) —	1-16
X	WO 9703069 A1 (GLAXO GROUP LIMITED), 30 de enero de 1997 (30.01.97) —	1-16
X	WO 9515758 A1 (RHÔNE POULEC RORER PHARMACEUTICALS INC), 15 de junio de 1995 (15.06.95) —	1-16
A	WO 9909016 A1 (AMERICAN CYANAMID COMPANY) 25 de febrero de 1999 (125.02.99) — -/-	1-16

☒ Otros documentos se enumeran en la continuación de cuadro C.

☒ Miembros de la familia de patente se enumeran en el anexo.

[1] Categorías especiales de los documentos citados:

"A" documento que define el estado general del arte pero que no se considera que sea de relevancia particular

"E" documento anterior pero publicado en la fecha de presentación internacional o después

"L" documento que puede arrojar dudas con respecto a la reivindicación (reivindicaciones) de prioridad o que se cita para establecer la fecha de publicación de otra designación u otra razón especial (como se especifica)

"O" documento referente a una revelación verbal, uso, exhibición u otros medios

"P" documento publicado con anterioridad a la fecha de presentación internacional, pero con posterioridad a la fecha de prioridad reclamada

"T" documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y no en conflicto con la aplicación pero citado para entender el principio o teoría subyacente a la invención.

"X" documento de particular relevancia; la invención reivindicada no puede considerarse nueva o no puede considerarse que implica un paso innovador si el documento se toma solo.

"Y" documento de particular relevancia; la invención reivindicada no puede considerarse que implica un paso innovador si el documento se combina con uno o más de dichos documentos, siendo obvia dicha combinación a una persona con habilidades en el arte.

"&" documento miembro de la misma familia de patente

Fecha de la conclusión actual de la búsqueda internacional	Fecha de envío por correo del informe de búsqueda internacional
30 de octubre de 2001	08/11/2001
Nombre y dirección postal de la Oficina de Búsqueda Internacional (ISA) Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Fax No. +46 8 666 0286	**Funcionario autorizado** Eva Johansson/BS Teléfono No. + 46 8 782 25 00

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INFORME INTERNACIONAL DE BÚSQUEDA	Solicitud Internacional No. PCT/SE 01/01450

C. (Continuación) DOCUMENTOS CONSIDERADOS RELEVANTES

Categoría [1]	Designación del documento, con indicación, si se considera apropiado, de los pasajes relevantes	Relevante para la Reivindicación No.
P, A	WO 0121597 A1 (ASTRAZENECA AB), 29 de marzo de 2001 (29.03.01)	1-16

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INFORME INTERNACIONAL DE BÚSQUEDA

Solicitud Internacional No.
PCT/SE 01/01450

Cuadro I **Observaciones donde se consideró imposible la búsqueda de ciertas reivindicaciones (continuación del ítem 1 de la primera hoja)**

Este informe de búsqueda internacional no se ha establecido con respecto a ciertas reivindicaciones bajo el Artículo 17(2)(a) por las siguientes razones:

1. ☒ Reivindicaciones Nos.: 2, 4, 13 y 16
porque se refieren a un asunto para el que no se requiere búsqueda por esta oficina, a saber:

Ver siguiente hoja

2. ☐ Reivindicaciones Nos.:
Porque se refieren a partes de la solicitud internacional que no cumplen los requerimientos prescritos en tal medida que no puede llevarse a cabo una búsqueda internacional significativa, específicamente:

3. ☐ Reivindicaciones Nos.:
Porque son reivindicaciones dependientes y no se han redactado de acuerdo con las frases segunda y tercera de Regla 6.4(a).

Cuadro II **Observaciones donde falta la unidad de invención (continuación de ítem 2 de la primera hoja)**

Esta Oficina de Búsqueda Internacional encontró múltiples invenciones en esta solicitud internacional, como sigue:

1. ☐ Como el solicitante canceló todos los honorarios requeridos adicionales de búsqueda, este informe de búsqueda internacional cubre todas las reivindicaciones que pueden buscarse.

2. ☐ Como todas las reivindicaciones susceptibles de búsqueda podrían buscarse sin esfuerzo que justificara un honorario adicional, esta Oficina no solicitó oficialmente el pago de un honorario de ninguna clase.

3. ☐ Como el solicitante sólo canceló oportunamente algunos de los honorarios requeridos adicionales de búsqueda, este informe de búsqueda internacional cubre únicamente aquellas reivindicaciones para las cuales se pagaron honorarios, específicamente las reivindicaciones Nos.:

4. ☐ El solicitante no canceló oportunamente los honorarios requeridos adicionales de búsqueda. En consecuencia, este informe internacional de búsqueda se restringe a la invención primeramente mencionada en las reivindicaciones; está cubierto por las reivindicaciones Nos.:

Observación de Protesto

☐ Los honorarios adicionales de búsqueda fueron acompañados por el protesto del solicitante.

☐ Ningún protesto acompañó el pago de honorarios adicionales de búsqueda.

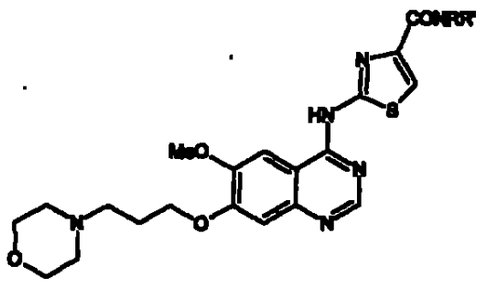
Reivindicaciones 2, 4, 13, y 16 se refieren a métodos de tratamiento del organismo humano o animal mediante cirugía o mediante terapia/métodos de diagnóstico practicados en el organismo humano o animal/Regla 39.1 (iv). No obstante, para estas reivindicaciones se ha realizado una búsqueda. La búsqueda se ha basado en los pretendidos efectos de los compuestos/composiciones.

INFORME INTERNACIONAL DE BÚSQUEDA 01/10/01 | Solicitud Internacional No. PCT/SE 01/01450

Documento de patente citado en el informe de búsqueda	Fecha de Publicación	Miembro (s) de familia de patente	Fecha de publicación
WO 9935132 A1	15/07/99	AU 733047 B AU 1978699 A AU 6302498 A EP 0969813 A GB 9800575 D IL 131477 D	03/05/01 26/07/99 09/09/98 12/01/00 00/00/00 00/00/00
WO 9703069 A1	30/01/97	AU 6613996 A EP 0843671 A GB 9514265 D HR 960316 A JP 11508906 T	10/02/97 27/05/98 00/00/00 28/02/98 03/08/99
WO 9515758 A1	15/06/95	AU 1305095 A EP 0871448 A SG 54172 A US RE36256 E US 5480883 A US 5646153 A US 5710158 A US 5714493 A US 5721237 A US 5795889 A US 6057320 A	27/06/95 21/10/98 16/11/98 20/07/99 02/01/96 08/07/97 20/01/98 03/02/98 24/02/98 18/08/98 02/05/00
WO 9909016 A1	25/02/99	AU 8802398 A BR 9811805 A CN 1271349 T EP 1000039 A HU 0002893 A NO 20000487 A	28/03/99 15/08/00 25/10/00 17/05/00 28/05/01 31/03/00
WO 0121597 A1	29/03/01	AU 7301900 A GB 9922171 D	24/04/01 00/00/00

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Tabla 3



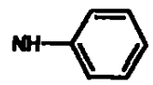
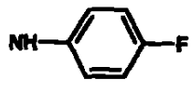
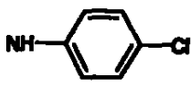
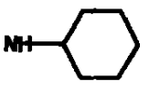
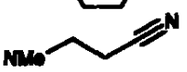
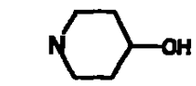
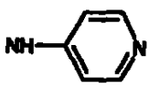
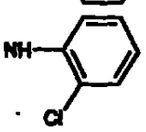
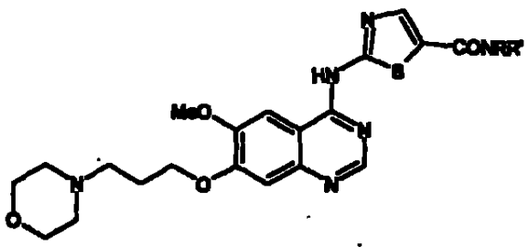
Compuesto No.	NRR'
59	
60	
61	
62	
63	
64	
65	
66	

Tabla 4



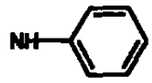
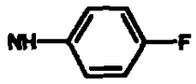
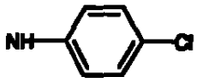
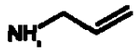
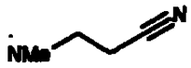
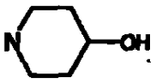
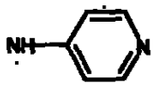
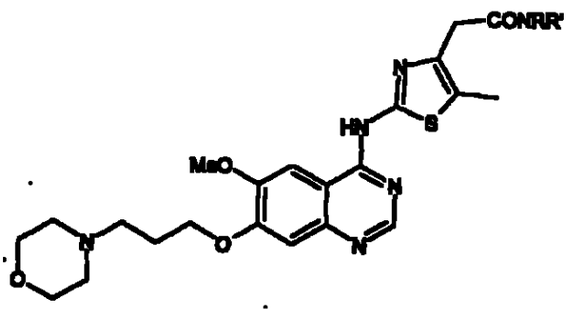
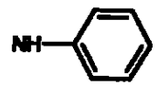
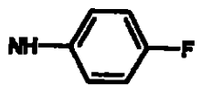
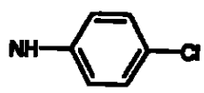
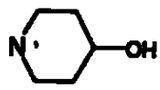
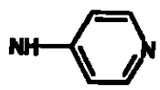
Compuesto No.	NRR'
67	
68	
69	
70	
71	
72	
73	

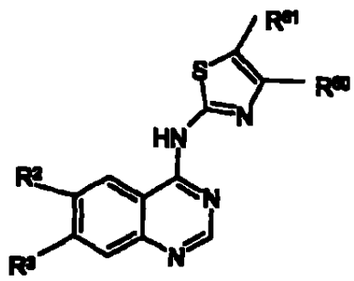
Tabla 5



Compuesto No.	NRR'
74	
75	
76	
77	
78	

675

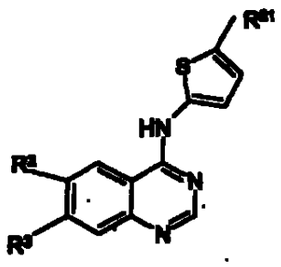
Tabla 7

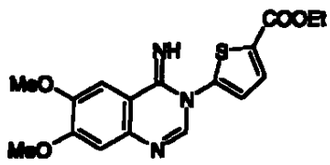


No.	R^2	R^3	R^{60}	R^{61}
200	OCH_3	OCH_3	$CH_2COOCH_2CH_3$	H
201	OCH_3	OCH_3	CH_2COOH	H
202	OCH_3	OCH_3	CH_3	$COOCH_2CH_3$
203	OCH_3	$O(CH_2)_3$-N-morfolino	CH_3	$COOCH_2CH_3$
204	OCH_3	$O(CH_2)_3$-N-morfolino	CH_3	COOCH
205	OCH_3	$O(CH_2)_3$-N-morfolino	$CH_2COOCH_2CH_3$	H
206[1]	OCH_3	$O(CH_2)_3$-N-morfolino	$COOCH_2CH_3$	H
207	OCH_3	$O(CH_2)_3$-N-morfolino	COOH	H
208	OCH_3	$O(CH_2)_3$-N-morfolino	H	$COOCH_2CH_3$
209	OCH_3	$O(CH_2)_3$-N-morfolino	H	COOH
210	OCH_3	$O(CH_2)_3$-N-morfolino	$CH_2COOCH_2CH_3$	CH_3
211	OCH_3	$O(CH_2)_3$-N-morfolino	CH_2COOH	CH_3

676

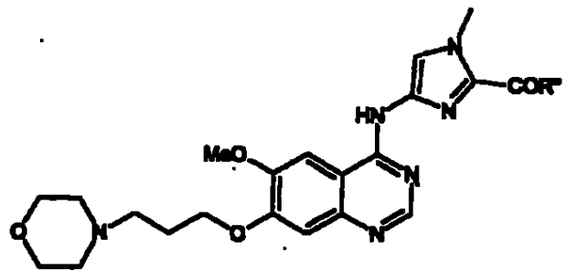
Tabla 8

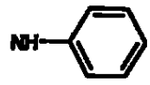
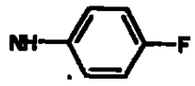
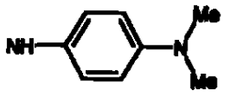
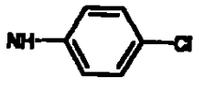
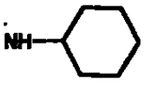


No.	R^2	R^3	R^{61}
212	OCH_3	$O(CH_2)_3$-N-morfolino	COOH
213			
214	OCH_3	OCH_3	COOH

637

Tabla 10

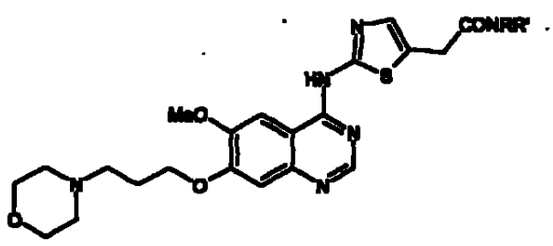


Compuesto No.	R"
260	$COOEt_3$
261	COOH
262	
263	
264	
265	
266	
267	

523	N,N,N' –trimetiletilendiamina	3-fluoroanilina
524	N-alilpiperazina	3-fluoroanilina
525	4-hidroxipiperidina	3-fluoroanilina
526	3-pirrolidinol	3-fluoroanilina
527	1-(aminoetil)pirrolidina	3-fluoroanilina
528	N-acetilpiperazina	3-fluoroanilina
529	1-(2-hidroxietil)piperazina	3-fluoroanilina
530	Ciclopentilamina	3-fluoroanilina
531	4-(2-hidroxietil)piperidina	3-fluoroanilina
532	3-hidroxipiperidina	3-fluoroanilina
533	4-hidroximetilpiperidina	3-fluoroanilina
534	1-amino-2-propanol	3-fluoroanilina
535	(R)-(-)-2-pirrolidinmetanol	3-fluoroanilina
536	(S)-(+)-2-pirrolidinmetanol	3-fluoroanilina
537	Piperazina	3-fluoroanilina
538	1-(2-morfolinoetil)piperazina	3-fluoroanilina
539	2-amino-2-metil-1-propanol	3-fluoroanilina

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TABLA 18

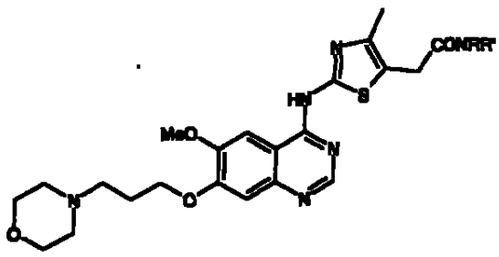


No.	NRR'
540	N-etilanilina
541	3-cloro-4-fluoro-N-metilanilina
542	etil-2-(3-cloro-4-fluoroanilino)acetato
543	2-anilinoacetronitrilo
544	3-anilinoproponitrilo
545	N-(2-ter-butoxietil)-3-cloro-4-fluoroanilina
546	N-alilanilina
547	N-etil-3,4-(metilmedioxi)anilina
548	etil-4-(N-butilamino)benzato
549	N-etil-M-toluidina
550	N-(2-hidroxietil)-3-cloro-4-fluoroanilina

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681

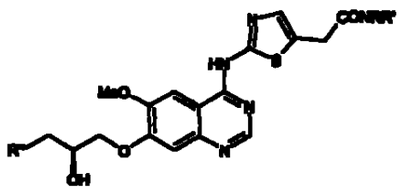
TABLA 19



No.	NRR'
551	Anilina
552	3-cloro-4-fluoroanilina
553	2-aminopiridina
554	3,4-difluoroanilina

82

TABLA 20

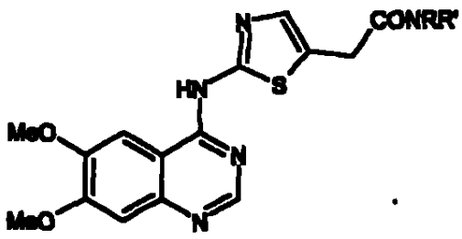


No.	R'''	NRR'
555	Piperidina	3-cloro-4-fluoroanilina
556	Pirrolidina	3-cloro-4-fluoroanilina
557	4-hidroxipiperidina	3-cloro-4-fluoroanilina
558	Piperazina	3-cloro-4- fluoroanilina
559	Ciclopentilamina	3-cloro-4-fluoroanilina
560	2-amino-2-metil-1-propanol	3-cloro-4-fluoroanilina
561	Piperidina	3,4-difluoroanilina
562	Pirrolidina	3,4-difluoroanilina
563	4-hidroxipiperidina	3,4-difluoroanilina
565	Ciclopentilamina	3,4-difluoroanilina

566	Pirrolidina	3-cloroanilina
567	4-hidroxipiperidina	3-cloroanilina
568	ciclopentilamina	3-cloroanilina
569	2-amino-2-metil-1-propanol	3-cloroanilina
570	piperazina	3-cloroanilina
571	OMe	3-cloroanilina
572	piperidina	3-cloroanilina
573	piperidina	3,5-difluoroanilina
574	pirrolidina	3,5-difluoroanilina
575	2-amino-2-metil-1-propanol	3,5-difluoroanilina
576	piperazina (acetato)	3,5-difluoroanilina
577	piperazina	3,5-difluoroanilina
578	pirrolidina	3-fluoroanilina
579	piperidina	3-fluoroanilina
580	piperazina	3-fluoroanilina
581	piperazina (acetato)	3-fluoroanilina
582	ciclopentilamina	3-fluoroanilina

684

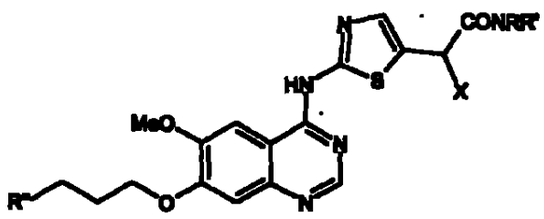
TABLA 21



No.	NRR'
583	3,5-difluoroanilina
584	3-cloroanilina
585	3-cloro-4-fluoroanilina
586	3,4-difluoroanilina

685

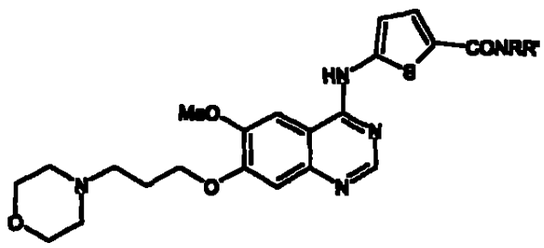
TABLA 22



No.	R"	X	NRR'
587	morfolina	OH	anilina
588	morfolina	OH	3,4-difluoroanilina
589	N-Me-piperazina	OH	3,4-difluoroanilina
590	piperidina	OH	3-fluoroanilina
591	piperidina	OH	3-cloroanilina
592	N-Me-piperazina	=N-OH	3,4-difluoroanilina

696

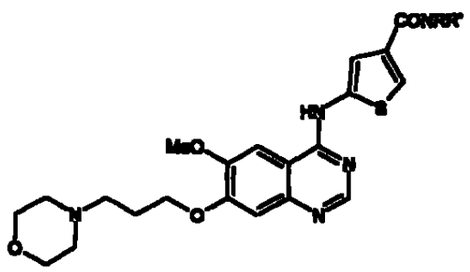
TABLA 23



No.	NRR'	No.	NRR'
593	2-aminopiridina	601	2-metoxianilina
594	4-metilanilina	602	3-(2-hidroxietil)anilina
595	2-metilanilina	603	3-fluoro-4-metoxianilina
596	3-metoxianilina	604	2-metil-4-fluoroanilina
597	2-hidroximetilanilina	605	2-fluoro-5-metilanilina
598	3-nitroanilina	606	3-cianoanilina
599	4-trifluorometilanilina	607	isoamilamina
600	3-cloroanilina	608	2-cloroanilina

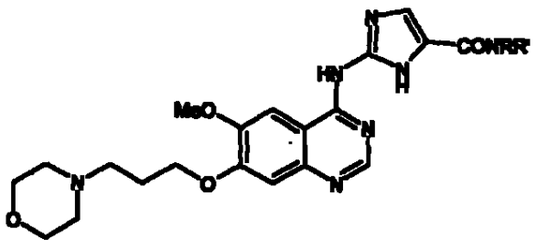
87

TABLA 24



No.	NRR'
609	Anilina
610	4-fluoroanilina
611	3-hidroxianilina
612	3-(metiltio)anilina
613	4-fluoro-3-cloroanilina
614	2,4-difluorobencilamina
615	3-fluoroanilina

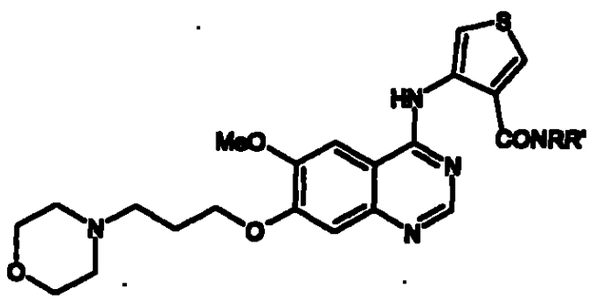
TABLA 25



No.	NRR'
616	Anilina
617	4-fluoroanilina
618	Alilamina

689

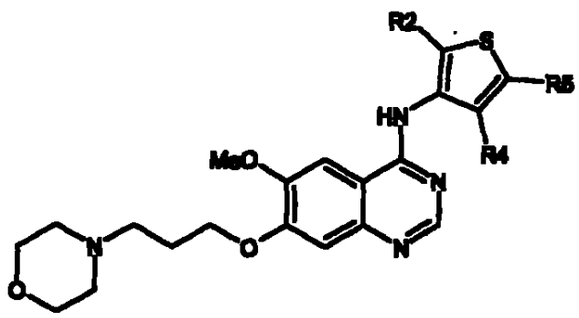
TABLA 26



No.	NRR'
619	Anilina
620	Alilamina

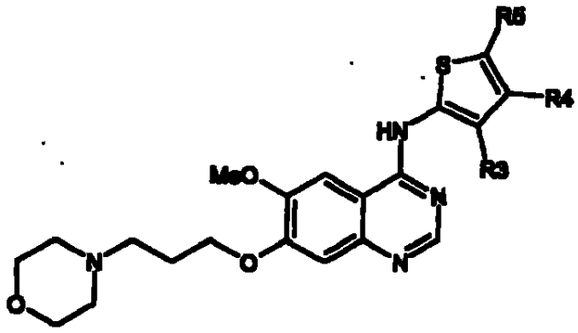
690

TABLA 27



No.	R_3	R_4	R_5
621	COOMe	H	H

TABLA 28

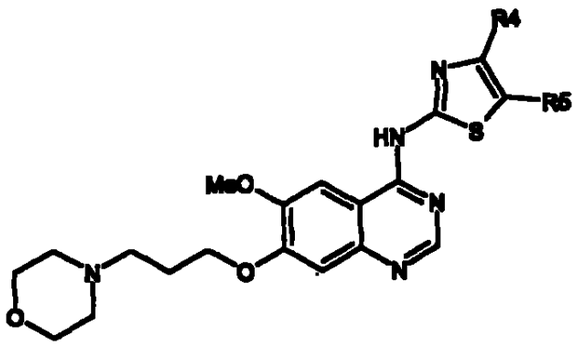


No.	R_3	R_4	R_5
622	CONH2	H	isopropilo
623	H	H	COO alilo

624	CONH2	H	H
625	CONH2	H	etilo

82

TABLA 29

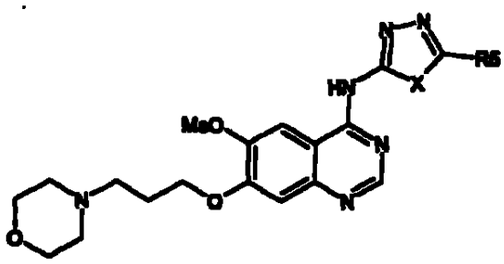


	R4	R5
626	Ph	H
627	Me	COCH3
628	CF3	COOEt
629	Ph	COOEt
630		-(CH2)4-
631	4-acetilaminofenilo	H
632	CF3	Ph
633	CF3	H
634	Tert-butilo	H
635	Me	Me
636	Me	H
637	Me	-C(=N-OH)-Me
638	H	-NHCOO-tert-butilo
639	Me	-C(=NOMe)-Me
640	Me	-C(=NOPh)-Me
641	H	4-metoxifenilo
642	H	Ph
643	H	Et
644	H	Isopropilo

645	H	-CH2Ph
646	H	Me
647	H	n-butilo
648	H	CHO
649	H	-CH=N-OH

894

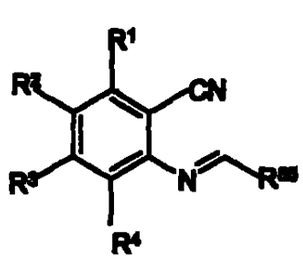
TABLA 30



	X	R5
650	S	tert-butilo
651	S	ciclopropilo
652	S	-S-CH2-CH3
653	S	-Ph
654	NH	-NH-Ph

Otros compuestos de Fórmula (I) o Fórmula (IA), en particular aquellos en los cuales R^5 lleva un sustituyente de éster carboxi o carboxilo se describen más adelante en los Ejemplos.

Compuestos de la Fórmula (I) o Fórmula (IA) pueden prepararse por varios métodos que serán evidentes de la literatura. Por ejemplo, compuestos de fórmula (I) donde X es NH pueden prepararse haciendo reaccionar un compuesto de fórmula (VII).



(VII)

^{1}HNMR ($CDCl_3$): 3.08 (s, 6H); 3.86 (s, 3H); 3.91 (s, 3H); 6.48 (s, 1H); 6.94 (s, 1H); 7.58 (s, 1H).
MS ES^+: 234 $(M^+H)^+$

Compuesto 200

Una mezcla de amidina B (1.4 g, 6 mmol), 2-amimo-4-tiazolacetato de etilo (1.4 g, 7.5 mmol) en ácido acético (14 ml) se calentó a 130°C durante 3 horas. El solvente se retiró bajo vacío, el residuo se trituró en etanol (5 ml) y una soución de $NaHCO_3$ (pH 8) durante 10 minutos. El sólido se recuperó por filtración, se lavó con agua, se disolvió en CH_2Cl_2, y se secó sobre $MgSO_4$. Se evaporó el CH_2Cl_2, el aceite residual se trató con éter y pet. éter para producir el compuesto del título (1.8 g, 80 %).
^{1}HNMR (DMSO-d_6): 1.2 (t, 3H); 3.74 (s, 2H); 3.95 (s, 6H); 4.1 (q, 2H); 7.02 (s, 1H); 7.26 (s, 1H); 8.14 (s, 1H); 8.68 (s, 1H).

Compuesto 201

Éster 200 (1.8 g, 4.8 mmol) se hizo reaccionar con 2N NaOH (4.8 ml, 9.6 mmol) en etanol (20 ml) a temperatura ambiente durante 2 horas. La mezcla se enfrió a temperatura ambiente, se acidificó con EtOH, HCl (2N) a pH 3. Se realizó agitación durante 15 minutos, y se recuperó por filtración un sólido amarillo del título (1.7 g, 100 %).
^{1}HNMR (DMSO-d_6): 3.71 (s, 2H); 3.96 (s, 3H); 3.97 (s, 3H); 7.11 (s, 1H); 7.28 (s, 1H); 8.3 (brs, 1H); 8.88 (s, 1H).

Síntesis de amida c, procedimiento general

El ácido 201 (86.5 mg, 0.25 mmol) en DMF (1 ml) se hizo reaccionar con diferentes aminas (2.6 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-lil) N,N,N',N',-tetrametiluronio (98 mg, 0.26 mmol), DIEA (33 mg, 0.26 mmol) a temperatura ambiente durante 0.5 hora. A la mezcla se añadió una solución de $NaHCO_3$ (1 ml) y agua (7 ml). La mezcla se dejó de un día para otro, y el sólido precipitado se recuperó entonces por filtración, se lavó con agua y se secó bajo vacío en presencia de P_2O_5, para producir compuestos de fórmula C como se enumera más adelante.

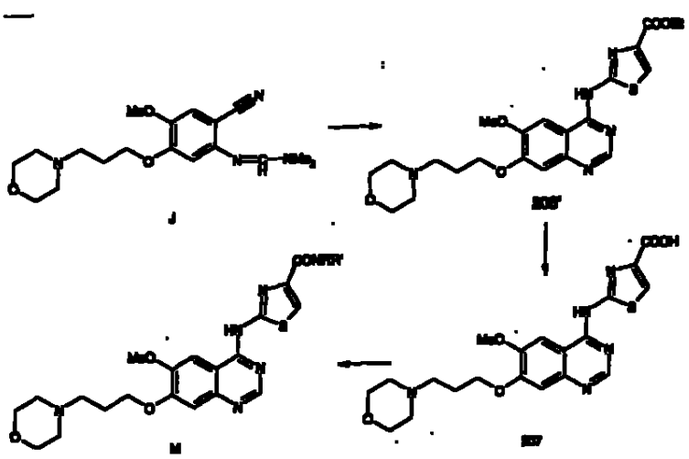
^{1}HNMR (DMSO-d_6, TFA): 1.82 (m, 2H); 1.93 (m, 2H); 2.28 (m, 2H); 3.16 (t, 2H); 3.36 (m, 4H); 3.55 (m, 4H); 3.68 (t, 2H); 3.71 (s, 2H); 3.99 (s, 3H); 4.04 (d, 2H); 4.3 (t, 2H); 7.17 (s, 1H); 7.3 (s, 1H); 7.94 (s, 1H); 9.08 (s, 1H).
MS ES$^+$: 513 $(M+H)^+$

Ejemplo 58.

Una reacción análoga a la descrita en Esquema General 3, comenzando con ciclohexilamina (20 mg, 0.2 mmol) produjo Compuesto 58 en Tabla 2 (80 mg, 87 %).

^{1}HNMR (DMSO-d_6, TFA): 1.25 (m, 4H); 1.75 {m, 4H); 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.56 (d, 2H); 3.6 (s, 2H); 3.69 (t, 2H); 3.99 (s, 3H); 4.04 (d, 2H); 4.3 (t, 2H); 7.15 (s, 1H); 7.97 (s, 1H); 9.09 (s, 1H).
MS ES$^+$: 541 $(M+H)^+$

Esquema General 4



Compuesto 206[1]

La amidina J (1.38 g, 4 mmol) en ácido acético (14 ml) se hizo reaccionar con etil 2-amino-4-tiazolcarboxilato (0.72 g, 4.2 mmol) a 130°C durante 6 horas. El solvente se evaporó, el residuo se disolvió en etanol, y se agitó con una solución saturada de $NaHCO_3$. La mezcla

se extrajo con CH_2Cl_2, se secó, y se purificó mediante cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH 98/2 → 90/10, para producir el compuesto del título(0.738 g, 52 %).

^{1}HNMR (DMSO-d_6, TFA): 1.34 (t, 3H); 2.28 (m, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 4.03 (s, 3H); 4.04 (d, 2H); 4.34 (m, 4H); 7.45 (s, 1H); 8.33 (s, 1H); 8.44 (s, 1H); 9.26 (s, 1H).

MS ES$^+$: 474 $(M+H)^+$

Compuesto 207

Éster **206**[1] (946 mg, 2 mmol) en suspensión en etanol (20 ml) se trató con hidróxido de sodio (6N, 4 ml) a 75°C durante 45 minutos. A continuación la mezcla de la reacción se enfrió a temperatura ambiente, se acidificó (pH 3) con 6N HCl. El precipitado se filtró, se lavó con etanol, se trituró con éter, se secó bajo vacío, para producir el compuesto del título (795 mg, 80)

Síntesis de amidas de estructura general M, procedimiento general

El ácido **207** (79 mg, 0.16 mmol) en DMF (1 ml) se hizo reaccionar con amina (0.19 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il) N,N,N',N'-tetrametiluronio (73 mg, 0.19 mmol), DIEA (52 mg, 0.4 mmol), durante 1 hora a temperatura ambiente. La mezcla de la reacción se trató luego con una solución de $NaHC0_3$ (5 ml) agitando durante 0.5 hora, y el sólido se filtró, se secó bajo vacío sobre P_2O_5. Para los compuestos que no se precipitaron, la solución se concentró a sequedad, los residuos se lavaron con cloruro de metileno / metanol, se filtraron. Se añadió alúmina a la solución de cloruro de metileno / metanol y el solvente se evaporó. La purificación de los compuestos se llevó a cabo mediante cromatografía sobre alúmina, eluyente CH_2Cl_2; CH_2Cl_2 / MeOH: 95/5, para producir los compuestos del título.

Ejemplo 59.

Una reacción análoga a la descrita en Esquema General 4, comenzando con anilina (18 mg, 0.19 mmol) produjo Compuesto 59 en Tabla 3 (50 mg, 60%). ^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.03 (d, 2H); 4.05 (s, 3H); 4.34 (t, 2H); 7.14 (t, 1H); 7.39 (t, 2H); 7.45 (s, 1H); 7.8 (d, 2H); 8.29 (s, 1H); 8.41 (s, 1H); 9.29 (s, 1H).

^{1}HNMR (DMSO-d_6, TFA): 2.34 (m, 5H); 3.13 (t, 2H); 3.32 (t, 2H); 3.52 (d, 2H); 3.74 (s, 2H); 3.78 (t, 2H); 3.98 (s, 3H); 4.01 (d, 2H); 4.31 (t, 2H); 7.37 (s, 1H); 7.91 (s, 1H); 9.03 (s, 1H). MS ES$^+$: 474 $(M+H)^+$

Síntesis de amidas de estructura general Q, procedimiento general

El ácido **211** (87 mg, 0.13 mmol) en DMF (1 ml) se hizo reaccionar con amina (0.169 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il) N,N,N',N'-tetrametiluronio (69 mg, 0.182 mmol), diisopropiletilamina (84 mg, 0.65 mmol) de un día para otro, a temperatura ambiente. La mezcla de la reacción se diluyó con agua (5 ml) y una solución concentrada de bicarbonato de sodio (1 ml). El sólido se filtró, se lavó con agua, etanol, éter, y se secó bajo vacío, para producir los compuestos del título. Para los compuestos que no precipitaron, la solución se concentró a sequedad, los residuos se lavaron con cloruro de metileno, metanol, se filtró. Se añadió alúmina a la solución de cloruro de metileno / metanol, y el solvente se evaporó. La purificación de los compuestos se llevó a cabo mediante cromatografía sobre alúmina, eluyente CH_2Cl_2 / MeOH: 98/2 a 95/5, para producir los compuestos del título.

Ejemplo 74.

Una reacción análoga a la descrita en Esquema General 6, comenzando con anilina (16 mg, 0.17 mmol) produjo Compuesto 74 en Tabla 5 (50 mg, 70 %).

^{1}HNMR (DMSO-d_6, TFA): 2.28 (m, 2H); 2.37 (s, 3H); 3.15 (t, 2H); 3.34 (t, 2H); 3.56 (d, 2H); 3.68 (t, 2H); 3.84 (s, 2H); 3.96 (s, 3H); 4.03 (d, 2H); 4.28 (t, 2H); 7.07 (t, 1H); 7.29 (s, 1H); 7.3 (t, 2H); 7.61 (d, 2H); 7.89 (s, 1H); 9.02 (s, 1H). MS ES$^+$: 549 $(M+H)^+$

Ejemplo 75.

Una reacción análoga a la descrita en Esquema General 6, comenzando con 4-fluoroanilinA (19 mg, 0.17 mmol) produjo Compuesto 75 en Tabla 5 (50 mg, 67 %). ^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 2.38 (s, 3H); 3.16 (t, 2H); 3.34 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.84 (s, 2H); 3.97 (s, 3H); 4.03 (d, 2H); 4.29 (t, 2H); 7.16 (t, 2H); 7.29 (s, 1H); 7.64 (m, 2H); 7.9 (s, 1H); 9.03 (s, 1H). MS ES$^+$: 567 $(M+H)^+$

Ejemplo 76.

Una reacción análoga a la descrita en Esquema General 6, comenzando con 4-cloroanilina (22 mg, 0.17 mmol) produjo Compuesto 76 en Tabla 5 (45 mg, 59 %).

^{1}HNMR (DMSO-d_6, TFA): 2.28 (m, 2H); 2.37 (s, 3H); 3.15 (t, 2H); 3.34 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.85 (s, 2H); 3.97 (s, 3H); 4.03 (d, 2H); 4.29 (t, 2H); 7.29 (s, 1H); 7.37 (d, 2H); 7.65 (d, 2H); 7.9 (s, 1H); 9.03 (s, 1H).

MS ES^+ : 583 $(M+H)^+$

Ejemplo 77.

Una reacción análoga a la descrita en Esquema General 6, comenzando con 4- hidroxipiperidina (17 mg, 0.17 mmol) produjo Compuesto 77 en Tabla 5 (45 mg, 62 %).

^{1}HNMR (DMSO-d_6, TFA): 1.42 (m, 2H); 1.82 (m, 2H); 2.31 (m, 5H); 3.08 (m, 1H); 3.16 (t, 2H); 3.27 (m, 1H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.78 (m, 2H); 3.83 (s, 2H); 3.92 (m, 1H); 3.97 (s, 3H); 4.03 (d, 2H); 4.29 (t, 2H); 7.28 (s, 1H); 7.85 (s, 1H); 9.0 (s, 1H).

MS ES^+: 557 $(M+H)^+$

Ejemplo 78.

Una reacción análoga a la descrita en Esquema General 6, comenzando con 4-aminopiridina (16 mg, 0.17 mmol) produjo Compuesto 78 en Tabla 5 (35 mg, 49 %).

^{1}HNMR (DMSO-d_6, TFA): 2.29 (m, 2H); 2.39 (s, 3H); 3.15 (t, 2H); 3.34 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.96 (s, 3H); 4.02 (d, 2H); 4.04 (s, 2H); 4.29 (t, 2H); 7.33 (s, 1H); 7.92 (s, 1H); 8.1 (d, 2H); 8.76 (d, 2H); 9.06 (s, 1H).

MS ES^+: 550 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.33 (t, 3H); 2.28 (m, 2H); 3.12 (t, 2H); 3.32 (t, 2H); 3.53 (d, 2H); 3.73 (t, 2H); 3.96 (s, 3H); 4.02 (d, 2H); 4.37 (m, 4H); 7.45 (s, 1H); 7.67 (d, 1H); 7.95 (d, 1H); 8.12 (s, 1H); 8.52 (s, 1H).
MS ES$^+$: 473 $(M+H)^+$

Compuesto 212

Éster **V** (1.1 g, 2.3 mmol) in metanol (20 ml) se trató con hidróxido de sodio (2N, 20 ml) a 75°C durante 4 horas, y a temperatura ambiente de un día para otro. Metanol se evaporó, y la solución acuosa restante se guardó durante 24 horas a 5°C. El sólido se filtró, se lavó con agua, MeOH / CH_2Cl_2: 1/1, se secó bajo vacío para producir el compuesto del título (0.9 g, 87 %).

^{1}HNMR (DMSO-d_6, TFA): 2.31 (m, 2H); 3.14 (t, 2H); 3.33 (t, 2H); 3.53 (d, 2H); 3.76 (t, 2H); 4.01 (d, 2H); 4.07 (s, 3H); 4.33 (t, 2H); 7.44 (s, 1H); 7.54 (d, 1H); 7.68 (d, 1H); 8.54 (s, 1H); 9.22 (s, 1H).
MS ES$^+$: 445 $(M+H)^+$

Síntesis de amidas de estructura general W, procedimiento general

Ácido **212** (80 mg, 0.18 mmol) in DMF (1.5 ml) se hizo reaccionar con amina (0.216 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il) N,N,N',N'-tetrametilfuronio (80 mg, 0.21 mmol), DIEA (80µl, 0.46 mmol), durante 3 horas a temperatura ambiente. La mezcla de la reacción se trató entonces con una solución of $NaHCO_3$ (2 ml) agitando durante 0.5 hora, el sólido de filtró, se lavó con agua, éter, se secó bajo vacío sobre P_2O_5, para producir el compuesto del título.

Ejemplo 79.

Una reacción análoga a la descrita en Esquema General 7, comenzando con anilina (17 µl, 0.186 mmol) produjo Compuesto 79 en Tabla 6 (80 mg, 86 %).

^{1}HNMR (DMSO-d_6, TFA): 2.32 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.53 (d, 2H); 3.69 (t, 2H); 4.01 (d, 2H); 4.03 (s, 3H); 4.3 (t, 2H); 7.7 (t, 1H); 7.32 (m, 4H); 7.73 (d, 2H); 7.98 (d, 1H); 8.18 (s, 1H); 9.22 (s, 1H).
MS ES$^+$: 520 $(M+H)^+$

Ejemplo 80.

Una reacción análoga a la descrita en Esquema General 7, comenzando con 4-fluoroanilinA (24 mg, 0.216 mmol) produjo Compuesto 80 en Tabla 6 (62 mg, 64 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 4.05 (m, 5H); 4.33 (t, 2H); 7.21 (t, 2H); 7.33 (d, 1H); 7.4 (s, 1H); 7.77 (m, 2H); 7.98 (d, 1H); 8.2 (s, 1H); 9.25 (s, 1H).

MS ES$^+$: 538 $(M+H)^+$

Ejemplo 81.

Una reacción análoga a la descrita en Esquema General 7, comenzando con 3-aminofenol (24 mg, 0.216 mmol) produjo Compuesto 81 en Tabla 6 (60 mg, 66 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.7 (t, 2H); 4.04 (d, 2H); 4.06 (s, 3H); 4.33 (t, 2H); 6.53 (m, 1H); 7.13 (m, 2H); 7.3 (d, 1H); 7.36 (d, 1H); 7.4 (s, 1H); 7.96 (s, 1H); 8.0 (d, 1H); 8.26 (s, 1H); 9.25 (s, 1H).

MS ES$^+$: 536 $(M+H)^+$

Ejemplo 82.

Una reacción análoga a la descrita en Esquema General 7, comenzando con 4-aminopiridina (20 mg, 0.216 mmol) produjo Compuesto 82 en Tabla 6 (16 mg, 19 %). ^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 4.03 (d, 2H); 4.05 (s, 3H); 4.32 (t, 2H); 7.01 (d, 1H); 7.03 (s, 1H); 8.18 (d, 1H); 8.22 (s, 1H); 8.3 (d, 2H); 8.76 (d, 2H); 9.3 (s, 1H). MS ES$^+$: 521 $(M+H)^+$

Ejemplo 83.

Una reacción análoga a la descrita en Esquema General 7, comenzando con 4-amino-1-butanol (19 mg, 0.216 mmol) produjo Compuesto 83 en Tabla 6 (22 mg, 28 %). ^{1}HNMR (DMSO-d_6, TFA): 1.46 (m, 2H); 1.58 (m, 2H); 2.3 (m, 2H); 3.16 (t, 2H); 3.26 (t, 2H); 3.36 (t, 2H); 3.44 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.04 (m, 5H); 4.32 (t, 2H); 7.26 30 (d, 1H); 7.39 (s, 1H); 7.7 (d, 1H); 8.19 (s, 1H); 9.21 (s, 1H).

MS ES$^+$: 516 $(M+H)^+$

Ejemplo 84.

Una reacción análoga a la descrita en Esquema General 7, comenzando con 3-aminobenzamida (29 mg, 0.216 mmol) produjo Compuesto 84 en Tabla 6 (60 mg, 77 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.67 (t, 2H); 4.03 (d, 2H); 4.05 (s, 3H); 4.32 (t, 2H>); 7.34 (d, 1H); 7.39 (s, 1H); 7.42 (t, 1H); 7.62 (d, 1H); 7.96 (d, 1H); 8.05 (d, 1H); 8.21 (m, 2H); 9.27 (s, 1H). MS ES^+: 563 $(M+H)^+$

Ejemplo 85.

Una reacción análoga a la descrita en Esquema General 7, comenzando con alilamina (12 mg, 0.216 mmol) produjo el Compuesto 85 del título en Tabla 6 (20 mg, 43 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.91 (d, 2H); 4.04 (m, 5H); 4.32 (t, 2H); 5.12 (d, 1H); 5.2 (d, 1H); 5.91 (m, 1H); 7.26 (d, 1H); 7.38 (s, 1H); 7.75 (d, 1H); 8.19 (s, 1H); 9.22 (s, 1H). MS ES^+: 484 $(M+H)^+$

Ejemplo 86.

Una reacción análoga a la descrita en Esquema General 7, comenzando con metil-4-aminobutirato (25.mg, 0.216 mmol) produjo Compuesto 86 en Tabla 6 (18 mg, 23 %).

^{1}HNMR: 1.8 (t, 2H); 2.3 (m, 2H); 2.39 (t, 2H); 3.16 (t, 2H); 3.28 (t, 2H); 3.35 (t, 2H); 3.56 (d, 2H); 3.6 (s, 3H); 3.67 (t, 2H); 4.04 (m, 5H); 4.32 (t, 2H); 7.26 (d, 1H); 7.38 (s, 1H); 7.69 (d, 1H); 8.19 (s, 1H); 9.22 (s, 1H).
MS ES^+: 544 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.34 (t, 2H); 3.54 (d, 2H); 3.72 (t, 2H); 4.02 (m, 5H); 4.3 (t, 2H); 7.19 (s, 1H); 7.32 (s, 1H); 7.62 (s, 1H); 8.17 (s, 1H); 8.93 (s, 1H). MS ES$^+$: 428 $(M+H)^+$

Ejemplo 91. Síntesis de amidas N, procedimiento general

Ácido **251** (79 mg, 0.15 mmol) en DMF (1 ml) se hizo reaccionar con hexafluorofosfato de O-(benzotriazol-1-il)-N,N,N',N'-tetrametiluronio (62 mg, 0.165 mmol), la amina apropiada (1.65 mmol) and DIEA (68 mg, 0.525 mmol) a temperatura ambiente durante 1.5 hora. La mezcla de la reacción se diluyó entonces con agua (4 ml) y una solución acuosa de bicarbonato de sodio (1 ml). El sólido se recuperó por filtración, se disolvió nuevamente en tetrahidrofurano, cloruro de metileno, y se concentró, el sólido precipitado se recuperó, se lavó con éter, se secó bajo vacío, para producir el compuesto del título.

Ejemplo 92. Preparación del Compuesto 252 en Tabla 9

Compuesto de Ejemplo 1 se obtuvo por reacción del éster de N-hidroxibenzotriazol de **251** (56 mg, 0.1 mmol) con anilina (11 mg, 0.12 mmol) en DMF (1 ml) a 105°C durante 3 horas. Se agregó agua a la mezcla de reacción enfriada, la cual se extrajo con acetato de etilo, se lavó la fase orgánica con agua, se secó sobre $MgSO_4$, se filtró y se concentró para producir el compuesto del título (12 mg, 23 %). El éster de N-hidroxibenzotriazol se obtuvo como se describe en el procedimiento general del Ejemplo 91.

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.97 (s, 3H); 4.02 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 7.08 (t, 1H); 7.33 (m, 3H); 7.4 (s, 1H); 7.63 (s, 1H); 7.74 (d, 2H); 8.1 (s, 1H); 8.93 (s, 1H). MS ES$^+$: 517 $(M+H)^+$

Ejemplo 93. Preparación de Compuesto 253 en Tabla 9

Una reacción análoga a la descrita en el Ejemplo 92, pero comenzando con 4-fluoroanilina (22 mg, 0.195 mmol) produjo el compuesto del título (40 mg, 57 %). ^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.72 (t, 2H); 3.97 (s, 3H); 4.02 (s, 3H); 4.04 (d, 2H); 4.3 (t, 2H); 7.18 (t, 2H); 7.34 (s, 1H); 7.4 (d, 1H), 7.63 (d, 1H), 7.76 (m, 1H), 8.11 (s, 1H), 8.94 (s, lH).

el sólido se recuperó por filtración y se lavó con éter. Este sólido se trató entonces con una solución diluida de bicarbonato de sodio, se filtró, se lavó con agua y se secó bajo vacío sobre P_2O_5 para producir el compuesto del título (1.34 g, 73 %). ^{1}HNMR (DMSO-d_6): 1.3 (t, 3H); 1.95 (t, 2H); 2.38 (m, 4H); 2.44 (t, 2H); 3.58 (m, 4H); 3.94 (s, 3H); 4.16 (d, 2H); 4.23 (q, 2H); 7.05 (d, 1H); 7.14 (s, 1H); 7.59 (d, 1H); 7.75 (s, 1H); 8.46 (s, 1H); 9.53 (s, 1H); 11.72 (s, 1H). MS ES$^+$: 456 $(M+H)^+$

Ejemplo 96[1]. Preparación de Compuesto 257 en Tabla 9

Éster **256** (1.34 g, 3 mmol) en etanol (25 ml) se trató con hidróxido de sodio (6N, 3 ml) a 75°C durante 2 horas. La solución se enfrió, y se acidificó con ácido clorhídrico (6N) a pH 3. El precipitado se filtró, se lavó con etanol, éter, se secó bajo vacío sobre P_2O_5, para producir el compuesto del título (0.63 g, 42 %).

^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.15 (t, 2H); 3.34 (t, 2H); 3.54 (d, 2H); 3.72 (t, 2H); 4.02 (s, 3H); 4.03 (d, 2H); 4.3 (t, 2H); 7.19 (d, 1H); 7.32 (s, 1H); 7.62 (d, 1H); 8.17 (s, 1H); 8.93 (s, 1H). MS ES$^+$: 428 $(M+H)^+$

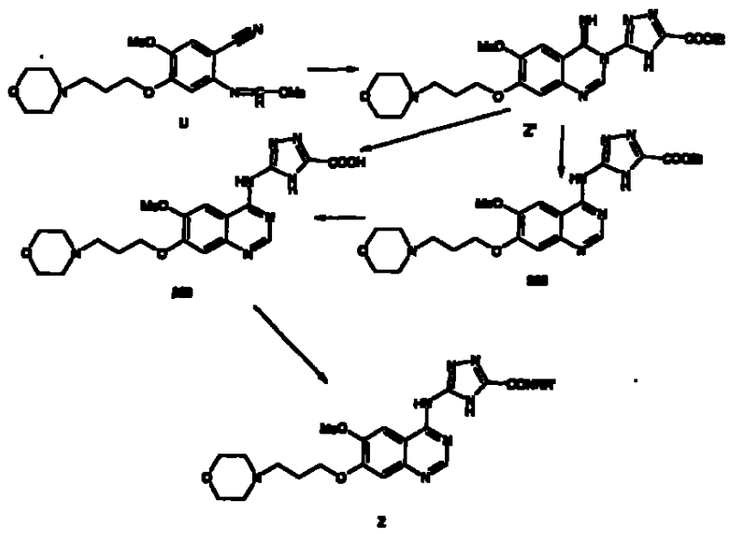
Ejemplo 97. Preparación de Compuesto 258 en Tabla 9

Ácido **257** (75 mg, 0.15 mmol) en DMF (0.7 ml) se hizo reaccionar con hexafluorofosfato de O-(benzotriazol-1-il)-N,N,N',N'-tetrametiluronio (68 mg, 0.18 mmol), anilina (17 mg, 0.18 mmol) y DIEA (62 mg, 0.48 mmol) a temperatura ambiente de un día para otro. La mezcla de la reacción se diluyó entonces con una solución saturada de bicarbonato de sodio (5 ml), y se agitó durante 1 hora. El sólido se filtró, se lavó con agua, se secó bajo vacío sobre sobre P_2O_5, para producir el compuesto del título (30 mg, 40 %). ^{1}HNMR (DMSO-d_6, TFA): 2.3 (m, 2H); 3.16 (t, 2H); 3.37 (t, 2H); 3.54 (d, 2H); 3.69 (t, 2H); 4.01 (s, 3H); 4.03 (d, 2H); 4.31 (t, 2H); 7.08 (t, 1H); 7.35 (m, 3H); 7.46 (d, 1H); 7.56 (d, 1H); 7.77 (d, 1H); 8.1 (s, 1H); 8.93 (s, 1H). MS ES$^+$: 503 $(M+H)^+$

Ejemplo 98. Preparación de Compuesto 259 en Tabla 9

Una reacción análoga a la descrita en Ejemplo 97, pero comenzando con ciclohexilamina (18 mg, 0.18 mmol) produjo el compuesto del título (30 mg, 39 %).

Esquema General 12



Ejemplo 108.

Paso (a) Preparación de Intermedios de la fórmula General Z^1

Imidato **U** (2 g, 6 mmol) en dimetilformamida (40 ml) se hizo reaccionar con ácido clorhídrico de etil 5-amino-4H-1,2,4-triazol-3-carboxilato (1.16 g, 6 mmol) en presencia de hidruro de sodio (60 %, 504 mg, 12.6 mmol) a 110°C durante 7 horas, bajo argón. La mezcla se enfrió entonces a temperatura ambiente, y se añadió ácido acético (1.03 ml, 18 mmol), el solvente se evaporó bajo vacío, el residuo se purificó por cromatografía de gel de sílice, eluyente: CH_2Cl_2 / MeOH, 90/10 para producir el compuesto del título (1.07 g, 39 %).

^{1}HNMR (DMSO-d_6, TFA): 1.39 (t, 3H); 2.28 (m, 2H); 3.15 (t, 2H); 3.32 (t,2H); 3.56 (d, 2H); 3.68 (t, 2H); 3.98 (s, 3H); 4.05 (d, 2H); 4.37 (t, 2H); 4.52 (q, 2H); 7.49 (s, 1H); 8.1 (s, 1H); 8.71 (s, 1H).

MS ES^+: 458 $[M+H]^+$

Paso (b) : Preparación de Compuesto 268 en Tabla 11

Triazol éster Z^1 (80 mg, 0.17 mmol) en dimetilformamida (3 ml) se trató con acetato de dimetilamina (0.52 mmol) a 70°C durante 20 minutos. La mezcla se enfrió, el

^{1}HNMR (DMSO-d_6): 1.22 (t, 3H); 1.96 (t, 2H); 2.37 (m, 4H); 2.35 (t, 2H); 3.58 (m, 4H); 3.91 (s, 2H); 3.95 (s, 3H); 4.13 (q, 2H); 4.20 (t, 2H); 7.25 (s, 1H); 7.36 (s, 1H); 8.10 (s, 1H); 8.66 (s, 1H).

4-((2-amino-1,3-tiazol-5-il)ácido acético)-6-metoxi-7-(3-morfolinopropoxi)quinazolina. 4-(etil(2-amino-1,3-tiazol-5-il)acetato)-6-metoxi- 7-(3-morfolinopropoxi)quinazolina (4.38 g, 8 mmol) en etanol (44 ml) se trató con hidróxido de sodio (2N, 10 ml) a 50°C durante 4 horas. La mezcla se enfrió a temperatura ambiente y se ajustó el pH a 3.5 con 2N HCl. El residuo se disolvió en CH_2Cl_2 / MeOH, 60/40, se agregó DIEA (3 g, 24 mmoles). La mezcla se agitó durante 10 minutos, se filtró, y la solución se concentró para producir un residuo oleoso. Este residuo se disolvió en etanol, y el solvente se evaporó parcialmente. Se recuperó un sólido cristalino, se suspendió en etanol, se lavó con éter y se secó bajo vacío para producir el compuesto del título (3.7 g, 100 %).

^{1}HNMR (DMSO-d_6, TFA): 2.28 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.70 (t, 2H); 3.92 (s, 2H); 3.99 (s, 3H); 4.03 (d, 2H); 4.30 (t, 2H); 7.32 (s, 1H); 7.60 (s, 1H); 7.90 (s, 1H); 9.08 (s, 1H).

Ejemplo 161. Preparación de Compuesto 338 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 3-cloro-4-fluoroanilina (30 mg, 0.2 mmol) produjo el compuesto del título (24 mg, 24 %). MS ES^+: 587 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3.34 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 3.99 (m, 5H); 4.03 (d, 2H); 4.30 (t, 2H); 7.30 (s, 1H); 7.39 (t, 1H); 7.50 (m, 1H); 7.65 (s, 1H); 7.85 (s, 1H); 7.97 (d, 1H); 9.09 (s, 1H).

Ejemplo 162. Preparación del Compuesto 339 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 4-cloroanilina (26 mg, 0.2 mmol) produjo el compuesto del título (73 mg, 76 %). MS ES^+ : 569 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3.89 (m, 5H); 4.04 (d, 2H); 4.30 (t, 2H); 7.30 (s, 1H); 7.39 (d, 2H); 7.64 (s, 1H); 7.65 (d, 2H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 163. Preparación de Compuesto 340 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 3,4-difluoroanilina (26 mg, 0.2 mmol) produjo el compuesto del título (75 mg, 77 %). MS ES^+: 571 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.72 (t, 2H); 3.99 (m, 5H); 4.04 (d, 2H); 4.30 (t, 2H); 7.31 (s, 1H); 7.32 (m, 1H); 7.41 (q, 1H); 7.65 (s, 1H); 7.81 (m, 1H); 7.92 (s, 1H); 9.09 (s, 1H).

Ejemplo 164. Preparación de Compuesto 341 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 3-metoxianilina (25 mg, 0.2 mmol) produjo el compuesto del título (40 mg, 42 %). MS ES^+ : 565 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.70 (t,2H) 15 ; 3.74 (s, 3H); 3.97 (s, 2H); 3.99 (s, 3H); 4.04 (d, 2H); 4.31 (t,2H); 6.68 (d, 1H); 7.15 (d, lH); 7.23 (t, 1H); 7.29 (s, 1H); 7.33 (s, lH); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 165. Preparación de Compuesto 342 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2-cloroanilina (26 20 mg, *0.2* mmol) produjo el compuesto del título (15 mg, 16 %).

MS ES^+ : 569 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.30 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 3.99 (s, 3H); 4.05 (m, 4H); 4.31 (t, 2H);,7.22 (t, 1H); 7.30 (s, 1H); 7.35 (t, 1H); 7.51 (d, 1H); 7.65 (s, 1H); 7.75 (d, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 166. Preparación de Compuesto 343 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 4-metoxianilina (26 mg, 0.21 mmol) produjo el compuesto del título (55 mg, 57 %). MS ES^+ : 565.6 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 3.19 (t, 2H); 3.39 (t, 2H); 3.58 (d, 2H); 3.73 (t, 2H); 3.80 (s, 3H); 3.97 (s, 2H); 4.02 (s, 3H); 4.07 (d, 2H); 4.33 (t, 2H); 6.93 (d, 2H); 7.09 (s, 1H); 7.33 (s, 1H); 7.56 (d, 2H); 7.66 (s, 1H); 7.94 (s, 1H); 9.12 (s, 1H).

Ejemplo 167. Preparación de Compuesto 344 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 4-metilanilina (23 mg, 0.21 mmol) produjo el compuesto del título (5; mg, 54 %).

MS ES^+: 549.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.29 (s, 3H); 2.31 (t, 2H); 3.19 (t, 2H); 3.38 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 3.99 (s, 2H); 4.02 (s, 3H); 4.04 (d, 2H); 4.33 (t, 2H); 7.16 (d, 2H); 7.33 (s, 1H); 7.54 (d, 2H); 7.67 (s, 1H); 7.94 (s, 1H); 9.12 (s, 1H).

Ejemplo 168. Preparación de Compuesto 345 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2-metilanilina (23 mg, 0.21 mmol) produjo el compuesto del título (42 mg, 45 %). MS ES^+: 549.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.24 (s, 3H); 2.31 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H: ; 3.69 (t, 2H); 3.99 (s, 2H); 4.02 (s, 3H); 4.04 (d, 2H); 4.30 (t, 2H); 7.12 (t, 1H); 7.19 (t, 1H); 7.24 (d, 1H); 7.31 (s, 1H); 7.43 (t, 1H); 7.66 (s, 1H); 7.92 (s, 1H); 9.08 (s, 1H).

Ejemplo 169. Preparación de Compuesto 346 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2-aminopiridina (20 mg, 0.21 mmol) produjo el compuesto del título (12 mg, 13 %).

MS ES^+: 536.6 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.18 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 4.00 (m, 5H); 4.04 (d, 2H); 4.33 (t,2H); 7.34 (s, 1H); 7.37 (t, 1H); 7.68 (s, 1H); 7.93 (d, 1H); 7.94 (s, 1H); 8.10 (t, 1H); 8.42 (d, 1H); 9.10 (s, 1H).

Ejemplo 170. Preparación de Compuesto 347 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con alcohol 2-aminobencílico (26 mg, 0.21 mmol) produjo el compuesto del título (24 mg, 24 %). MS ES^+ : 565.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6): 1.97 (t, 2H); 2.41 (m, 6H); 3.59 (m, 4H); 3.91 (s, 2H); 3.97 (s, 3H); 30 4.21 (t, 2H); 4.50 (d, 2H); 5.27 (t, 1H); 7.18 (t, 1H); 7.25 (d, 1H); 7.26 (s, 1H); 7.42 (m, 2H); 7.52 (d, 1H); 8.67 (s, 1H); 9.59 (s, 1H).

Ejemplo 171. Preparación de Compuesto 348 en TabIe 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2-amino-3-metil-1-butanol (22 mg, 0.21 mmol) produjo el compuesto del título (25 mg, 27 %).

MS ES^+: 545.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 0.87 (d, 3H); 0.89 (d, 3H); 1.86 (m, 1H); 2.31 (t, 2H); 3.18 (t, 2H); 3.37 (t, 2H); 3.44 (2s, 2H); 3.57 (d, 2H); 3.63 (q, 1H); 3.70 (t, 2H); 3.80 (d, 2H); 4.01 (t, 3H); 4.07 (d, 2H); 4.31 (t, 2H); 7.32 (s, 1H); 7.58 (s, 1H); 7.92 (s, 1H); 9.09 (s, 1H).

Ejemplo 172. Preparación de Compuesto 349 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2-anilinoetanol (29 mg, 0.21 mmol) produjo el compuesto del título (11 mg, 11 %). MS ES^+ : 579.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.38 (t, 2H); 3.40 (m, 2H); 3.50 (t, 2H); 3.54 (d, 2H); 3.67 (m, 2H); 3.75 (t, 2H); 3.98 (s, 3H); 4.07 (d, 2H); 4.31 (t, 2H); 7.30 (s, 1H); 7.40 (s, 1H); 7.45 (m, 2H); 7.52 (m, 3H); 7.89 (s, 1H); 9.08 (s, 1H).

Ejemplo 173. Preparación de Compuesto 350 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 3-cloro-4-metilamina (30 mg, 0.21 mmol) produjo el compuesto del título (3 mg, 3 %).

MS ES^+ : 583.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (m, 5H); 3.20 (t, 2H); 3.40 (t, 2H); 3.60 (d, 2H); 3.72 (t, 2H); 4.01 (s, 2H); 4.02 (s, 3H); 4.07 (d, 2H); 4.33 (t, 2H); 7.32 (m, 2H); 7.42 (d, 1H); 7.68 (s, 1H); 7.87 (s, 1H); 7.95 (s, 1H); 9.13 (s, 1H).

Ejemplo 174. Preparación de Compuesto 351 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 3-nitroanilina (29 mg, 0.21 mmol) produjo el compuesto del título (20 mg, 21 %). MS ES^+ : 580.6 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.33 (t, 2H); 3.20 (t, 2H); 3.39 (t, 2H); 3.60 (d, 2H); 3.73 (t, 2H); 4.02 (s, 3H); 4.06 (d, 2H); 4.09 (s, 2H); 4.34 (t, 2H); 7.34 (s, 1H); 7.67 (d, 1H); 7.70 (s, 1H); 7.95 (s, 1H); 7.98 (m, 2H); 8.74 (s, 1H); 9.15 (s, 1H).

Ejemplo 175. Preparación de Compuesto 352 en Tabla 14 .

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con aminoacetonitrilo (19 mg, 0.21 mmol) produjo el compuesto del título (28 mg, 31 %).

MS ES^+: 498.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.18 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 3.84 (s, 2H); 3.99 (s, 3H); 4.04 (d, 2H); 4.21 (s, 2H); 4.31 (t, 2H); 7.31 (s, 1H); 7.60 (s, 1H); 9.10 (s, 1H).

Ejemplo 176. Preparación de Compuesto 353 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2-metil-5-nitroanilina (32 mg, 0.21 mmol) produjo el compuesto del título (11 mg, 11 %).

MS ES^+ : 594.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 2.44 (s, 3H); 3.19 (t, 2H); 3.40 (t, 2H); 3.59 (d, 2H); 3.73 (t, 2H); 4.03 (s, 3H); 4.07 (d, 2H); 4.16 (s, 2H); 4.34 (t, 2H); 7.34 (s, 1H); 7.57 (d, 1H); 7.71 (s, 1H); 7.95 (s, 1H); 8.01 (d, 1H); 8.58 (s, 1H); 9.13 (s, 1H).

Ejemplo 177. Preparación de Compuesto 354 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2-amino-5-cloropiridina (27 mg, 0.21 mmol) produjo el compuesto del título (13 mg, 13 %).

MS ES^+: 570.6 $(M_4H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 3.99 (s, 3H); 4.04 (d, 2H); 4.07 (s, 2H); 4.31 (t, 2H); 7.02 (d, 1H); 7.36 (s, 1H); 7.64 (s, 1H); 7.92 (s, 1H); 7.98 (dd, 1H); 8.21 (d, 1H); 9.1 (s, 1H).

Ejemplo 178. Preparación de Compuesto 355 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 4-trifluorometilanilina (34 mg, 0.21 mmol) produjo el compuesto del título (26 mg, 25 %); MS ES^+ : 603.7 $(M_4H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.30 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.72 (t, 2H) 30 ; 3.99 (s, 3H); 4.05 (m, 4H); 4.31 (t, 2H); 7.31 (s, 1H); 7.66 (s, 1H); 7.70 (d, 2H); 7.84 (d, 2H); 7.92 (s, 1H); 9.10 (s, 1H).

Ejemplo 179. Preparación de Compuesto 356 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 3-cloroanilina (27 mg, 0.21 mmol) produjo el compuesto del título (47 mg, 48 %).

MS ES^+: 569.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2 H); 3.69 (t, 2H); 3.99 (s, 3H); 4.00 (s,.2H); 4.04 (d, 2H); 4.31 (t, 2H); 7.14 (d, 1H); 7.30 (s, 1H); 7.37 (t, 1H); 7.47 (d, 1H); 7.65 (s, 1H); 7.87 (s, 1H); 7.92 (s, 1H); 9.10 (s, 1H).

Ejemplo 180. Preparación de Compuesto 357 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2-metoxianilina (26 mg, 0.21 mmol) produjo el compuesto del título (44 mg, 46 %).

MS ES^+: 565.7 $(M_4H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.33 (t, 2H); 3.20 (t, 2H); 3.40 (t, 2H); 3.60 (d, 2H); 3.73 (t, 2H); 3.91 (s, 3H); 4.03 (s, 3H); 4.08 (d, 2H); 4.11 (s, 2H); 4.34 (t, 2H); 6.96 (t, 1H); 7.12 (m, 2H); 7.34 (s, 1H); 7.66 (s, 1H); 7.95 (s, 1H); 8.01 (d, 1H); 9.12 (s, 1H).

Ejemplo 181. Preparación de Compuesto 358 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2-fluoroanilina (23 20 mg, 0.21 mmol) produjo el compuesto del título (43 mg, 46 %). MS ES^+ : 553.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.18 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 4.00 (s, 3H); 4.05 (d, 2H); 4.08 (s, 2H); 4.31 (t, 2H); 7.19 (m, 2H); 7.28 (m, 1H); 7.31 (s, 1H); 7.64 (s, 1H); 7.93 (m, 2H); 9.06 (, 1H).

Ejemplo 182. Preparación de Compuesto 359 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con tifen-2-metilamina (24 mg, 0.21 mmol) produjo el compuesto del título (50 mg, 53 %). MS ES^+: 555.7 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 3.18 (t, 2H); 3.38 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 3.80 (s, 2H); 4.01 (s, 3H); 4.06 (d, 2H); 4.33 (t, 2H); 4.52 (s, 2H), 6.98 (dd, 1H); 7.02 (dd, 1H); 7.32 (s, 1H); 7.41 (dd, 1H); 7.60(sq, 1H); 7.93 (s, 1H); 9.11 (s, 1H).

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Ejemplo 183. Preparación de Compuesto 360 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2-amino-1-feniletanol (29 mg, 0.21 mmol) produjo el compuesto del título (32 mg, 33 %).

MS ES^+: 579.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2R); 3.18 (m, 3H); 3.36 (m, 3H); 3.56 (d, 2H); 3.69 (t, 2H); 3.74 (s, 2H); 3.99 (s, 3H); 4.05 (d, 2H); 4.30 (t, 2H); 4.66 (m, 1H); 7.3 (m, 6H); 7 .53 (s, 1H); 7.90 (s, 1H); 9.09 (s, 1H).

Ejemplo 184. Preparación de Compuesto 361 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 3-(1- hidroxietil)anilina (29 mg, 0.21 mmol) produjo el compuesto del título (50 mg, 50 %).

MS ES^+ : 579.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.34 (d, 3H); 2.31 (t, 2H); 3.18 (t, 2H); 3.38 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 4.00 (s, 2H); 4.02 (s, 3H); 4.07 (d, 2H); 4.33 (t, 2H); 4.72 (q, 1H); 7.07 (d, 1H); 7.29 (t, 1H); 7.33 (s, 1H); 7.53 (d, 1H); 7.67 (s, 2H); 7.93 (s, 1H); 9.12 (s, 1H).

Ejemplo 185. Preparación de Compuesto 362 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con neopentilamina (18 mg, 0.21 mmol) produjo el compuesto del título (57 mg, 64 %).

MS ES^+: 529.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 0.89 (s, 9H); 2.33 (t, 2H); 2.97 (s, 2H); 3.19 (t, 2H); 3.39 (t, 2H); 3.59 (d, 2H); 3.80 (s, 2H); 4.02 (s, 3H); 4.07 (d, 2H); 4.32 (t, 2H); 7.33 (s, 1H); 7.60 (s, 1H); 7.93 (s, 1H); 9.11 (s, 1H).

Ejemplo 186. Preparación de Compuesto 363 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 3-fluoro-4-metoxianilina (30 mg, 0.21 mmol) produjo el compuesto del título (64 mg, 65 %). MS ES^+: 583.7 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H) .30 ; 3.82 (s, 3H); 3.96 (s, 2H); 4.00 (s, 3H); 4.04 (d, 2H); 4.31 (t, 2H); 7.15 (t, 1H); 7.30 (d, 1H); 7.31 (8, 1H); 7.61 (8, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 9.10 (s, lH).

Ejemplo 187. Preparación de Compuesto 364 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2-metil-4-fluoroanilina (26 mg, 0.21 mmol) produjo el compuesto del título (60 mg, 62 %).

MS ES^+: 567.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 4.00 (s, 3H); 4.01 (s, 2H); 4.04 (d, 2H); 4.31 (t, 2H); 7.02 (t, 1H); 7.10 (d, 1H); 7.31 (s, 1H); 7.41 (q, 1H); 7.66 (s, 1H); 7.92 (s, 1H); 9.09 (s, 1H).

Ejemplo 188. Preparación de Compuesto 365 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2,5-difluoroanilinA (27 mg, 0.21 mmol) produjo el compuesto del título (14 mg, 14 %).

MS ES^+: 571.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.19 (t, 2H); 3.39 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 4.01 (s, 3H); 4.06 (d, 2H); 4.12 (s, 2H); 4.33 (t, 2H); 7.00 (m, 1H); 7.33 (m, 2H); 7.65 (s, 1H);7.95 (m, 2H); 9.11 (s, 1H).

Ejemplo 189. Preparación de Compuesto 366 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2-fluoro-4-cloroanilina (31 mg, 0.21 mmol) produjo el compuesto del título (12 mg, 12 %).

MS ES^+ : 587.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 3.99 (s, 3H); 4.04 (m, 4H); 4.31 (t, 2H); 7.29 (d, 1H); 7.52 (dd, 1H); 7.64 (s, 1H); 7.97 (d, 1H); 9.09 (s, 1H).

Ejemplo 190. Preparación de Compuesto 367 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160pero comenzando con 2-fluoro-4-metilanilina (26 mg, 0.21 mmol) produjo el compuesto del título (20 mg, 20 %). MS ES^+: 567.7 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.31 (s, 3H); 2.32 (t, 2H); 3.20 (t, 2H); 3.39 (t, 2H); 3.59 (d, 2H); 3.73 (t, 2H); 4.03 (s, 3H); 4.07 (d, 2H); 4.09 (s, 2H); 4.34 (t, 2H); 7.02 (m, 1H); 7.18 (dd, 1H); 7.34 (s, 1H); 7.67 (s, 1H); 7.77 (d, 1H); 7.95 (s, 1H); 9.12 (s, 1H).

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Ejemplo 191. Preparación de Compuesto 368 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160pero comenzando con 3-metilanilina (23 mg, 0.21 mmol) produjo el compuesto del título (45 mg, 48 %). MS ES^+: 549.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (m, 5H); 3.19 (t, 2H); 3.39 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 4.00 (s, 2H); 4.02 (s, 3H); 4.07 (d, 2H); 4.33 (t, 2H); 6.93 (d, 1H); 7.24 (t, 1H); 7.33 (s, 1H); 7.43 (d, 1H); 7.51 (s, 1H); 7.67 (s, 1H); 7.94 (s, 1H); 9.12 (8, 1H).

Ejemplo 192. Preparación de Compuesto 369 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160pero comenzando con 2-(metilltio)anilina (29 mg, 0.21 mmol) produjo el compuesto del título (13 mg, 13 %). MS ES^+ : 581.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.46 (s, 3H); 3.19 (t, 2H); 3.39 (t, 2H); 3.59 (d, 2H); 3.72 (t, 2H); 3.99 (s, 3H); 4.02 (s, 2H); 4.07 (d, 2H); 4.33 (t, 2H); 7.22 (t, 1H); 7.27 (t, 1H); 7.34 (s, 1H); 7.39 (d, 1H); 7.45 (d, 1H); 7.68 (s, 1H); 7.93 (s, 1H); 9.10 (8, 1H).

Ejemplo 193. Preparación de Compuesto 370 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160pero comenzando con 5-aminoindol (28 20 mg, 0.21 mmol) produjo el compuesto del título (33 mg, 34 %).

MS ES^+: 574.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.18 (t, 2H); 3.36 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 3.97 (s, 2H); 4.00 (s, 3H); 4.03 (d, 2H); 4.31 (t, 2H); 7.32 (m, 6H); 7.65 (8, 1H); 7.91 (s, 1H); 9.10 (8, 1H).

Ejemplo 194. Preparación de Compuesto 371 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2,4-difluoroanilina (27 mg, 0.21 mmol) produjo el compuesto del título (28 mg, 29 %).

MS ES^+: 571.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 3.19 (t, 2H); 3.39 (t, 2H); 3.59 (d, 2H); 3.72 (t, 2H); 4.02 (s, 3H); 4.07 (d, 2H); 4.08 (s, 2H); 4.34 (t, 2H); 7.12 (t, 1H); 7.34 (s, 1H); 7.36 (m, 1H); 7.89 (m, 1H); 7.95 (s, 1H); 9.12 (s, 1H).

Ejemplo 195. Preparación de Compuesto 372 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2-fluoro-4-metilanilina (26 mg, 0.21 mmol) produjo el compuesto del título (35 mg, 37 %).

MS ES^+: 567.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.33 (s, 5H); 3.19 (t, 2H); 3.39 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 4.02 (s, 3H); 4.07 (s, 2H); 4.08 (d, 2H); 4.33 (t, 2H); 7.04 (d, 1H); 7.12 (d, 1H); 7.34 (s, 1H); 7.66 (s, 1H); 7.78 (t, 1H); 7.94 (s, 1H); 9.12 (s, 1H).

Ejemplo 196. Preparación de Compuesto 373 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 3-cianoanilina (25 mg, 0.21 mmol) produjo el compuesto del título (21 mg, 22 %). MS ES^+ : 560.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.19 (t, 2H); 3.39 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 4.02 (s, 3H); 4.06 (s, 2H); 4.07 (d, 2H); 4.33 (t, 2H); 7.34 (s, 1H); 7.6 (m, 2H); 7.69 (s, 1H); 7.85 (m, 1h); 7.95 (s, 1h); 8.18 (s, 1H); 9.13 (s, 1H).

Ejemplo 197. Preparación de Compuesto 374 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160 pero comenzando con 2-metil-5-fluoroanilina (26 mg, 0.21 mmol) produjo el compuesto del título (15 mg, 16 %).

MS ES^+: 567.7 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.27 (s, 3H); 2.32 (t, 2H); 3.20 (t, 2H); 3.39 (t, 2H); 3.59 (d, 2H); 3.72 (t, 2H); 4.02 (s, 3H); 4.07 (d, 2H); 4.09 (s, 2H); 4.33 (t, 2H); 6.96 (t, 1H); 7.29 (t, 1H); 7.34 (s, 1H); 7.48 (d, 1H); 7.69 (s, 1H); 7.95 (s, 1H); 9.12 (s, 1H).

Ejemplo 198. Preparación de Compuesto 375 en Tabla 14

Una reacción análoga a la descrita en ejemplo 160pero comenzando con 2-metil-5-cloroanilina (30 mg, 0.21 mmol) produjo el compuesto del título (20 mg, 21 %).MS ES^+: 583.6 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.26 (s, 3H); 2.32 (t, 2H); 3.17 (t, 2H); 3.38 (t 2H); 3.58 (d, 2H); 3.71 (t, 2H); 4.01 (s, 3H); 4.05 (d, 2H); 4.07 (s, 2H); 4.32 (t, 2H); 7.16 (dd, 1H); 7.27 (d, 1H); 7.31 (s, 1H); 7.65 (d, 1H); 7.65 (s, 1H); 7.93 (s, 1H); 9.10 (s, 1H).

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Ejemplo 199. Preparación de Compuesto 376 en Tabla 15

4-((2-amino-1,3-tiazol-5-il)ácido acético)-6-metoxi-7-((1-metil-piperidin-4-il)metoxi)quinazolina (89 mg, 0.2 mmol) en DMF (1.5 ml), se hizo reaccionar con aniline (22 mg, 0.24 mmol) en presencia de hexatluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (99 mg, 0.26 mmol) y DIEA (50 mg, 0.4 mmol) a 60°C de un día para otro. Luego de enfriar a temperatura ambiente la mezcla de la reacción se diluyó con diclorometano, y se purificó por cromatografía de gel de sílice, eluyendo sucesivamente conh CH_2Cl_2, CH_2Cl_2 / MeOH 90/10, y CH_2Cl_2 / MeOH sat. NH_3 90/10 para producir el compuesto del título (50 mg, 42 %).

MS ES^+: 519.6 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.58 (m, 2H); 2.02 (m, 2H); 2.13 (m, 1H); 2.80 (s, 3H); 3.03 (t, 2H); 3.52 (d, 2H); 3.98 (s, 2H); 3.98 (s, 3H); 4.10 (d, 2H); 7.06 (t, 1H); 7.29 (s, 1H); 7.33 (t, 2H); 7.60 (d, 2H); 7.61 (s, 1H); 7.90 (s, 1H); 9.08 (s, 1H). El espectro NMR de ejemplo 199 en presencia de ácido muestra la existencia de 2 formas en una proporción de aproximadamente 9:1. Señales debidas a la forma menor se aprecian a 1.95 (m) 3.23 (m) 3.32 (m) 4.28 (d) 9.38 (m).

4-benciloxi-3-metoxibenzonitrilo.

4-benciloxi-3-metoxibenzaldehído (4.84 g, 20 mmol) en ácido acético (25 ml) y acetato de sodio (3.3 g, 40 mmol) se hicieron reaccionar con clorhidrato de hidroxilamina (2.8 g, 40 mmol) a reflujo durante 6 horas. La mezcla se enfrió, se dilujó con agua, se extrajo con cloruro de metileno, se secó sobre $MgSO_4$, se concentró para producir el compuesto del título (4.8 g, 100 %). ^{1}HNMR (DMSO-d_6,): 3.83 (s, 3H); 5.20 (s, 2H); 7.21 (d, 1H); 7.40 (m, 7H). 2-nitro-4-benciloxi-5-metoxibenzonitrilo.

4-benciloxi-3-metoxibenzonitrilo (4.78 g, 20 mmol) en ácido acético (10 ml) se agregó lentamente a ácido nítrico (25 ml) a 20°C hasta 30°C. La mezcla se agitó a temperatura ambiente durante 6 horas, se basificó (pH 10-11) con enfriamiento (KOH 10N), se extrajo con cloruro de metileno, se secó sobre $MgSO_4$, se evaporó. El sólido se recristalizó en EtOAc caliente, se obtuvo un sólido amarillo del compuesto del título (3.62 g, 64 %).

MS ES^+: 285 $(M+H)^+$ ^{1}HNMR (DMSO-d_6): 3.97 (s, 3H); 5.33 (s, 2H); 7.40 (m, 5H); 7.71 (s, 1H); 8.01 (s, 1H).

2-nitro-4-hidroxi-5-metoxibenzonitrilo

(exceso). El insoluble se filtró, el filtrado se concentró, se añadió etanol, el sólido se filtró, se lavó con éter, para producir el compuesto del título (102 mg, 77 %). MS ES^+: 444.6 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.61 (m, 2H); 2.03 (d, 2H); 2.16 (m, 1H); 2.80 (s, 3H); 3.03 (t, 2H); 3.5 (d, 2H); 3.92 (s, 2H); 3.98 (s, 3H); 4.10 (d, 2H); 7.32 (s, 1H); 7.59 (s, 1H); 7.89 (s, 1H); 9.07 (s, 1H).

Ejemplo 200. Preparación de Compuesto 377 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 3-cloro-4-fluoroanilina (44 mg, 0.3 mmol) produjo el compuesto 377 en tabla 15 (63 mg, 60 %)

MS ES^+: 571 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.64 (m; 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.8 (s, 3H); 3.04 (t, 2H); 3.51 (d, 2H); 3.99 (s, 3H); 4.0 (s, 2H); 4.11 (d, 2H); 7.34 (s, 1H); 7.39 (t, 1H); 7.5 (m, 1H); 7.65 (s, 1H); 7.91 (dd, 1H); 9.09 (s, 1H).

Ejemplo 201. Preparación de Compuesto 378 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 2-aminopiridina (40 mg, 0.42 mmol) produjo el compuesto 378 en tabla 15 (100 mg, 53 %).

MS ES^+: 520 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.65 (m, 2H); 2.02 (m, 2H); 2.15 (m, 1H); 2.78 (s, 3H); 3.02 (t, 2H); 3.48 (d, 2H); 3.99 (s, 3H); 4.1 (d, 2H); 4.14 (s, 2H); 7.32 (m, 1H); 7.39 (s, 1H); 7.66 (s, 1H); 7.91 (s, 1H); 7.97 (d, 1H); 8.16 (t, 1H); 8.4 (d, 1H); 9.079 (s, 1H).

Ejemplo 202. Preparación de Compuesto 379 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 3,4-difluoroanilina (54 mg, 0.42 mmol) produjo el compuesto 379 en tabla 15 (120 mg, 72 %)

MS ES^+: 555 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.63 (m, 2H); 2.02 (m, 2H); 2.15 (m, 1H); 2.79 (s, 3H); 3.03 (t, 2H); 3.49 (d, 2H); 3.99 (s, 3H); 4.0 (s, 2H); 4.10 (d, 2H); 7.35 (s, 1H); 7.39 (m, 2H); 7.64 (s, 1H);7.82 (dd, 1H); 7.90 (s, 1H); 9.08 (s, 1H).

Ejemplo 203. Preparación de Compuesto 380 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 2-cloroanilina (54 5 mg, 0.42 mmol) produjo el compuesto 380 en tabla 15 (29 mg, 16 %)

MS ES^+: 553 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.62 (m, 2H); 2.03 (m, 2H); 2.15 (m, 1H); 2.81 (s, 3H); 3.04 (t, 2H); 3.51 (d, 2H); 4.0 (s, 3H);.4.08 (s, 2H); 4.11 (d, 2H); 7.24 (t, 1H); 7.31 (s, 1H); 7.34 (dd, 1H); 7.53 (d, 1H); 7.66 (s, 1H); 7.75 (d, 1H); 7.91 (s, 1H); 9.09 (s, IH).

Ejemplo 204. Preparación de Compuesto 381 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 4-metilanilina (45 mg, 0.42 mmol) produjo el compuesto 381 en tabla 15 (155 mg, 85 %)

MS ES^+: 533 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.65 (m, 2H); 2.02 (m, 2H); 2.16 (m, 1H); 2.27 (s, 3H); 2.8 (s, 3H); 3.05 (t, 2H); 3.50 (d, 2H); 3.97 (s, 2H); 3.99 (s, 3H); 4.11 (d, 2H); 7.14 (d, 2H); 7.34 (s, 1H); 7.52 (d, 2H); 7.63 (s, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 205. Preparación de Compuesto 382 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 2-metilanilina (45 mg, 0.42 mmol) produjo el compuesto 382 en tabla 15 (126 mg, 69 %) MS ES^+: 533 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.62 (m, 2H); 2.02 (m, 2H); 2.15 (m, 1H); 2.24 (s, 3H); 2.8 (s, 3H); 3.04 (t, 2H); 3.51 (d, 2H); 3.99 (s, 3H); 4.02 (s, 2H); 4.10 (d, 2H); 7.11 (t, 1H); 7.19 (t, 1H); 7.24 (d, 1H); 7.33 (s, 1H); 7.43 (d, 1H); 7.65 (s, 1H); 7.91 (s, 1H); 9.07 (s, 1H).

Ejemplo 206. Preparación de Compuesto 383 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 4-cloroanilina (54 mg, 0.42 mmol) produjo el compuesto 383 en tabla 15 (128 mg, 68 %) MS ES^+: 553 $(M_4H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.65 (m, 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.79 (s, 3H); 3.04 (t, 2H); 3.50 (d, 2H); 3.99 (s, 3H); 4.0.(s, 2H); 4.1 (d, 2H); 7.36 (s, 1H); 7.38 (d, 2H); 7.64 (s, 1H); 7.68 (d, 2H); 7.9 (s, 1H); 9.08 (s, 1H).

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Ejemplo 207. Preparación de Compuesto 384 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 4-fluoroanilina (47 mg, 0.42 mmol) produjo el compuesto 384 en tabla 15 (136 mg, 84 %)

MS ES^+: 537 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.62 (m, 2H); 2.02 (m, 2H); 2.15 (m, 1H); 2.79 (s, 3H); 3.03 (t, 2H); 3.50 (d, 2H); 3.97 (s, 2H); 3.98 (s, 3H); 4.1 (d, 2H); 7;16 (t, 2H); 7.34 (s, 1H); 7.63 (s, 1H); 7.65 (m, 2H); 7.9 (s, 1R); 9.07 (s, 1H).

Ejemplo 208. Preparación de Compuesto 385 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 2-amino-6-metilpirimidina (45 mg, 0.42 mmol) produjo el compuesto 385 en tabla 15 (91 mg, 57 %)

MS ES^+: 534 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.61 (m, 2H); 2.05 (m, 2H); 2.15 (m, 1H); 2.50 (s, 3H); 2.8 (s, 3H); 3.03 (t, 2H); 3.52 (d, 2H); 4.02 (s, 3H); 4.1 (s, 2H); 4.11 (d, 2H); 7.15 (m, 1H); 7.33 (s, 1H); 7.65 (s, 1H); 7.8 (m, 2H); 7.91 (s, 1H); 9.07 (s, 1H).

Ejemplo 209. Preparación de Compuesto 386 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 3-metoxianilina (52 mg, 0.42 mmol) produjo el compuesto 386 en tabla 15 (125 mg, 67 %) MS ES^+: 549 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.63 (m, 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.8 (s, 3H); 3.04 (t, 2H); 3.52 (d, 2H); 3.75 (s, 3H); 3.98 (s, 2H); 3.99 (s, 3H); 4.11 (d, 2H); 6.68 (m, 1H); 7.17 (d, 1H); 7.24 (t, 1H); 7.33 (s, 1H); 7.35 (d, 1H); 7.64 (s, 1H); 7.92 (s, 1H); 9.09 (s, 1H).

Ejemplo 210. Preparación de Compuesto 387 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 2-amino-5-cloropiridina (54 mg, 0.42 mmol) produjo el compuesto 387 en tabla 15 (22 mg, 11 %) MS ES^+: 554 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.61 (m, 2H); 2.03 (m, 2H); 2.15 (m, 1H); 2.8 (s, 3H); 3.03 (t, 2H); 3.5 (d, 2H); 3.98 (s, 3H); 4.07 (s, 2H); 4.11 (d, 2H); 7.30 (s, 1H); 7.63 (s, 1H); 7.9 (s, 1H); 7.93 (dd, 1H); 8.12 (d, 1H); 8.41 (d, 1H).

Ejemplo 211 Preparación de Compuesto 388 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 3-cloroanilina (54 mg, 0.42 mmol) produjo el compuesto 388 en Tabla 15 (130 mg, 69 %).

MS ES^+: 553 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.62 (m, 2H); 2.02 (m, 2H); 2.15 (m, 1H); 2.78 (s, 3H); 3.02 (t, 2H); 3.49 (d, 2H); 3.97 (s, 3H); 3.99 (s, 2H); 4.08 (d, 2H); 7.13 (d, 1H); 7.3 (s, 1H); 7.38 (t, 1H); 7.64 (s, 1H); 7.86 (s, 1H); 7.90 (s, 1H); 9.07 (s, 1H).

Ejemplo 212. Preparación de Compuesto 389 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 2-fluoroanilina (47 mg, 0.42 mmol) produjo el compuesto 389 en Tabla 15 (116 mg, 63 %). MS ES^+: 537 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.64 (m, 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.79 (s, 3H); 3.03 (t, 15 2H); 3.50 (d, 2H); 3.99 (s, 3H); 4.07 (s, 2H); 4.10 (d, 2H); 7.19 (m, 2H); 7.25 (m, 1H); 7.35 (s, 1H); 7.63 (s, 1H); 7.90 (s, 1H); 7.91 (m, 1H); 9.07 (s, 1H).

Ejemplo 213. Preparación de Compuesto 390 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 3-fluoro-4-metoxianilina (59 mg, 0.42 mmol) produjo el compuesto 390 en Tabla 15 (151 mg, 85 %). MS ES^+: 567 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.62 (m, 2H); 2.01 (m, 2H); 2.15 (m, 1H); 2.79 (s, 3H); 3.03 (t, 2H); 3.51 (d, 2H); 3.81 (s, 3H); 3.96 (s, 2H); 3.98 (s, 3H); 4.10 (d, 2H); 7.14 (t, 1H); 7.28 (d, 1H); 7.34 (s, 1H); 7.59 (dd, 1H); 7.6 (s, 1H); 7.90 (s, 1H); 9.07 (s, 1H).

Ejemplo 214. Preparación de Compuesto 391 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 2-metil-4-fluoroanilina (53 mg, 0.42 mmol) produjo el compuesto 391 en Tabla 15 (151 mg, 81 %).

MS ES^+: 551 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.62 (m, 2H); 2.02 (m, 2H); 2.15 (m, 1H); 2.33 (s, 3H); 2.79 (s, 3H); 2.93 (t, 2H); 3.48 (d, 2H); 3.97 (s, 3H); 3.99 (s, 2H) ,4.09 (d, 2H); 7.01 (dt, 1H); 7.1 (dd, 1H); 7.37 (s, 1H); 7.39 (m, 1H); 7.64 (s, 1H); 7.89 (s, 1H); 9.05 (s, 1H).

Ejemplo 215. Preparación de Compuesto 392 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 2-amino-4-metilpiridina (45 mg, 0.42 mmol) produjo el compuesto 392 en Tabla 15 (119 mg, 66 %). MS ES^+: 534 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.66 (m, 2H); 2.05 (m, 2H); 2.15 (m, 1H); 2.77 (s, 3H); 3.03 (t, 2H); 3.48 (d, 2H); 3.97 (s, 3H); 4.09 (d, 2H); 4.21 (s, 2H); 7.35 (m, 1H); 7.45 (s, 1H); 7.69 (s, 1H); 7.70 (s, 1H); 7.90 (s, 1H); 8.31 (d, 1H); 9.06 (s, 1H).

Ejemplo 216. Preparación de Compuesto 393 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 2,5-difluoroanilina (54 mg, 0.42 mmol) produjo el compuesto 393 en Tabla 15 (42 mg, 22 %).

MS ES^+: 555 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.60 (m, 2H); 2.02 (m, 2H); 2.15 (m, 1H); 2.81 (s, 3H); 3.04 (t, 2H); 3.52 (d, 2H); 3.99 (s, 3H); 4.10 (s, 2H); 4.11 (d, 2H); 7.02 (m, 2H); 7.32 (s, 1H); 7.34 (m, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 7.92 (m, 1H); 9.08 (s, 1H).

Ejemplo 217. Preparación de Compuesto 394 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 2-fluoro-4-cloroanilina (61 mg, 0.42 mmol) produjo el compuesto 394 en Tabla 15 (97 mg, 50 %).

MS ES^+: 571 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.63 (m, 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.77 (s, 3H); 3.03 (t, 2H); 3.48 (d, 2H); 3.98 (s, 3H); 4.07 (s, 2H); 4.09 (d, 2H); 7.26 (d, 1H); 7.38 (s, 1H); 7.5 (dd, 1H); 7.62 (s, 1H); 7.89 (s, 1H); 7.96 (t, 1H); 9.06 (s, 1H).

Ejemplo 218. Preparación de Compuesto 395 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 2-fluoro-5-metilanilina (53 mg, 0.42 mmol) produjo el compuesto 395 en Tabla 15 (119 mg, 63 %). MS ES^+: 551 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.63 (m, 2H); 2.03 (m, 2H); 2.15 (m, 1H); 2.28 (s, 3H); 2.77 (s, 3H); 3.03 (t, 2H); 3.49 (d, 2H); 3.98 (s, 3H); 4.05 (s, 2H); 4.09 (d, 2H); 6.98 (m, 1H); 7.15 (dd, 1H); 7.38 (s, 1H); 7.62 (s, 1H); 7.72 (m, 1H); 7.89 (s, 1H); 9.06 (s, 1H).

Ejemplo 219. Preparación de Compuesto 396 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 3-metilanilina (45 mg, 0.42 mmol) produjo el compuesto 396 en Tabla 15 (144 g, 79 %). MS ES^+: 533 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.64 (m, 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.3 (s, 3H); 2.79 (s, 3H); 3.04 (t, 2H); 3.51 (d, 2H); 3.98 (s, 2H); 3.99 (3H); 4.10 (d, 2H); 6.90 (d, 1H); 7.21 (t, 1H); 7.36 (s, 1H); 7.42 (d, 1H); 7.49 (s, 1H); 7.63 (s, 1H); 7.9 (s, 1H); 9.07 (s, 1H).

Ejemplo 220. Preparación de Compuesto 397 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 2,4- difluoroanilina (54 mg, 0.42 mmol) produjo el compuesto 397 en Tabla 15 (121 mg, 74 %).

MS ES^+: 555 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 1.63 (m, 2H); 2.03 (m, 2H); 2.15 (m, 1H); 2.78 (s, 3H); 3.03 (t, 2H); 3.5 (d, 2H); 3.98 (s, 3H); 4.04 (s, 2H); 4.1 (d, 2H); 7.08 (m, 1H); 7.36 (s, 1H); 7.63 (s, 1H); 7.86 (m, 1H); 7.90 (s, 1H); 9.07 (s, 1H).

Ejemplo 221. Preparación de Compuesto 398 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 2-fluoro-4-metilanilina (53 mg, 0.42 mmol) produjo el compuesto 398 en Tabla 15 (147 mg, 79 %). MS ES^+: 551 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.63 (m, 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.3 (s, 3H); 2.79 (s, 3H); 3.04 (t, 2H); 3.51 (d, 2H); 3.99 (s, 3H); 4.04 (s, 2H); 4.1 (d, 2H); 6.99 (d, 1H); 7.10 (d, 1H); 7.35 (s, 1H); 7.62 (s, 1H); 7.75 (t, 1H); 7.90 (s, 1H); 9.07 (s, 1H).

Ejemplo 222. Preparación de Compuesto 399 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 3-cianoanilina (50 mg, 0.42 mmol) produjo el compuesto 399 en Tabla 15 (118 mg, 71 %). MS ES^+: 544 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.66 (m, 2H); 2.07 (m, 2H); 2.17 (m, 1H); 2.81 (s, 3H); 3.06 (t, 2H); 3.53 (d, 2H); 4.0 (s, 3H); 4.05 (s, 2H); 4.11 (d, 2H); 7.36 (s, 1H); 7.54 (m, 2H); 7.65 (s, 1H); 7.86 (dd, 1H); 7.92 (s, 1H); 8.18 (s, 1H), 9.09 (s, 1H).

Ejemplo 223. Preparación de Compuesto 400 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 2-metil-5-fluoroanilina (53 mg, 0.42 mmol) produjo el compuesto 400 en Tabla 15 (107 mg, 57 %). MS ES^+: 551 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.65 (m, 2H); 2.04 (m, 2H); 2.15 (m, 1H); 2.24 (s, 3H); 2.76 (s, 3H); 3.02 (t, 2H); 3.47 (d, 2H); 3.98 (s, 3H); 4.07 (s, 2H); 4.08 (d, 2H); 6.92 (m, 1H); 7.25 (t, 1H); 7.4 (s, 1H); 7.43 (m, 1H); 7.64 (s, 1H); 7.88 (s, 1H); 9.04 (s, IH).

Ejemplo 224. Preparación de Compuesto 401 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 3,5-difluoroanilina (54 mg, 0.42 mmol) produjo el compuesto 401 en Tabla 15 (83 mg, 44 %). MS ES^+: 555 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.66 (m, 2H); 2.02 (m, 2H); 2.16 (m, 1H); 2.76 (s, 3H); 3.03 (t, 2H); 3.45 (d, 2H); 3.97 (s, 3H); 4.03 (s, 2H); 4.08 (d, 2H); 6.90 (dd, 1H); 7.38 (m, 2H); 7.39 (s, 1H); 7.87 (s, 1H); 9.05 (s, 1H).

Ejemplo 225. Preparación de Compuesto 402 en Tabla 15

Una reacción análoga a la descrita en ejemplo 199 pero comenzando con 3-fluoroanilina (47 mg, 0.42 mmol) produjo el compuesto 402 en Tabla 15 (142 mg, 77 %). MS ES^+: 537 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.62 (m, 2H); 2.03 (m, 2H); 2.15 (m, 1H); 2.78 (s, 3H); 3.02 (t, 2H); 3.49 (d, 2H); 3.98 (s, 3H); 4.0 (s, 2H); 4.1 (d, 2H); 6.9 (s, 1H); 7.35 (s, 1H); 7.36 (m, 2H); 7.62 (m, 1H); 7.64 (s, 1H); 7.9 (s, 1H); 9.08 (s, 1H).

Ejemplo 226. Preparación de Compuesto 403 en Tabla 16

4-((2-amino-1,3-tiazol-5-il)ácido acético)-6-metoxi-7-(3-N-metilpiperazinilpropoxi)quinazolina (142 mg, 0.3 mmol) en NMP (1.5 ml) se hizo reaccionar con anilina (42 µl, 0.45 mmol) en presencia de hexafluorofosfiato de O-(7-azabenzotriazol-l-ilo)-N,N,N',N',tetrametiluronio (173 mg, 0.45 mmol) y diisopropiletilamina (105 µl, 0.6 mmol) a 65°C bajo nitrógeno de un día para otro. Luego de enfriar a temperatura ambiente, la mezcla de la reacción se diluyó con diclorometano y se purificó por cromatografía de gel de sílice) eluyente CH_2Cl_2, CH_2Cl_2 / MeOH, 9/1, CH_2Cl_2 / MeOH sat. NH_3, 9/1 para producir el compuesto del título (24 mg, 15 %).

MS ES^+: 548.6 $(M+H)^+$

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MS ES$^+$: 360.7 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.28 (t, 2H); 2.96 (s, 3H); 3.26 (s, 3H); 3.35 (s, 3H); 3.40 (t, 2H); 3.1-4 (m, 8H); 3.88 (s, 3H); 4.21 (t, 2H); 7.32 (s, 1H); 7.53 (s, 1H); 8.56 (s, 1H).

4-(metil(2-amino-1,3-tiazol-5-il)acetato)-6-metoxi-4-((3-N-metilpiperazinilpropoxi)quinazolina.

N'-(2-ciano-4-metoxi-5-(3-N-piperazinilpropoxi)fenil)-N,N-dimetilimidoformamida (9.7 g, 27 mmol) en ácido acético (100 ml) se hizo reaccionar con metil (2-amino-1,3-tiazol-5-il)acetato (5.2 g, 30 mmol) a reflujo durante 4 horas. El solvente se evaporó y el residuo se purificó por cromatografía de gel de sílice. Eluyente: CH_2Cl_2 / MeOH 99/1 a 97/3 para producir el compuesto del título (9.15 g, 70 %).

MS ES$^+$: 487.6 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 2.97 (s, 3H); 3.2-4.2 (m, 8H); 3.48 (t, 2H); 3.97 (s, 2H); 4.00 (s, 3H); 4.33 (t, 2H); 7.36 (s, 1H); 7.61 (s, 1H); 7.93 (s, 1H); 9.10 (s, 1H).

4-((2-amino-1,3-tiazol-5-il)ácido acético)-6-metoxi-7-(3-(N-metilpiperazinilpropoxi) quinazolina (8.25 g, 17 mmol) en etanol (80 ml) se trató con hidróxido de sodio (2N, 42.5 ml, 85 mmol) a temperatura ambiente durante 1 hora. Ácido de clohidrato (2N) se añadió a la solución (pH 3). La solución se evaporó, el residuo se disolvió en etanol y N-etil diisopropil amina (8.9 ml, 51 mmol). Se agregó éter a la solución, se recuperó el sólido, se secó, para producir el compuesto del título (7.44 g, 93 %). MS ES$^+$: 473.5 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.30 (t, 2H); 2.94 (s, 3H); 3.2-4.1 (m, 8H); 3.45 (t, 2H); 3.89 (s, 2H); 3.97 (s, 3H); 4.29 (t, 2H); 7.30 (s, 1H); 7.56 (s, 1H); 7.90 (s, 1H); 9.06 (s, 1H).

Ejemplo 227. Preparación de Compuesto 404 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 3,4-difluoroanilina (77 mg, 0.6 mmol) produjo el compuesto del título (105 mg, 60 %). MS ES$^+$: 584.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 2.94 (s, 3H); 3.2-4.1 (m, 8H); 3.44 (t, 2H); 3.99 (s, 5H); 4.30 (t, 2H); 7.32 (s, 1H); 7.32 (m, 1H); 7.40 (q, 1H); 7.65 (s, 1H); 7.81 (m, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 228. Preparación de Compuesto 405 en Tabla 16

Una reacción análoga a la descrita en Ejemplo 226 pero comenzando con 2-aminopiridina (56 mg, 0.6 mmol) produjo el compuesto del título (53 mg, 36 %). MS ES^+: 549.6 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.30 (t, 2H); 2.94 (s, 3H); 3.1-4.1 (m, 8H); 3.41 (t, 2H); 3.99 (s, 3H); 4.02 (s, 2H); 4.32 (t, 2H); 7.21 (m, 1H); 7.34 (s, 1H); 7.64 (s, 1H); 7.91 (m, 2H); 8.03 (d, 1H); 8.37 (m, 1H); 9.98 (s, 1H).

Ejemplo 229. Preparación de Compuesto 406 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 3-cloro-4-fluoroanilina (87 mg, 0.6 mmol) produjo el compuesto del título (134 mg, 74 %).

MS ES^+: 600.5 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.94 (s, 3H); 3.43 (t, 2H); 3.1-4.1 (m, 8H); 3,99 (s, 5H); 4.32 (t, 2H); 7.33 (s, 1H); 7.38 (t, 1H); 7.50 (m, 1H); 7.64 (s, 1H); 7.90 (s, 1H); 7.96 (m, 1H); 9.09 (s, 1H).

Ejemplo 230. Preparación de Compuesto 407 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 3-cloroanilina (77 mg, 0.6 mmol) produjo el compuesto del título (46 mg, 26 %).

MS ES^+: 582.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2,95 (s, 3H); 3.2-4.1 (m, 8H); 3.45 (t, 2H); 3.99 (s, 3H); 4.07 (s, 2H); 4.30 (t, 2H); 7.22 (t, 1H); 7.31 (s, 1H); 7.35 (t, 1H); 7.53 (d, 1H); 7.65 (s, 1H); 7.74 (d, 1H); 7.92 (s, 1H); 9.08 (s, 1H).

Ejemplo 231. Preparación de Compuesto 408 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 4-metilanilina (64 mg, 0.6 mmol) produjo el compuesto del título (105 mg, 62 %). MS ES^+: 562.6 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.26 (s, 3H); 2.31 (t, 2H); 2.95 (s, 3H); 3.1-4.1 (m, 8H); 3.43 (t, 30 2H); 3.95 (s, 2H); 3.98 (s, 3H); 4.30 (t, 2H); 7.12 (d, 2H); 7.31 (s, 1H); 7.50 (d, 2H); 7.63 (s, 1H); 7.90 (s, 1H); 9.08 (s, 1H).

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Ejemplo 232. Preparación de Compuesto 409 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 2-metilanilina (64 mg, 0.6 mmol) produjo el compuesto del título (127 mg, 75 %). MS ES^+: 562.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.24 (s, 3H); 2.31 (t, 2H); 2.95 (s, 3H); 3.2-4.1 (m, 8H); 3.44 (t, 2H); 3.99 (s, 3H); 4.02 (s, 2H); 4.31 (t, 2H); 7.12 (t, 1H); 7.19 (t, 1H); 7.24 (d, 1H); 7.33 (s, 1H); 7.44 (d, 1H); 7.66 (s, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 233. Preparación de Compuesto 410 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 4-cloroanilina (77 mg, 0.6 mmol) produjo el compuesto del título (101 mg, 58 %). MS ES^+: 582.5 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32 (t, 2H); 2.95 (s, 3H); 3.1-4.1 (m, 8H); 3.44 (t, 2H); 4.00 (s, 5H); 4.31 (t, 2H); 7.33 (s, 1H); 7.40 (d, 2H); 7.65 (s, 1H); 7.66 (d, 2H); 7.92 (s, 1H); 9.10 (s, 1H).

Ejemplo 234. Preparación de Compuesto 411 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 4-fluoroanilina (67 mg, 0.6 mmol) produjo el compuesto del título (97 mg, 57 %). MS ES^+: 566.5 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.94 (s, 3H); 3.1-4.1 (m, 8H); 3.44 (t, 2H); 3.97 (s, 2H); 3.99 (s, 3H); 4.30 (t, 2H); 7.17 (t, 2H); 7.34 (s 1H); 7.64 (m, 3H); 7.90 (s, 1H); 9.09 (s, 1H).

Ejemplo 235. Preparación de Compuesto 412 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 2-amino-6-metilpiridina (65 mg, 0.6 mmol) produjo el compuesto del título (70 mg, 42 %).

MS ES^+: 563.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.30 (t, 2H); 2.46 (s, 3H); 2.94 (s, 3H); 3.10-4.10 (m, 8R); 3.43 (t, 2H); 3.98 (s, 3H); 4.06 (s, 2H); 4.30 (t, 2H); 7.08 (d, 1H); 7.32 (s, 1H); 7.63 (s, 1H); 7.79 (t, 1H); 7.88 (d, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

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Ejemplo 236. Preparación de Compuesto 413 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 2-metoxianilina (74 mg) 0.6 mmol) produjo el compuesto del título (99 mg) 57 %). MS ES^+: 578.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.30 (t) 2H); 2.94 (s) 3H); 3.1-4.1 (m) 8H); 3.43 (t, 2H); 3.74 (s, 3H); 3.97 (s, 2H); 3.99 (s, 3H); 4.30 (t, 2H); 6.67 (d, 1H); 7.15 (d, 1H); 7.24 (t, 1H); 7.33 (s, 2H); 7.64 (s, 1H); 7.90 (s, 1H); 9.09 (s, 1H).

Ejemplo 237. Preparación de Compuesto 414 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 2-amino-5-cloropiridina (77 mg, 0.6 mmol) produjo el compuesto del título (23 mg, 13 %).

MS ES^+: 583.5 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.30 (t, 2H); 2.94 (s, 3H); 3.10-4.10 (m, 8H); 3.45 (t, 2H); 3.98 (s, 3H); 4.06 (s, 2H); 4.30 (t, 2HR); 7.31 (s, 1H); 7.63 (s, 1H); 7.90 (s, 1H); 7.91 (dd, 1H); 8.11 (d, 1H); 8.40 (d, 1H); 9.09 (s, 1H).

Ejemplo 238. Preparación de Compuesto 415 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 3-cloroanilina (77 mg, 0.6 mmol) produjo el compuesto del título (96 mg, 55 %).

MS ES^+: 582.5 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.94 (s, 3H); 3.2-4.2 (m, 8H); 3.45 (t, 2H); 3.98 (s, 5H); 4.28 (t, 2H); 7.12 (d, 1H); 7.31 (s, 1H); 7.34 (t, 1H); 7.46 (d, 1H); 7.62 (s, 1H); 7.85 (s, 1H); 7.91 (s, 1H); 9.07 (s, 1H).

Ejemplo 239. Preparación de Compuesto 416 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 2-fluoroanilina (67 mg, 0.6 mmol) produjo el compuesto del título (68 mg, 40 %). MS ES^+: 596.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.28 (t, 2H); 2.91 (s, 3H); 3.1-4.1 (m, 8H); 3.40 (t, 2H); 3.95 (s, 3H); 4.03 (s, 2H); 4.26 (t, 2H); 7.13 (m, 2H); 7.25 (m, 2H); 7.28 (s, 1H); 7.60 (s, 1H); 7.87 (s, 1H); 9.05 (s, 1H).

Ejemplo 240. Preparación de Compuesto 417 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 3-cianoanilina (71 mg, 0.6 mmol) produjo el compuesto del título (101 mg, 63 %). MS ES^+: 573.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.95 (s, 3H); 3.1-4.1 (m, 8H); 3.45 (t, 2H); 4.00 (s, 3H); 4.04 (s, 2H); 4.31 (t, 2H); 7.33 (s, 1H); 7.56 (s, 1H); 7.57 (m, 1H); 7.66 (s, 1H); 7.82 (m, 1H); 7.92 (s, 1H); 8.15 (s, 1H); 9.10 (s, 1H).

Ejemplo 241. Preparación de Compuesto 418 en Tabla 16:

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 2-fluoro-4-metilanilina (75 mg, 0.6 mmol) produjo el compuesto del título (109 mg, 63 %).

MS ES^+: 580.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.29 (m, 5H); 2.94 (s, 3H); 3.1-4.1 (m, 8H); 3.44 (t, 2H); 3.98 (s, 3H); 4.03 (s, 2H); 4.30 (t, 2H); 6.98 (d, 1H); 7.09 (d, 1H); 7.32 (s, 1H); 7.63 (s, 1H); 7.74 (t, 1H); 7.90 (s, 1H); 9.08 (s, 1H).

Ejemplo 242. Preparación de Compuesto 419 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 3-fluoro-4-metoxianilina (85 mg, 0.6 mmol) produjo el compuesto del título (121 mg, 68 %).

MS ES^+: 596.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.95 (s, 3H); 3.1-4.1 (m, 8H); 3.44 (t, 2H); 3.81 (s, 3H); 3.95 (s, 2H); 3.99 (s, 3H); 4.30 (t, 2H); 7.13 (t, 1H); 7.27 (m, 1H); 7.31 (s, 1H); 7.60 (m, 1H); 7.64 (s, 1H); 7.90 (s, 1H); 9.09 (s, 1H).

Ejemplo 243. Preparación de Compuesto 420 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 2-metil-4-fluoroanilina (75 mg, 0.6 mmol) produjo el compuesto del título (130 mg, 75 %). MS ES^+: 580.6 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.23 (s, 3H); 2.29 (t, 2H); 2.95 (s, 3H); 3.1-4.1 (m, 8H); 3.44 (t, 2H); 3.99 (s, 3H); 4.00 (s, 2H); 4.30 (t, 2H); 7.01 (m, 1H); 7.09 (dd, 1H); 7.32 (s, 1H); 7.40 (m, 1H); 7.65 (s, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 244. Preparación de Compuesto 421 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 2-amino-4-metilpiridina (65 mg, 0.6 mmol) produjo el compuesto del título (87 mg, 52 %).

MS ES^+: 563.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.29 (t, 2H); 2.45 (s, 3H); 2.94 (s, 3H); 3.1-4.1 (m, 8H); 3.44 (t, 2H); 3.99 (s, 3H); 4.15 (s, 2H); 4.30 (t, 2H); 7.24 (d, 1H); 7.37 (s, 1H); 7.67 (s, 1H); 7.72 (s, 1H); 7.92 (s, 1H); 8.29 (d, 1H); 9.08 (s, 1H);

Ejemplo 245. Preparación de Compuesto 422 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 2,5-difluoroanilina (77 mg, 0.6 mmol) produjo el compuesto del título (56 mg, 32 %). MS ES^+: 584.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.30 (t, 2H); 2.94 (s, 3H); 3.1-4.1 (m, 8H); 3.43 (t, 2H); 3.98 (s, 3H); 4.10 (s, 2H); 4.30 (t, 2H); 7.0 (m, 1H); 7.32 (s, 1H); 7.33 (m, 1H); 7.64 (s, 1H); 7.91 (m, 2H); 9.09 (s, 1H).

Ejemplo 246. Preparación de Compuesto 423 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 2-fluoro-4-cloroanilina (87 mg, 0.6 mmol) produjo el compuesto del título (69 mg, 38 %).

MS ES^+: 600.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.32.(t, 2H); 2.94 (s, 3H); 3.2-4.2 (m, 8H); 3.44 (t, 2H); 3.99 (s, 3H); 4.07 (s, 2H); 4.30 (t, 2H); 7.20 (dd, 1H); 7.33 (s, 1H); 7.51 (dd, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 7.97 (t, 1H); 9.09 (s, 1H).

Ejemplo 247. Preparación de Compuesto 424 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 2-fluoro-5-metilanilina (75 mg, 0.6 mmol) produjo el compuesto del título (81 mg, 46 %).

MS ES^+: 580.6 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.27 (s, 3H); 2.32 (t, 2H); 2.94 (s, 3H); 3.1-4.1 (m, 8H); 3.44 (t, 30 2H); 3.99 (s, 3H); 4.05 (s, 2H); 4.30 (t, 2H); 6.97 (m, 1H); 7.13 (dd, 1H); 7.34 (s, 1H); 7.63 (s, 1H);7.74 (d, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

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Ejemplo 248. Preparación de Compuesto 425 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 3-metilanilina (64 mg, 0.6 mmol) produjo el compuesto del título (116 mg, 69 %). MS ES^+: 584.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.28 (s, 3H); 2.31 (t, 2H); 2.95 (s, 3H); 3.1-4.1 (m, 8H); 3.45 (t, 2H); 3.96 (s, 2H); 3.98 (s, 3H); 4.30 (t, 2H); 6.88 (d, 1H); 7.19 (t, 1H); 7.30 (s, 1H); 7.39 (d, 1H); 7.47 (s, 1H); 7.62 (s, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 249. Preparación de Compuesto 426 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 2,4-difluoroanilina (77 mg, 0.6 mmol) produjo el compuesto del título (84 mg, 48 %). MS ES^+: 584.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.95 (s, 3H); 3.1-4.1 (m, 8H); 3.99 (s, 3H); 4.05 *(s,* 2H); 4.30 (t, 2H); 7.07 (t, 1H); 7.32 (m, 2H); 7.64 (s, 1H); 7.86 (m, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 250. Preparación de Compuesto 427 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 2-metil-5-fluoroanilina (75 mg, 0.6 mmol) produjo el compuesto del título (98 mg, 57 %).

MS ES^+: 580.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.23 (s, 3H); 2.31 (t, 2H); 2.94 (s, 3H); 3.1-4.1 (m, 8H); 3.43 (t, 2H); 3.98 (s, 3H); 4.05 *(s,* 2H); 4.30 (t, 2H); 6.91 (m, 1H); 7.25 (t, 1H); 7.32 (s, 1H); 7.44 (dd, 1H); 7.65 (s, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 251. Preparación de Compuesto 428 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 3,5-difluoroanilina (77 mg, 0.6 mmol) produjo el compuesto del título (54 mg, 31 %). MS ES^+: 584.6 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.95 (s, 3H); 3.1-4.1 (m, 8H); 3.45 (t, 2H); 3.99 (s, 3H); 4.02 (s, 2H); 4.31 (t, 2H); 6.92 (m, 1H); 7.33 (s, 1H); 7.35 (m, 2H); 7.66 (s, 1H); 7.92 (s, 1H); 9.10 (s, 1H).

Ejemplo 252. Preparación de Compuesto 429 en Tabla 16

Una reacción análoga a la descrita en ejemplo 226 pero comenzando con 3-fluoroanilina (67 mg, 0.6 mmol) produjo el compuesto del título (120 mg, 70 %). MS ES$^+$: 566.6 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 2.94 (s, 3H); 3.2-4.2 (m, 8H); 3.44 (t, 2H); 3.98 (s, 3H); 3.99 (s, 2H); 4.30 (t, 2H); 6.90 (s, 1H); 7.34 (s, 1H); 7.36 (m, 2H); 7.61 (m, 1H); 7.64 (s, 1H); 7.90 (s, 1H); 9.09 (s, 1H).

Ejemplo 253. Preparación de Compuesto 430 en Tabla 17

N-(3-clorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4-il-amino)1,3-tiazol-5-il)acetamida (141 mg, 0.22 mmol) en acetonitrilo (2 ml) se hizo reaccionar con pirrolidina (3.3 mmol) en presencia de yoduro de potasio (100 mg, 0.6 mmol) a 80°C durante 15 / 30 horas. Una vez concluida la reacción (tlc) DMF (2 ml), se añadió gel de sílice (2 g), la mezcla se evaporó, y el residuo se purificó por cromatografía de gel de sílice, eluyente: CH_2Cl_2 / MeOH 95/5, CH_2Cl_2 / MeOH sat. NH_3 90/10 para producir el compuesto del título (81 mg, 29 %).

MS ES$^+$: 553.4, 554.4 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.90 (m, 2H); 2.06 (m, 2H); 2.26 (t, 2H); 3.09 (m, 2H); 3.36 (t, 2H); 3.67 (m, 2H); 3.99 (s, 3H); 4.00 (s, 2H); 4.29 (t, 2H); 7.14 (d, 1H); 7.30 (s, 1H); 7.37 (t, 1H); 7.47 (d, 1H); 7.65 (s, 1H); 7.85 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

3-metoxi-4-benciloxibenzonitrilo.

3-metoxi-4-benciloxibenzoldehído (4.87 g, 20 mmol) en ácido acético (25 ml) se trató con hidroxilamina HCl (2.8 g, 40 mmol), acetato de sodio (3.3 g, 40 mmol) a reflujo durante 6 horas. La mezcla se enfrió, se extrajo con agua y cloruro de metileno, se secó sobre $MgSO_4$, se evaporó, para producir el compuesto del título (4.8 g, 100 %). ^{1}HNMR (DMSO-d_6, TFA): 3.72 (s, 3H); 5.15 (s, 2H); 7.18 (d, 1H); 7.39 (m, 7H).

2-nitro-4-benciloxi-5-metoxibenzonitrilo.

3-metoxi-4-benciloxibenzonitrilo (4.78 g, 20 mmol) en ácido acético (10 ml) se adicionó lentamente a ácido nítrico (d = 1.42, 25 ml) a 20-30° con enfriamiento en un baño de hielo. La mezcla se agitó luego a temperatura ambiente durante 6 horas. La mezcla de la reacción se trató con hidróxido de potasio (10N) a 0°C. La mezcla básica (pH 10) se extrajo con CH_2Cl_2, la fase orgánica se secó sobre $MgSO_4$, se concentró para producir el compuesto del título (3.62 g, 64 %).

MS ES$^+$: 285 $(M+H)^+$

MS ES$^+$: 296.6 $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 2.26 (t, 2H); 3.26 (s, 3H); 3.37 (s, 3H); 3.81 (t, 2H); 3.87 (s, 3H); 4.23 (t, 2H); 7.34 (s, 1H); 7.53 (s, 1H); 8.56 (s, 1H).

g) N-(3-clorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4-ilamino)1,3- tiazol-5- il)acetamida.

N'-(2-ciano-4-metoxi-5-(3-cloropropoxifenil)-N,N-dimetilimidoformamida (296 mg, 1 mmol) y 2-(2-amino-1,3-tiazol-5-il)-N-(3-clorofenil)acetamida (268 mg, 1 mmol) en AcOH (1.5 ml), se irradió en un horno microondas a 120°C durante 40 minutos. La mezcla se enfrió, el sólido se filtró para producir el compuesto del título (445 mg, 72 %).

^{1}HNMR (DMSO-d_6, TFA): 2.31 (t, 2H); 3.84 (t, 2H); 3.98 (s, 3H); 3.99 (s, 2H); 4.32 (t, 2H); 7.13 (d, 1H); 7.29 (s, 1H); 7.36 (t, 1H); 7.46 (d, 1H); 7.63 (s, 1H); 7.85 (s, 1H); 7.88 (s, 1H); 9.07 (s, 1H).

Ejemplo 254. Preparación de Compuesto 431 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253 pero comenzando con N-(3,4-difluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4-il-amino)1,3- tiazol-5-il)acetamida (52 mg, 0.1 mmol) y pirrolidina (150µ, 1.8 mmol) produjo el compuesto del título (26 mg, 47 %).

^{1}HNMR (DMSO-d_6, TFA): 1.91 (m, 2H); 2.07 (m, 2H); 2.28 (t, 2H); 3.10 (m, 2H); 3.37 (t, 2H); 3.67 (m, 2H); 3.99 (s, 5H); 4.30 (t, 2H); 7.30 (s, 1H); 7.33 (m, 1H); 7.40 (q, 1H); 7.65 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Material inicial: N-(3,4-difluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxi quinazolin-4-il-amino)1,3-tiazol-5-il)acetamida se obtuvo por una reacción análoga a la descrita en ejemplo 130 pero comenzando con 2-(2-amino-1,3-tiazol-5-il)-N-(3,4-difluorofenil)acetamida (540 mg, 2 mmol) para producir el compuesto del título (980 mg, 78 %).

MS ES$^+$: 520.4, 522.4 $(M+H)^+$

^{1}HNMR (DMSO-d_6): 1.26 (t, 2H); 3.82 (t, 2H); 3.88 (s, 2H); 3.97 (s, 3H); 4.29 (t, 2H); 7.29 (s, 1H); 7.32 (m, 1H); 7.36 (s, 1H); 7.39 (t, 1H); 7.80 (m, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

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Ejemplo 255. Preparación de Compuesto 432 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253 pero comenzando con N-(3,5-difluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4-il-ámino)1,3-tiazol-5-il)acetamida (138 mg, 0.22 mmol) y dimetilamina (3.6 M en CH_2Cl_2, 3 ml, 3.6 mmol) produjo el compuesto del título (47 mg, 40 %).

MS ES^+: 529.5 $(M+H)^+$

^{1}HNMR (DMSO-d_6, TFA): 2.25 (t, 2H); 3.28 (t, 2H); 3.99 (s, 3H); 4.01 (s, 2H); 4.28 (t, 2H); 6.93 (m, 1H); 7.30 (s, 1H); 7.34 (m, 2H); 7.65 (s, 1H); 7.90 (s, 1H); 9.09 (s, 1H).

Material inicial: N-(3,5-difluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4-il-amino)1,3-tiazol-5-il)acetamida se obtuvo por reacción análoga a la descrita en ejemplo 130 pero comenzando con 2-(2-amino-1,3-tiazol-5-il)-N-(3,5-difluorofenil)acetamida (810 mg, 3 mmol) para producir el compuesto del título (630 mg, 40 %).

MS ES^+: 520.4, 522.4 $(M+H)^+$ ^{1}HNMR (DMSO-d_6): 2.26 (t, 2H); 3.84 (t, 2H); 3.92 (s, 2H); 3.98 (s, 3H); 4.30 (t, 2H);; 6.94 (m, 1H); 7.30 (5, 1H); 7.35 (m, 2H); 7.40 (s, 1H); 8.14 (5, 1H); 8.69 (s, 1H); 10.64 (5, 1H).

Ejemplo 256. Preparación de Compuesto 433 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253 pero comenzando con N-(3-cloro-4-fluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4-il-amino)1,3-tiazol-5-il)acetamida (123 mg, 0.22 mmol) y 2-amino-2-metil-1-propanol (89.1 mg, 3.3 mmol) produjo el compuesto del título (6 mg, 5 %).

MS ES^+: 589.4, $(M+H)^+$ ^{1}HNMR (DMSO-d_6, TFA): 1.24 (s, 6H); 2.22 (t, 2H); 3.10 (t, 2H); 3.45 (s, 2H); 3.98 (s, 3H); 4.31 (t, 2H); 7.29 (s, 1H); 7.38 (t, 1R); 7.50 (m, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 7.97 (s, 1H); 9.09 (s, 1H).

Material inicial: N-(3.cloro-4-fluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4-il-amino)1,3-tiazol-5-il)acetamida se obtuvo por reacción análoga a la descrita en ejemplo 130 pero comenzando con 2-(2-amino-1,3-tiazol-5-il)-N-(3-cloro-4-fluorofenil)acetamida (2.29 g, 8.0 mmol) para producir el compuesto del título (3.62 g, 84 %). MS ES^+: 536.3, 538.3 $(M+H)^+$

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1HNMR ($DMSOd_6$) : 2.26 (t, 2H); 3.82 (t, 2H); 3.88 (s, 2H); 3.96 (s, 3H); 4.29 (t, 2H); 7.28 (s, 1H); 7.38 (t, 1H); 7.39 (s, 1H); 7.48 (m, 1H); 7.93 (m, 1H); 8.12 (s, 1H); 8.67 (s, 1H); 10.47 (s, 1H).

Ejemplo 257. Preparación de Compuesto 434 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con N-(3-fluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4-il-amino)1,3-tiazol-5-il)acetamida (116 mg, 0.22 mmol) y 2-amino-2-metil-1-propanol (89 mg, 3.3 mmol) produjo el compuesto del título (40 mg, 33 %).

MS ES^+ : 555.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.22 (t, 2H); 3.09 (t, 2H); 3.16 (s, 2H); 3.97 (s, 3H); 4.30 (t, 2H); 6.86 (t, 1H); 7.28 (s, 1H); 7.33 (m, 2H); 7.58 (m, 1H); 7.62 (s, 1H); 7.91 (s, 1H); 9.07 (s, 1H).

Material inicial: N-(3-fluorofenil)-2-(2-(7-(3-cloropropoxi)-6-metoxiquinazolin-4- il-amino)1,3-tiazol-5-il)acetamida se obtuvo mediante una reacción análoga a la descrita en ejemplo 253 pero comenzando con 2-(2-amino-1,3-tiazol-5-il)-N-(3-fluorofenil)acetamida (2.01 g, 8 mmol) para producir el compuesto del título (3.08 g, 77 %).

MS ES^+ : 502.4, 504.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.28 (t, 2H); 3.84 (t, 2H); 3.90 (s, 2H); 3.98 (s, 3H); 4.31 (t, 2H); 6.91 20 (t, 1H); 7.30 (s, 1H); 7.35 (m, 2H); 7.39 (s, 1H); 7.63 (d, 1H); 8.14 (s, 1H); 8.69 (s, 1H); 10.48 (s, 1H).

Ejemplo 258. Preparación de Compuesto 435 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con 4-hidroxiperidina 25 (405 mg, 4.0 mmol) produjo el compuesto 435 en Tabla 17 (82 mg, 70 %).

MS ES^+ : 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.43 (m, 2H); 1.73 (m, 2H); 1.95 (m, 2H); 2.03 (t, 2H); 2.44 (t, 2H); 2.74 (m, 2H); 3.38 (m, 1H); 3.90 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.53 (d, 1H); 7.26 (s, 1H); 7.31 (m, 1H); 7.39 (s, 1H); 7.42 (ddd, 1H); 7.83 (m, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.50 (s, 1H).

Ejemplo 259. Preparación de Compuesto 436 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con N,N- dimetilendiamina (0.44 ml, 4.0 mmol) produjo el compuesto 436 en Tabla 17 (40 mg, 35 %).

MS ES^+ : 572.5 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.95 (m, 2H); 2.14 (s, 6H); 2.33 (t, 2H); 2.63 (t, 2H); 2.73 (t,2H); 3.89 (s, 2H); 3.97 (s, 3H); 4.22 (t, 2H); 7.26 (s, 1H); 7.34 (m, 1H); 7.38 (s, 1H); 7.41 (ddd, 1H); 7.82 (m, 1H); 8.11 (s, 1H); 8.67 (s, 1H); 10.50 (s, 1H).

Ejemplo 260. Preparación de Compuesto 437 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 254, pero comenzando con piperidina (0.4 ml, 3.0 mmol) produjo el compuesto 437 en Tabla 17 (67 mg, 59 %). MS ES^+ : 569.5 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H); 1.52 (m, 4H); 1.95 (m, 2H); 2.42 (m, 4H); 2.48 (t,2H); 3.89 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 7.25 (s, 1H); 7.33 (m, 1H); 7.39 (8, 1H); 7.41 (ddd, 1H); 7.82 (m, 1H); 8.11 (s, 1H); 8.68 (s, 1H); 10.51 (s, 1H).

Ejemplo 261. Preparación de Compuesto 438 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con 2-metilaminoetanol (248 mg, 3.3 mmol) produjo el compuesto 438 en Tabla 17 (23 mg, 19 %). MS ES^+ : 559 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.95 (m, 2H); 2.23 (s, 3H); 2.47 (m, 2H); 3.32 (m, 2H); 3.49 (m, 2H); 3.90 (s, 2H); 3.98 (s, 3H); 4.21 (t, 2H); 4.37 (m, 1H); 7.27 (s, 1H); 7.34 (m, 1H); 7.38 (s, 1H); 7.40 (dd, 1H); 7.82 (ddd, 1H); 8.13 (brs, 1H); 8.68 (s, 1H); 10.50 (s, 1H).

Ejemplo 262. Preparación de Compuesto 439 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con 1,2-diamino-2-metilpropano (291 mg, 3.3 mmol) produjo el compuesto 439 en Tabla 17 (16 mg, 13 %).

MS ES^+ : 572 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.10 (s, 6H); 1.96 (m, 2H); 2.48 (s, 2H); 2.75 (t, 2H); 3.89 (s, 2H); 3.97 (s, 3H); 4.26 (t, 2H); 7.27 (s, 1H); 7.34 (m, 1H); 7.37 (s, 1H); 7.42 (dd, 1H); 7.83 (ddd, 1H); 8.10 (s, 1H); 8.66 (s, 1H); 10.50 (s, 1H).

Ejemplo 263. Preparación de Compuesto 440 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con ciclohexilamina (327 mg, 3.3 mmol) produjo el compuesto 440 en Tabla 17 (70 mg, 55 %).

MS ES^+ : 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.12 (m, 1H); 1.27 (m, 4H); 1.63 (brd, 1H); 1.78 (m, 2H); 2.04 (m, 2H); 2.16 (m, 2H); 3.03 (m, 1H); 3.16 (t, 2H); 3.90 (s, 2H); 3.98 (s, 3H); 4.29 (t, 2H); 7.31 (s, 1H); 7.34 (m, 1H); 7.40 (s, 1H); 7.42 (dd, 1H); 7.82 (ddd, 1H); 8.16 (brs, 1H); 8.70 (s, 1H); 10.51 (s, 1H).

Ejemplo 264. Preparación de Compuesto 441 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con N,N, N'-trimetiletilendiamina (337 mg, 3.3 mmol) produjo el compuesto 441 en Tabla 17 (63 mg, 49 %).

MS ES^+ : 587 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (m, 2H); 2.88 (s, 6H); 2.93 (s, 3H); 3.38 (m, 2H); 3.56 (m, 4H); 3.98 (s, 5H); 4.30 (t, 2H); 7.29 (m, 1H); 7.33 (s, 1H); 7.35 (dd, 1H); 7.63 (5, 1H); 7.80 (ddd, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 265. Preparación de Compuesto 442 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con (R)-(-)-2-pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 442 en Tabla 17 (90 mg, 70 %).

MS ES^+ : 585 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 1.79 (m, 1H); 1.91 (m, 1H); 2.03 (m, 1H); 2.11 (m, 1H); 2.29 25 (m, 2H); 3.21 (m, 2H); 3.62 (m, 4H); 3.77 (m, 1H); 3.98 (s, 5H); 4.29 (t, 2H); 7.30 (s, 1H); 7.32 (m, 1H); 7.39 (dd, 1H); 7.64 (s, 1H); 7.80 (ddd, 1H); 7.90 (s, 1H); 9.08 (s, 1H).

Ejemplo 266. Preparación de Compuesto 443 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con (S)-(+)-2-pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 443 en Tabla 17 (82 mg, 63 %).

MS ES^+: 585 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.76 (m, 1H); 1.88 (m, 1H); 2.01 (m, 1H); 2.10 (m, 1H); 2.26 (m, 2H); 3.21 (m, 2H); 3.59 (m, 4H); 3.74 (dd, 1H); 3.95 (s, 5H); 4.27 (t, 2H); 7.27 (s, 1H); 7.28 (m, 1H); 7.34 (dd, 1H); 7.60 (s, 1H); 7.77 (ddd, 1H); 7.88 (s, 1H); 9.05 (s, 1H).

Ejemplo 267. Preparación de Compuesto 444 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con 3-pirrolidinol (288 mg, 3.3 mmol) produjo el compuesto 444 en Tabla 17 (15 mg, 12 %).

MS ES$^+$: 571 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.85-2.04 (m, 2H); 2.28 (m, 2H); 3.03-3.54 (m, 4H); 3.75 (m, 2H); 3.99 (s, 5H); 4.28 (m, 2H); 4.40-4.52 (m, 1H); 7.29 (s, 1H); 7.33 (m, 1H); 7.39 (dd, 1H); 7.64 (s, 1H); 7.81 (ddd, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 268. Preparación de Compuesto 445 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con 1-(2-aminoetil)pirrolidina (377 mg, 3.3 mmol) produjo el compuesto 445 en Tabla 17 (20 mg, 15 %).

MS ES$^+$: 598 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.92 (m, 2H); 2.06 (m, 2H); 2.24 (m, 2H); 3.11 (m,2H); 3.23 (t, 2H); 3.42 (m, 2H); 3.49 (m, 2H); 3.52 (m, 2H); 4.00 (3, 5H); 4.32 (t, 2H); 7.32 (s, 1H); 7.33 (m, 1H); 7.39 (dd, 1H); 7.65 (s, 1H); 7.81 (ddd, 1H); 7.92 (s, 1H); 9.10 (s, 1H).

Ejemplo 269. Preparación de Compuesto 446 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con 1-acetilpiperazina (423 mg, 3.3 mmol) produjo el compuesto 446 en Tabla 17 (100 mg, 74 %). MS ES$^+$: 612 $(M+H)^+$ ^{1}HNMR (DMSOd_6): 2.00 (s, 5H); 2.35 (m, 2H); 2.42 (m, 2H); 3.92-3.06 (m, 1H); 3.45 (m, 4H); 3.56 (t, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4.23 (t, 2H); 7.28 (s, 1H); 7.34 (m, 1H); 7.40 (s, 1H); 7.42 (dd, 1H); 7.83 (ddd, 1H); 8.13 (brs, 1H); 8.69 (s, 1H).

Ejemplo 270. Preparación de Compuesto 447 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con 1-(2-morfolinoetil)-piperazina (658 mg, 3.3 mmol) produjo el compuesto 447 en Tabla 17 (44 mg, 29%). MS ES^+ : 683 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.98 (m, 2H); 2.30-2.70 (m, 18H); 3.58 (m, 4H); 3.90 (s, 2H); 3.97 (s, 3H); 4.21 (t, 2H); 7.26 (s, 1H); 7.33 (m, 1H); 7.40 (s, 1H); 7.41 (dd, 1H); 7.82 (ddd, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.54 (s, 1H).

Ejemplo 271. Preparación de Compuesto 448 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con 2-piperidinetanol (426 mg, 3.3 mmol) produjo el compuesto 448 en Tabla 17 (19 mg, 14 %).

MS ES^+ : 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.45-1.92 (m, 7H); 2.00-2.15 (m, 1H); 2.20-2.40 (m, 2H); 3.10-3.70 (m, 7H); 3.99 (s, 5H); 4.30 (m, 2H); 7.30 (s, 1H); 7.34 (m, 1H); 7.40 (dd, 1H); 7.64 (s, 1H); 7.81 (ddd, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 272. Preparación de Compuesto 449 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con 1-(2-hidroxietil)piperazina (430 mg, 3.3 mmol) produjo el compuesto 449 en Tabla 17 (90 mg, 66 %).

MS ES^+ : 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H); 2.35-2.47 (m, 12H); 3.49 (q, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.20 (t, 1H); 4.37 (t, 1H); 7.25 (s, 1H); 7.33 (m, 1H); 7.39 (s, 1H); 7.41 (dd, 1H); 7.81 (ddd, 1H); 8.12 (brs, 1H); 8.68 (s, 1H); 10.50 (s, 1H); 12.03 (brs, 1H).

Ejemplo 273. Preparación de Compuesto 450 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con ciclopentilamina (281 mg, 3.3 mmol) produjo el compuesto 450 en Tabla 17 (43 mg, 34 %). MS ES^+ : 614 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.53 (m, 4H); 1.69 (m, 2H); 1.93 (m, 2H); 2.10 (m, 2H); 3.00 (m, 2H); 3.38 (m,2H); 3.90 (s, 2H); 3.98 (s, 3H); 4.28 (t, 2H); 7.30 (s, 1H); 7.32 (m, 1H); 7.42 (dd, 1H); 7.81 (ddd, 1H); 8.15 (brs, 1H); 8.70 (s, 1H); 10.51 (s, 1H).

Ejemplo 274. Preparación de Compuesto 451 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con 4-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 451 EN Tabla 17 (53 mg, 39 %).

MS ES^+ : 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H); 1.36 (m, 3H); 1.63 (brd, 2H); 1.87 (m, 2H); 1.95 (m, 2H); 2.45 (m, 1H); 2.86 (m, 2H); 3.44 (m, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.32 (t, 1H); 7.26 (s, 1H); 7.31 (m, 1H); 7.40 (s, 1H); 7.42 (dd, 1H); 7.82 (ddd, 1H); 8.13 (brs, 1H); 8.68 (s, 1H); 10.50 (s, 1H); 12.02 (brs, 1H).

Ejemplo 275. Preparación de Compuesto 452 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con clorhidrato de L-alanin-T-butiléster (599 mg, 3.3 mmol) y tratando la mezcla de la reacción cruda con una solución 1:1 de CH_2Cl_2-TFA (4 ml) produjo el compuesto 452 en Tabla 17 (75 mg, 60 %).

MS ES^+ : 573 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.48 (d, 3H); 2.24 (m, 2H); 3.22 (m, 2H); 3.97 (s, 5H); 4.15 (q, 1H); 4.30 (m, 2H); 7.30 (s, 1H); 7.34 (m, 1H); 7.40 (dd, 1H); 7.64 (s, 1H); 7.81 (ddd, 1H); 7.90 (s, 1H); 9.08 (s, 1H); 10.60 (s, 1H).

Ejemplo 276. Preparación de Compuesto 453 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con 3-hidroxipiperidina (334 mg, 3.3 mmol) produjo el compuesto 453 en Tabla 17 (84 mg, 65 %).

MS ES^+ : 585 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.07 (m, 1H); 1.41 (m, 1H); 1.62 (m, 1H); 1.76 (m, 2H); 1.87 (m, 1H); 1.95 (m, 2H); 2.47 (m, 2H); 2.68 (m, 1H); 2.85 (m, 1H); 3.48 (m, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4.20 (t, 2H); 4.59 (d, 1H); 7.26 (s, 1H); 7.31 (m, 1H); 7.39 (s, 1H); 7.42 (dd, 1H); 7.81 (ddd, 1H); 8.12 (brs, 1H); 8.68 (s, 1H); 10.50 (s, 1H); 12.02 (brs, 1H).

740

Ejemplo 277. Preparación de Compuesto 454 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con 4-hidroximetilpiperidina (380 mg, 3.3 mmol) produjo el compuesto 454 en Tabla 17 (42 mg, 32 5 %).

MS ES^+ : 599 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.13 (m, 2H); 1.33 (m, 1H); 1.62 (brd, 2H); 1.90 (m, 2H); 1.95 (m, 2H); 2.44 (m, 2H); 2.88 (m, 2H); 3.22 (t, 2H); 3.86 (s, 2H); 3.93 (s, 3H); 4.17 (t, 2H); 4.38 (t, 1H); 7.22 (s, 1H); 7.31 (m, 1H); 7.36 (s, 1H); 7.38 (dd, 1H); 7.80 (ddd, 1H); 8.09 (brs, 1H); 8.65 (s, 1H); 10.46 (s, 1H); 12.00 (brs, 1H).

Ejemplo 278. Preparación de Compuesto 455 en Tabla 17

Una reacción análoga a la descrita en ejemplo 254, pero comenzando con 1-amino-2-propanol (248 mg, 3.3 mmol) produjo el compuesto 455 en Tabla 17 (52 mg, 42 %).

MS ES^+ : 573 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H); 1.95 (m, 2H); 2.48 (m, 2H); 2.72 (t, 2H); 3.68 (m, 1H); 3.89 (s, 2H); 3.97 (s, 3H); 4.23 (t, 2H); 4.46 (m, 1H); 7.26 (s, 1H); 7.32 (m, 1H); 7.38 (s, 1H); 7.41 (dd, 1H); 7.81 (ddd, 1H); 8.11 (s, 1H); 8.67 (s, 1H); 10.49 (s, 1H).

Ejemplo 279. Preparación de Compuesto 456 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con clorhidrato de L-alamin-t-butiléster (599 mg, 3.3 mmol) y tratando la mezcla de la reacción cruda con CH_2Cl_2-TFA (1/1, 4 ml) produjo el compuesto 456 en Tabla 17 (106 mg, 84 %).

MS ES^+ : 571 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.40 (d, 3H); 2.25 (m, 2H); 3.20 (m, 2H); 3.98 (s, 3H); 4.00 (s, 2H); 4.14 (m, 1H); 4.31 (t, 2H); 7.13 (dd, 1H); 7.32 (s, 1H); 7.35 (t, 1H); 7.47 (dd, 1H); 7.63 (s, 1H); 7.86 (t, 1H); 7.90 (s, 1H); 8.30 (m, 1H); 9.08 (s, 1H); 10.60 (s, 1H).

Ejemplo 280. Preparación de Compuesto 457 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con 2-metilaminoetanol (248 mg, 3.3 mmol) produjo el compuesto 457 en Tabla 17 (86 mg, 70 %). MS ES^+: 557 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.93 (m, 2H); 2.20 (s, 3H); 2.43 (t, 2H); 2.48 (m, 1H); 2.55 (m, 1H); 3.47 (dd, 2H); 3.89 (s, 2H); 3.96 (s, 3H); 4.19 (t, 2H); 4.34 (t, 1H); 7.13 (brd, 1H); 7.25 (s, 1H); 7.35 (t, 1H); 7.38 (s, 1H); 7.47 (s, 1H); 7.84 (s, 1H); 8.11 (dd, 1H); 8.66 (s, 1H); 10.44 (s, 1H); 12.00 (dd, 1H).

Ejemplo 281. Preparación of comnound 458 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con 1,2-diamino-2-metilpropano (291 mg, 3.3 mmol) produjo el compuesto 458 en Tabla 17 (21 mg, 17 %).

MS ES^+ : 570 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.39 (s, 1H); 2.28 (m, 2H); 3.23 (m, 4H); 3.98 (s, 3H); 4.00 (s, 2H); 4.32 (m, 2H); 7.14 (ddd, 1H); 7.31 (s, 1H); 7.36 (t, 1H); 7.47 (ddd, 1H); 7.64 (s, 1H); 7.86 (t, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 282. Preparación de Compuesto 459 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con ciclohexilamina (327 mg, 3.3 mmol) produjo compuesto 459 en Tabla 17-85 mg, 66 %).

MS ES^+ : 581 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.13 (m, 1H); 1.26 (m, 4H); 1.62 (brd, 1H); 1.77 (m, 2H); 2.03 (m, 2H); 2.15 (m, 2H); 3.07 (m, 1H); 3.14 (t, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.29 (t, 2H); 7.13 (brd, 1H); 7.29 (s, 1H); 7.36 (t, 1H); 7.39 (s, 1H); 7.46 (dd, 1H); 8.16 (dd, 1H); 8.26 (brs, 1H); 8.69 (s, 1H); 10.45 (s, 1H).

Ejemplo 283. Preparación de Compuesto 460 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con N,N-dimetiletilendiamina (291 mg, 3.3 mmol) produjo el compuesto 460 en Tabla 17 (41 mg, 32 %)

MS ES^+ : 570 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 2.00 (m, 1H); 2.17 (s, 6H); 2.38 (t, 2H); 2.72 (t, 2H); 2.81 (t, 2H); 3.91 (s, 2H); 3.98 (s, 3H); 4.24 (t, 2H); 7.14 (dd, 1H); 7.27 (s, 1H); 7.37 (t, 1H); 7.40 (s, 1H); 7.49 (dd, 1H); 7.86 (t, 1H); 8.13 (s, 1H); 8.69 (s, 1H); 10.50 (s, 1H).

Ejemplo 284. Preparación de Compuesto 461 en Tabla 11

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con N,N,N'-trimetiletilendiamina (337 mg, 3.3 mmol) produjo el compuesto 461 en Tabla 17 (11 mg, 8 %).

MS ES^+ : 584 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.91 (m, 2H); 2.12 (s, 6H); 2.20 (s, 3H); 2.33 (m, 3H); 2.42 (m, 3H); 3.76 (s, 2H); 3.91 (s, 3H); 4.12 (t, 2H); 6.98 (s, 1H); 7.11 (dd, 1H); 7.16 (s, 4H); 7.35 (t, 1H); 7.52 (dd, 1H); 7.83 (s, 1H); 7.88 (t, 1H); 8.37 (s, 1H); 10.56 (s, 1H).

Ejemplo 285. Preparación de Compuesto 462 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con (R)-(-)-2-pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 462 en Tabla 17 (76 mg, 59 %). MS ES^+ : 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.77 (m, 1H); 1.89 (m, 1H); 2.02 (m, 1H); 2.4 (m, 1H); 2.29 (m, 2H); 3.21 (m, 2H); 3.62 (m, 4H); 3.76 (m, 1H); 3.98 (s, 3H); 3.99 (s, 2H); 4.29 (t, 2H); 7.13 (dd, 1H); 7.29 (s, 1H); 7.35 (t, 1H); 7.46 (dd, 1H); 7.63 (s, 1H); 7.85 (t, 1H); 7.90 (s, 1H); 9.08 (s, 1H).

Ejemplo 286. Preparación de Compuesto 463 en Tabla 11

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con (S)-(+)-2- pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 463 en Tabla 17 (72 mg, 56 %). MS ES^+ : 583 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 1.78 (m, 1H); 1.90 (m, 1H); 2.03 (m, 1H); 2.13 (m, 1H); 2.30 (m, 2H); 3.23 (m, 2H); 3.62 (m, 4H); 3.77 (m, 1H); 3.98 (s, 3H); 4.00 (s, 2H); 4.30 (t, 2H) 25 ; 7.14 (dd, 1H); 7.30 (s, 1H); 7.36 (t, 1H); 7.46 (dd, 1H); 7.64 (s, 1H); 7.85 (s, 1H); 7.90 (s, 1H); 9.09 (s, 1H).

Ejemplo 287. Preparación de Compuesto 464 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con 4-hidroxipiperidina 30 (334 mg, 3.3 mmol) produjo el compuesto 464 en Tabla 17 (63 mg, 49 %). MS ES^+ : 583 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.41 (m, 2H); 1.73 (m, 2H); 1.96 (m, 2H); 2.04 (m, 2H); 2.74 (m, 2H); 2.50 (m, 2H); 3.43 (s, 1H); 3.91 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.54 (d, 1H); 7.14 (d,

1H); 7.26 (s, 1H); 7.37 (t, 1H); 7.40 (s, 1H); 7.49 (d, 1H); 7.86 (t, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.46 (s, 1H).

Ejemplo 288. Preparación de Compuesto 465 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con 3-pirrolidinol (288 mg, 3.3 mmol) produjo el compuesto 465 en Tabla 17 (57 mg, 45 %).

MS ES^+ : 569 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.56 (m, 1H); 1.99 (m, 4H); 2.36 (m, 1H); 2.56 (m, 4H); 2.74 (m, 1H); 3.91 (s, 2H); 3.98 (s, 3H); 4.21 (t, 2H); 4.70 (d, 1H); 7.14 (dd, 1H); 7.26 (s, 1H); 7.37 (t, 1H); 7.40 (s, 1H); 7.49 (dd, 1H); 7.86 (t, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.47 (s, 1H); 12.03 (brs, 1H).

Ejemplo 289. Preparación de Compuesto 466 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con 1-(2- aminoetil)pirrolidina (377 mg, 3.3 mmol) produjo el compuesto 466 en Tabla 17 (39 mg, 29 %).

MS ES^+ : 596 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.91 (m,2H); 2.06 (m, 2H); 2.24 (m, 2H); 3.11 (m, 2H); 3.23 (t, 2H); 3.42 (m, 2H); 3.48 (m, 2H); 3.67 (m, 2H); 3.98 (s, 3H); 3.99 (s, 2H); 4.31 (t, 2H); 7.14 (d, 1H); 7.31 (s, 1H); 7.35 (t, 1H); 7.47 (d, 1H); 7.64 (s, 1H); 7.85 (t, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 290. Preparación de Compuesto 467 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con 4-hidroximetilpiperidina (380 mg, 3.3 mmol) produjo el compuesto 467 en Tabla 17 (64 mg, 49 %).

MS ES^+ : 597 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H); 1.35 (m, 1H); 1.65 (brd, 2H); 1.88 (m, 2H); 1.97 (m, 2H); 2.47 (m, 2H); 2.90 (brd, 2H); 3.25 (t, 2H); 3.91 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.41 (t, 1H); 7.14 (d, 1H); 7.25 (s, 1H); 7.37 (t, 1H); 7.39 (s, 1H); 7.48 (s, 1H); 7.86 (s, 1H); 8.12 (brs, 1H); 8.68 (s, 1H); 10.46 (s, 1H); 12.03 (s, 1H).

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Ejemplo 291. Preparación de Compuesto 468 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con 1-(2-hidroxietil)piperazina (430 mg, 3.3 mmol) produjo el compuesto 468 en Tabla 17 (63 mg, 47 %).

MS ES^+ : 612 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H); 2.41 (m, 12H); 3.50 (q, 2H); 3.91 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.37 (t, 1H); 7.14 (dd, 1H); 7.25 (s, 1H); 7.37 (t, 1H); 7.39 (s, 1H); 7.48 (d, 1H); 7.86 (t, 1H); 8.12 (brs, 1H); 8.68 (s, 1H); 10.46 (s, 1H); 12.04 (s, 1H).

Ejemplo 292. Preparación de Compuesto 469 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con ciclopentilamina 281 mg, 3.3 mmol) produjo el compuesto 469 en Tabla 17 (77 mg, 61 %).

MS ES^+ : 567 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.58 (m, 4H);1.73 (m, 2H); 2.00 (m, 2H); 2.17 (m, 2H); 3.12 (t, 2H); 3.56 (m, 1H); 3.92 (s, 3H); 3.99 (s, 3H); 4.31 (t, 2H); 7.15 (d, 1H); 7.31 (s, 1H); 7.37 (t, 1H); 7.41 (s, 1H); 7.48 (d, 1H); 7.86 (s, 1H); 8.16 (brs, 1H); 8.71 (s, 1H); 10.47 (s, 1H); 12.03 (brs, 1H).

Ejemplo 293. Preparación de Compuesto 470 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con 4-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 470 en Tabla 17 (78 mg, 58 %). MS ES^+ : 611 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.16 (m, 2H); 1.36 (m, 3H); 1.63 (d, 2H); 1.88 (t, 2H); 1.96 (m, 2H); 25 2.44 (t, 2H); 2.87 (d, 2H); 3.44 (m, 2H); 3.9 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.33 (t, 1H); 7.14 (d, 1H); 7.25 (s, 1H); 7.37 (t, 1H); 7.40 (s, 1H); 7.49 (d, 1H); 7.86 (t, 1H); 8.12 (brs, 1H); 8.68 (s, 1H); 10.46 (s, 1H); 12.04 (s, 1H).

Ejemplo 294. Preparación de comnound 471 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con 3-hidroxipiperidina (339 mg, 3.3 mmol) produjo el compuesto 471 en Tabla 17 (117 mg, 91 %).

MS ES^+: 583 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.07 (m, 1H); 1.41 (m, 1H); 1.62 (m, 1H); 1.70-1.90 (m, 3H); 1.95 (m, 2H); 2.46 (m, 2H); 2.67 (m, 1H); 2.83 (brd, 1H); 3.47 (m, 1H); 3.89 (s, 2H); 3.96 (s, 3H); 4.20 (t, 2H); 4.57 (d, 1H); 7.13 (ddd, 1H); 7.24 (s, 1H); 7.36 (t, 1H); 7.38 (s, 1H); 7.47 (d, 1H); 7.84 (t, 1H); 8.11 (brs, 1H); 8.67 (s, 1H); 10.46 (s, 1H); 12.00 (brs, 1H).

Ejemplo 295. Preparación de Compuesto 472 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con (S)-1-amino-2-propanol (248 mg, 3.3 mmol) produjo el compuesto 472 en Tabla 17 (55 mg, 45 %).

MS ES^+ : 557 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H); 1.96 (m, 2H); 2.48 (m, 2H); 2.73 (t, 2H); 3.70 (m, 1H); 3.91 (s, 2H); 3.97 (s, 3H); 4.24 (t, 2H); 4.48 (brs, 1H); 7.14 (d, 1H); 7.27 (s, 1H); 7.37 (t, 1H); 7.39 (s, 1H); 7.49 (d, 1H); 7.86 (t, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.46 (s, 1H).

Ejemplo 296. Preparación de Compuesto 473 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con (R)-1-amino-2-propanol (248 mg, 3.3 mmol) produjo el compuesto 473 en Tabla 17 (84 mg, 68 %).

MS ES^+ : 557 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.04 (d, 3H); 1.93 (m, 2H); 2.45 (m, 2H); 2.70 (t, 2H); 3.67 (m, 1H); 3.88 (5, 2H); 3.95 (s, 3H); 4.21 (t, 2H); 4.46 (brs, 1H); 7.12 (d, 1H); 7.24 (s, 1H); 7.35 (t, 1H); 7.37 (s, 1H); 7.47 (d, 1H); 7.84 (t, 1H); 8.09 (s, 1H); 8.65 (s, 1H); 10.45 (s, 1H).

Ejemplo 297. Preparación de Compuesto 474 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con tert-butil-1-piperazincarboxilato (615 mg, 3.3 mmol) y tratando la mezcla de la reacción cruda con ácido hidroclorhídrico 1,4 dioxano (4.0 M, 2 ml) produjo el compuesto 474 (3 HCl) en Tabla 17 (89 mg, 61 %.

MS ES^+: 568 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 2.34 (m, 2H); 3.25-3.68 (m, 10H); 3.99 (s, 3H); 4.01 (s, 2H); 4.33 (t, 2H); 7.14 (dd, 1H); 7.35 (5, 1H); 7.37 (t, 1H); 7.49 (d, 1H); 7.65 (s, 1H); 7.86 (t, 1H); 7.91 (s, 1H); 9.09 (s, 1H); 10.66 (s, 1H).

Ejemplo 298. Preparación de Compuesto 475 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con 2-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 475 en Tabla 17 (29 mg, 22 %).

MS ES^+ : 611 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.30 (m, 2H); 1.48 (m, 4H); 1.60 (m ,2H); 1.76 (m, 1H); 1.93 (m, 2H); 2.26 (m, 1H); 2.48 (m, 1H); 2.79 (m, 2H); 3.46 (m, 2H); 3.89 (s, 2H); 3.96 (s, 3H); 4.18 (t, 2H); 4.40 (brs, 1H); 7.13 (d, 1H); 7.24 (s, 1H); 7.35 (t, 1H); 7.38 (s, 1H); 7.47 (d, 1H); 10 7.84 (s, 1H); 8.11 (brs, 1H); 8.67 (s, 1H); 10.44 (s, 1H).

Ejemplo 299. Preparación de Compuesto 476 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con 2-amino-2-metil-1-propanol (294 mg, 3.3 mmol) produjo el compuesto 476 en Tabla 17 (49 mg, 39 %).

MS ES^+ : 571 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.25 (s, 6H); 2.22 (m, 2H); 3.10 (m, 2H); 3.46 (s, 2H); 3.99 (s, 3H); 4.00 (s, 2H); 4.32 (t, 2H); 7.15 (d, 1H); 7.30 (s, 1H); 7.37 (t, 1H); 7.47 (d, 1H); 7.65 (s, 1H); 7.86 (s, 1H); 7.91 (s, 1H); 9.09 (s, 4H); 10.56 (s, 1H).

Ejemplo 300. Preparación de Compuesto 477 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con 1-(2-dimetilaminoetilpiperazina (519 mg, 3.3 mmol) produjo el compuesto 477 en Tabla 17 (19 mg, 15 %). MS ES^+ : 639 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H); 2.13 (s, 6H); 2.30-2.52 (m, 14H); 3.89 (s, 2H); 3.95 (s, 3H); 4.18 (t, 2H); 7.13 (d, 1H); 7.23 (s, 1H); 7.35 (t, 1H); 7.38 (s, 1H); 7.84 (t, 1H); 8.10 (s, 1H); 8.67 (s, 1H); 10.45 (s, 1H).

Ejemplo 301. Preparación de Compuesto 478 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con una solución de dimetilamina en cloroformo (3,6M, 3 ml, 3.6 mmol) produjo el compuesto 478 en Tabla 17 (44 mg, 34 %).

MS ES$^+$: 527 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.95 (m, 2H); 2.17 (s, 6H); 2.41 (t,2H); 3.89 (s, 2H); 3.96 (s, 3H); 4.18 (t, 2H); 7.12 (d, 1H); 7.23 (s, 1H); 7.35 (t, 1H); 7.38 (s, 1H); 7.47 (d, 1H); 7.84 (t, 1H); 8.11 (s, 1H); 8.67 (s, 1H); 10.45 (s, 1H).

Ejemplo 302. Preparación de Compuesto 479 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con aminometilciclopropano (234 mg, 3.3 mmol) produjo el compuesto 479 en Tabla 17 (88 mg, 65 %).

MS ES$^+$: 553 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 0.18 (m, 2H); 0.46 (m, 2H); 0.94 (m, 1H); 2.01 (m, 2H); 2.51 (d, 2H); 2.79 (t, 2H); 3.94 (s, 2H); 4.01 (s, 3H); 4.28 (t, 2H); 7.18 (d, 1H); 7.31 (s, 1H); 7.41 (t, 1H); 7.43 (s, 1H); 7.53 (d, 1H); 7.90 (s, 1H); 8.16 (s, 1H); 8.72 (s, 1H); 10.53 (s, 1H).

Ejemplo 303. Preparación de Compuesto 480 en Tabla 17

Una reacción análoga a la descrita en ejemplo 253, pero comenzando con piperidina (344 mg, 4.0 mmol) produjo el compuesto 480 en Tabla 17 (52 mg, 40 %).

MS ES$^+$: 565 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.43 (m, 1H); 1.69 (m, 3H); 1.87 (d, 2H); 2.30 (m, 2H); 2.96 (t, 2H); 3.27 (t, 2H); 3.55 (d, 2H); 3.99 (s, 3H); 4.00 (s, 2H); 4.31 (t, 2H); 7.15 (d, 1H); 7.31 (s, 1H); 7.37 (t, 1H); 7.47 (d, 1H); 7.65 (s, 1H); 7.86 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H); 10.56 (s, 1H).

Ejemplo 304. Preparación de Compuesto 481 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con 1-(2-dimetilaminometil)piperazina (281 mg, 3.3 mmol) produjo el compuesto 481 en Tabla 17 (81 mg, 64 %).

MS ES$^+$: 641 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (m, 2H); 2.80-3.70 (m, 14H); 2.84 (s, 6H); 3.98 (s, 3H); 4.01 (s, 2H); 4.30 (brt, 1H); 6.90 (m, 1H); 7.32 (s, 2H); 7.35 (dd, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 305. Preparación de Compuesto 482 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con (S)-(+)-2-pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 482 en Tabla 17 (58 mg, 45 %).

MS ES^+ : 585 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 1.79 (m, 1H); 1.90 (m, 1H); 2.02 (m, 1H); 2.13 (m, 1H); 2.30 (m, 2H); 3.33 (m, 2H); 3.62 (m, 4H); 3.77 (dd, 1H); 3.99 (s, 3H); 4.01 (s, 2H); 4.30 (brt, 2H); 6.91 (t, 1H); 7.30 (s, 1H); 7.35 (dd, 2H); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 306. Preparación de Compuesto 483 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con 4-hidroxipiperidina (334 mg, 3.3 mmol) produjo el compuesto 483 en Tabla 17 (28 mg, 22 %). MS ES^+ : 585 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H); 1.73 (m, 2H); 1.96 (m, 2H); 2.03 (m, 2H); 2.45 (m, 2H); 2.74 (m, 2H); 3.45 (m, 1H); 3.92 (s, 2H); 3.97 (s, 3H); 3.97 (t, 2H); 4.54 (d, 1H); 6.95 (m, 1H); 7.26 (s, 1H); 7.36 (dd, 2H); 7.40 (s, 1H); 8.14 (brs, 1H);8.68 (s, 1H); 10.65 (s, 1H); 12.04 (brs, 1H).

Ejemplo 307. Preparación de Compuesto 484 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con 3-pirrolidinol (288 20 mg, 3.3 mmol) produjo el compuesto 484 en Tabla 17 (30 mg, 23 %). MS ES^+ : 571 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.57 (m, 1H); 1.97 (m, 4H); 2.37 (m, 1H); 2.58 (m, 4H); 2.74 (m, 1H); 3.92 (s, 2H); 3.98 (s 3H); 4.22 (brt, 2H); 4.72 (brs, 1H); 6.95 (m, 1H); 7.26 (s, 1H); 7.36 (dd, 2H); 7.40 (s, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.65 (s, 1H); 12.04 (brs, 1H).

Ejemplo 308. Preparación de Compuesto 485 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con 1-(2-aminoetil)pirrolidina (377 mg, 3.3 mmol) produjo el compuesto 485 en Tabla 17 (25 mg, 19 %). MS ES^+ : 598 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA) : 1.91 (m, 2H); 2.06 (m, 2H); 2.24 (m, 2H); 3.11 (m, 2H); 3.23 (t,2H); 3.41 (1m, 2H); 3.49 (m, 2H); 3.67 (m, 2H); 3.99 (s, 3H); 4.01 (s, 2H); 4.31 (t, 2H); 6.89 (t, 1H); 7.32 (s, 1H); 7.34 (d, 2H); 7.64 (s, 1H); 7.92 (s, 1H); 9.09 (s, 1H).

Ejemplo 309. Preparación de Compuesto 486 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con 4-hidroximetilpiperidina (380 mg, 3.3 mmol) produjo el compuesto 486 en Tabla 17 (62 mg, 47 %).

MS ES^+ : 599 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H); 1.34 (m, 1H); 1.65 (d, 2H); 1.88 (t, 2H); 1.96 (m, 2H); 2.45 (t, 2H); 2.90 (d, 2H); 3.25 (t, 2H); 3.92 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.41 (t, 1H); 6.94 (m, 1H); 7.26 (s, 1H); 7.36 (dd, 2H); 7.40 (s, 1H); 8.13 (brs, 1H); 8.68 (s, 1H); 10.64 (s, 1H); 12.07 (brs, 1H).

Ejemplo 310. Preparación de Compuesto 487 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con 2-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 487 en Tabla 17 (61 mg, 45 %).

MS ES^+ : 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.47-1.90 (m, 7H); 2.09 (m, 1H); 2.27 (m, 2H); 3.08-3.70 (m, 7H); 3.99 (s, 3H); 4.00 (s, 2H); 4.30 (m, 2H); 6.84 (m, 1H); 7.29 (d, 1H); 7.34 (dd, 1H); 7.62 (s, 1H); 7.92 (s, 1H); 9.08 (s, 1H).

Ejemplo 311. Preparación de Compuesto 488 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con 1-(2- hidroxietil)piperazina (430 mg, 3.3 mmol) produjo el compuesto 488 en Tabla 17 (124 mg, 92 25 %).

MS ES^+ : 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.96 (m, 2H); 2.40 (m, 12H); 2.70 (m, 1H); 3.48 (m, 2H); 3.90 (s, 2H); 3.95 (s, 3H); 4.18 (t,2H); 4.35 (brt, 1H); 6.43 (m, 1H); 7.23 (s, 1H); 7.34 (dd, 2H); 7.38 (s, 1H); 8.10 (s, 1H); 8.66 (s, 1H); 10.63 (s, 1H).

Ejemplo 312. Preparación de Compuesto 489 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con 4-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 489 en Tabla 17 (54 mg, 40 %). MS ES^+: 613 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H); 1.36 (m, 3H); 1.63 (brd, 2H); 1.88 (m, 2H); 1.96 (m, 2H); 2.44 (m, 2H); 2.87 (brd, 2H); 3.44 (m, 2H); 3.92 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.33 (t, 1H); 6.95 (m, 1H); 7.26 (s, 1H); 7.36 (dd, 2H); 7.40 (s, 1H); 8.13 (brs, 1H); 8.68 (s, 1H); 10.64 (s, 1H); 12.04 (brs, 1H).

Ejemplo 313. Preparación de Compuesto 490 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con 3-hidroxipiperidina (334 mg, 3.3 mmol) produjo el compuesto 490 en Tabla 17 (53 mg, 41 %). MS ES^+ : 559 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.09 (m, 1H); 1.43 (m, 1H); 1.64 (m, 1H); 1.79 (m, 2H); 1.87 (m, 1H); 1.96 (m, 2H); 2.47 (m, 2H); 2.69 (m, 2H); 2.85 (m, 2H); 3.49 (m, 1H); 3.92 (s, 2H); 3.98 (s, 3H); 4.21 (t, 2H); 4.60 (d, 1H); 6.95 (t, 1H); 7.26 (s, 1H); 7.36 (d, 2H); 7.40 (s, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.65 (s, 1H); 12.04 (brs, 1H).

Ejemplo 314. Preparación de Compuesto 491 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con N,N,N'-trimetiletilendiamina (337 mg, 3.3 mmol) produjo el compuesto 491 en Tabla 17 (54 mg, 42 %). MS ES^+ : 586 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.32 (m, 1H); 2.34 (m, 1H); 2.88 (s, 6H); 2.93 (s, 3H); 3.39 (m, 2H); 3.56 (m, 4H); 3.99 (s, 3H); 4.01 (s, 2H); 4.30 (t, 2H); 6.91 (m, 1H); 7.33 (s, 1H); 7.35 (dd, 2H); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 315. Preparación de Compuesto 492 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con piperidina (281 mg, 3.3 mmol) produjo el compuesto 492 en Tabla 17 (81 mg, 64 %). MS ES^+: 569 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.38 (m, 2H); 1.50 (m, 4H); 2.34 (brs, 4H); 2.41 (t, 2H); 3.90 (s, 2H); 3.96 (s, 3H); 4.19 (t, 2H); 6.93 (t, 1H); 7.24 (s, 1H); 7.34 (d, 2H); 7.38 (s, 1H); 8.11 (brs, 1H); 8.67 (s, 1H); 10.63 (s, 1H); 11.98 (brs, 1H).

Ejemplo 316. Preparación de Compuesto 493 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con pirrolidina (235 mg, 3.3 mmol) produjo el compuesto 493 en Tabla 17 (66 mg, 54 %).

MS ES$^+$: 555 $(M+H)^+$

^{1}HNMR (DMSOd_6,TFA): MS ES+: 555 (M+H)+

lHN1vfR (DMSO~, TFA): 1.90 (m, 2H); 2.06 (m, 2H); 2.28 (m, 2H); 3.09 (m,2H); 3.36 (m, 2H); 3.68 (m, 2H); 3.99 (s, 3H); 4.01 (s, 2H); 4.29 (t, 2H); 6.93 (m; 1H); 7.30 (s, 1H); 7.34 (dd, 2H); 7.65 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 317. Preparación de Compuesto 494 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con 2-amino-2-metil-1-propanol (294 mg, 3.3 mmol) produjo el compuesto 494 en Tabla 17 (28 mg, 22 Ola).

MS ES$^+$: 573 $(M+H)^+$

^{1}HNMR (DMSOd_6,TFA): 1.24 (s, 6H); 2.23 (m, 2H); 3.10 (t, 2H); 3.45 (s, 2H); 3.99 (s, 3H); 4.01 (s, 2H); 4.31 (t, 2H); 6.91 (m, 1H); 7.30 (s, 1H); 7.34 (dd, 2H); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 318. Preparación de Compuesto 495 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con 2-metilaminoetanol (248 mg. 3.3 mmol) produjo el compuesto 495 en Tabla 17 (33 rng. 27 %).

MS ES$^+$: 559 $(M+H)^+$ ^{1}HNMR (DMSOd_6) : 1.95 (m. 2H); 2.24 (s, 3H); 2.48 (m, 2H); 2.45 (m, 2H); 3.49 (m, 2H); 3.93 (s, 2H); 3.98 (s, 3H); 4.21 (t, 2H); 4.38 (m, 1H); 6.95 (m, 1H); 7.27 (s, 1H); 7.36 (dd. 2H); 7.40 (s, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.65 (s, 1H); 12.04 (brs, 1H).

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Ejemplo 319. Preparación de Compuesto 496 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con N,N- dimetiletilendiamina (291 mg, 3.3 mmol) produjo el compuesto 496 en Tabla 17 (22 mg, 17 %).

MS ES^+ : 572 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.23 (m, 2H); 2.89 (s, 6H); 3.22 (m, 2H); 3.41 (s, 4H); 3.96 (s, 3H); 4.01 (s, 2H); 4.31 (t, 2H); 6.92 (m, 1H); 7.31 (s, 1H); 7.35 (dd, 2H); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 320. Preparación de Compuesto 497 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con (S(-(+)-1-amino-2-propanol (248 mg, 3.3 mmol) produjo el compuesto 497 en Tabla 17 (32 Mg, 26 %).

MS ES^+ : 559 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.15 (d, 3H); 2.24 (m, 2H); 2.83 (dd, 1H); 3.06 (dd, 1H); 3.15 (t, 2H); 3.95 (m, 1H); 3.99 (s, 3H); 4.01 (s, 3H); 4.29 (t, 1H); 6.92 (m, 1H); 7.28 (s, 1H); 7.34 (dd, 2H); 7.65 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 321. Preparación de Compuesto 498 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con (R)-(-)-1-amino-2-propanol (248 mg, 3.3 mmol) produjo el compuesto 498 en Tabla 17 (40 mg, 32 %). MS ES^+ : 559 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$,TFA): 1.15 (d, 3H); 2.24 (m, 2H); 2.83 (dd, 1H); 3.06 (dd, 1H); 3.15 (t, 2H); 3.95 (m, 1H); 3.99 (s, 3H); 4.01 (s, 3H); 4.29 (t, 1H); 6.90 (m, 1H); 7.28 (s, 1H); 7.34 (dd, 2H); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 322. Preparación de Compuesto 499 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con tert-butil-1-piperazina carboxilato (615 mg, 3.3 mmol) y tratando la mezcla de la reacción cruda con ácido hidroclorhídrico en 1,4-dioxano (4M, 2 ml) produjo el compuesto 499 en Tabla 17 (66 mg, 45 %, 3 HCl).

MS ES^+: 570 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.35 (m, 2H); 3.20-3.94 (m, 10H); 3.99 (s, 3H); 4.03 (s, 2H); 4.33 (t, 2H); 6.93 (m, 1H); 7.36 (s, 1H); 7.37 (dd, 2H); 7.65 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 323. Preparación de Compuesto 500 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con 5 N-alilpiperazina (416 mg, 3.3 mmol) produjo el compuesto 500 en Tabla 17 (33 mg, 25 %). MS ES^+ : 610 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H); 2.30-2.50 (m, 10H); 2.93 (d, 2H); 3.92 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 5.12 (d, 1H); 5.18 (d, 1H); 5.82 (m, 1H); 6.95 (m, 1H); 7.25 (s, 1H); 7.35 (dd, 2H); 7.40 (s, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.64 (s, 1H); 11.99 (brs, 1H).

Ejemplo 324. Preparación de Compuesto 501 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con (R)-(-)-2-pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 501 en Tabla 17 (51 mg, 40 %).

MS ES^+ : 585 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 1.57 (m, 1H); 1.67 (m, 2H); 1.82 (m, 1H); 1.96 (m, 2H); 2.18 (q, 1H); 2.45 (m, 3H); 2.98 (m, 1H); 3.10 (m, 1H); 3.20 (m, 1H); 3.92 (s, 2H); 3.98 (s, 3H); 4.22 (t, 2H); 4.35 (brs, 1H); 6.95 (m, 1H); 7.27 (s, 1H); 7.36 (dd, 2H); 7.40 (s, 1H); 8.13 (s, 1H); 8.68 (s, 1H); 10.66 (s, 1H); 12.00 (brs, 1H).

Ejemplo 325. Preparación de Compuesto 502 en Tabla 17

Una reacción análoga a la descrita en ejemplo 255, pero comenzando con ciclopentilamina (281 mg, 3.3 mmol) produjo el compuesto 502 en Tabla 17 (28 mg, 22 %). MS ES^+ : 569 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.31 (m,2H); 1.47 (m,2H); 1.62 (m, 2H); 1.73 (m, 2H); 1.93 (m, 2H); 2.70 (t, 2H); 3.03 (m, 1H); 3.92 (s, 2H); 3.97 (s, 3H); 4.23 (t, 2H); 6.94 (m, 1H); 7.26 (s, 1H); 7.36 (dd, 2H); 7.39 (s, 1H); 8.11 (s, 1H); 8.67 (s, 1H); 10.66 (s, 1H).

Ejemplo 326. Preparación de Compuesto 503 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con 2-metilaminoetanol (248 mg, 3.3 mmol) produjo el compuesto 503 en Tabla 17 (31 mg, 24 %).

MS ES^+ : 575 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.31 (m, 2H); 2.88 (s, 3H); 3.16-3.45 (m, 4H); 3.77 (t, 2H); 3.99 (s, 5H); 4.29 (t, 2H); 7.30 (s, 1H); 7.38 (t, 1H); 7.50 (m, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 7.97 (dd, 1H); 9.09 (s, 1H).

Ejemplo 327. Preparación de Compuesto 504 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con N,N,N'-trimetiletilendiamina (337 mg, 3.3 mmol) produjo el compuesto 504 en Tabla 17 (28 mg, 21 %).

MS ES^+ : 602 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.32 (m, 2H); 2.89 (s, 6H); 2.93 (s, 3H); 3.38 (m,2H); 3.56 (brs, 4H); 3.99 (s, 5H); 4.30 (t, 2H); 7.35 (s, 1H); 7.39 (t, 1H); 7.50 (m, 1H); 7.65 (s, 1H); 7.91 (s, 1H); 7.97 (dd, 1H); 9.09 (s, 1H).

Ejemplo 328. Preparación de Compuesto 505 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con N-alilpiperazina (416 mg, 3.3 mmol) produjo el compuesto 505 en Tabla 17 (42 mg, 30 %).

MS ES^+ : 626 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.33 (m, 2H); 3.20-3.80 (m, 10H); 3.91 (d, 2H); 3.99 (s, 5H); 20 4.32 (t, 2H); 5.60 (m, 2H); 5.94 (m, 1H); 7.33 (s, 1H); 7.39 (t, 1H); 7.50 (m, 1H); 7.65 (s, 1H); 7.91 (s, 1H); 7.97 (dd, 1H); 9.09 (s, 1H).

Ejemplo 329. Preparación de Compuesto 506 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con 4-hidroxipiperidina 25 (334 mg, 3.3 mmol) produjo el compuesto 506 en Tabla 17 (32 mg, 25 %).

MS ES^+ : 601 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.41 (m, 2H); 1.73 (m, 2H); 1.96 (m, 2H); 2.03 (m, 2H); 2.45 (m, 2H); 2.74 (m, 2H); 3.46 (m, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4.21 (t, 2H); 4.55 (brs, 1H); 7.26 (s, 1H); 7.40 (s, 1H); 7.41 (t, 1H); 7.51 (m, 1H); 7.97 (dd, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.49 (s, 1H); 12.03 (brs, 1H).

Ejemplo 330. Preparación de Compuesto 507 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con 3-pirrolidinol (288 mg, 3.3 mmol) produjo el compuesto 507 en Tabla 17 (24 mg, 19 %).

MS ES^+ : 587 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.57 (m, 1H); 1.98 (m, 3H); 2.30-2.81 (m, 6H); 3.38 (m, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4.22 (t, 2H); 4.74 (brs, 1H); 7.27 (s, 1H); 7.39 (s, 1H); 7.40 (t, 1H); 7.50 (m, 1H); 7.96 (dd, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.49 (s, 1H); 12.05 (brs, 1H).

Ejemplo 331. Preparación de Compuesto 508 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con 1-(2-aminoetil)pirrolidina (377 mg, 3.3 mmol) produjo el compuesto 508 en Tabla 17 (18 mg, 13 %).

MS ES^+ : 614 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.91 (m, 2H); 2.06 (m, 2H); 2.23 (m, 2H); 3.11 (m, 2H); 3.22 (t, 2H); 3.41 (m, 2H); 3.47 (m, 2H); 3.67 (m, 2H); 3.98 (s, 5H); 4.30 (t, 2H); 7.30 (s, 1H); 7.36 (t, 1H); 7.49 (m, 1H); 7.63 (s, 1H); 7.91 (s, 1H). 7.95 (dd, 1H); 9.09 (s, 1H).

Ejemplo 332. Preparación de Compuesto 509 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con N-acetilpiperazina (423 mg, 3.3 mmol) produjo el compuesto 509 en Tabla 17 (113 mg, 82 %).

MS ES^+ : 628 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.98 (m, 2H); 2.00 (s, 3H); 2.36 (t, 2H); 2.42 (t, 2H); 2.92 (t, 0.5H); 2.99 (t, 0.5H); 3.45 (m, 4H); 3.55 (t, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4:23 (t, 2H); 7.27 (s, 1H); 7.40 (s, 1H); 7.41 (t, 1H); 7.52 (m, 1H); 7.97 (dd, 1H); 8.13 (s, 1H); 8.69 (s, 1H); 10.51 (s, 1H).

Ejemplo 333. Preparación de Compuesto 510 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con 2-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 510 en Tabla 17 (34 mg, 24 %).

MS ES^+ : 629 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.48-1.90 (m, 7H); 2.08 (m, 1H); 2.27 (m, 2H); 3.09-3.69 (m, 7H); 3.99 (s, 5H); 4.30 (m, 2H); 7.30 (d, 1H); 7.38 (t, 1H); 7.50 (m, 1H); 7.64 (s, 1H); 7.91 (s, lH); 7.97 (dd, 1H); 9.09 (s, 1H).

Ejemplo 334. Preparación de Compuesto 511 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con 2-(2-hidroxietil)piperazina (430 mg, 3.3 mmol) produjo el compuesto 511 en Tabla 17 (80 mg, 58 %).

MS ES$^+$: 630 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.96 (m, 2H); 2;42 (m, 12H); 3.49 (dd, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.37 (t, 1H); 7.25 (s, 1H); 7.39 (s, 1H); 7.40 (t, 1H); 7.51 (m, 1H); 7.97 (dd, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.42 (s, 1H); 12.02 (brs, 1H).

Ejemplo 335. Preparación de Compuesto 512 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con ciclopentilamina (281 mg, 3.3 mmol) produjo el compuesto 512 en Tabla 17 (12 mg, 9 %).

MS ES$^+$: 585 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.59 (m, 4H); 1.73 (m, 2H); 2.00 (m, 2H); 2.21 (m, 2H); 3.13 (t, 2H); 3.56 (m, 1H); 3.99 (s, 5H); 4.31 (t, 2H); 7.29 (s, 1H); 7.37 (t, 1H); 7.49 (m, 1H); 7.64 (s, 1H); 7.92 (s, 1H); 7.96 (dd, 1H); 9.09 (s, 1H).

Ejemplo 336. Preparación de Compuesto 513 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con 4-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 513 en Tabla 17 (54 mg, 39 %).

MS ES$^+$: 629 $(M+H)^+$

^{1}HNMR (DMSOd_6): 1.15 (m, 2H); 1.36 (m, 3H); 1.63 (d, 2H); 1.88 (t, 2H); 1.96 (m, 2H); 2.44 (t, 2H); 2.87 (d, 2H); 3.44 (m, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2HJ); 4.33 (t, 1H); 7.25 (s, 1H); 7.40 (s, 1H); 7.41 (t, 1H); 7.51 (m, 1H); 7.97 (dd, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.48 (s, 1H); 12.03 (brs, 1H).

Ejemplo 337. Preparación de Compuesto 514 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con 3-hidroxipiperidina (334 mg, 3.3 mmol) produjo el compuesto 514 en Tabla 17 (96 mg, 73 %). MS ES^+ : 601 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.09 (m, 1H); 1.43 (m, 1H); 1.63 (m, 1H); 1.78 (m, 2H); 1.87 (m, 1H); 1.96 (m,2H); 2.47 (m, 2H); 2.68 (m, 1H); 2.84 (brd, 1H); 3.50 (m, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4.20 (t, 2H); 4.59 (d, 1H); 7.26 (s, 1H); 7.40 (s, 1H); 7.41 (t, 1H); 7.51 (m, 1H); 7.97 (dd, 1H); 8.13 (brs, 1H); 8.68 (s, 1H); 10.48 (s, 1H); 12.03 (brs, 1H).

Ejemplo 338. Preparación de Compuesto 515 en Tabla 17

Una reacción análoga a la descrita en Ejemplo 256, pero comenzando con 4- hidroximetilpiperidina (380 mg, 3.3 mmol) produjo el compuesto 515 en Tabla 17 (18 mg, 13 %). MS ES^+ : 615 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H); 1.35 (m, 1H); 1.65 (d, 2H); 1.88 (m, 2H); 1.97 (m, 2H); 2.46 (m, 2H); 2.91 (m, 2H); 3.25 (t, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.21 (t, 2H); 4.41 (t, 1H); 7.26 (s, 1H); 7.40 (s, 1H); 7.41 (t, 1H); 7.50 (m, 1H); 7.97 (dd, 1H); 8.13 (brs, 1H); 8.68 (s, 1H); 10.49 (s, 1H); 12.03 (brs, 1H).

Ejemplo 339. Preparación de Compuesto 516 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con 1-amino-2-propanol (248 mg, 3.3 mmol) produjo el compuesto 516 en Tabla 17 (14mg, 11 %). MS ES^+ : 575 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H); 1.96 (m, 2H); 2.49 (m, 2H); 2.74 (t, 2H); 3.71 (m, 2H); 3.90 (s, 2H); 3.98 (s, 3H); 4.24 (t, 2H); 4.50 (brs, 1H); 7.27 (s, 1H); 7.39 (s, 1H); 7.41 (t, 1H); 7.51 (m, 1H); 7.97 (dd, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.49 (s, 1H).

Ejemplo 340. Preparación de Compuesto 517 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con tert-butil-1-piperazincarboxilato (615 mg, 3.3 mmol) y tratando la mezcla de la reacción cruda con ácido clorhídrico en 1,4-dioxano (4.M, 2 ml) produjo el compuesto 517 en Tabla 17 (61 mg, 47 %).

MS ES$^+$: 586 $(M+H)^+$

^{1}HNMR (DMSOd_6,TFA): 2.31 (m, 2H); 3.00-3.95 (m, 10 H); 3.99 (s, 5H); 4.31 (t, 2H); 7.32 (s, 1H); 7.39 (t, 1H); 7.50 (m, 1H); 7.65 (s, 1H); 7.91 (s, 1H); 7.97 (dd, 1H); 9.10 (s, 1H).

Ejemplo 341. Preparación de Compuesto 518 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con 1-(2-morfolinoetil)piperazina (519 mg, 3.3 mmol) produjo el compuesto 518 en Tabla 17 (69 mg, 48 %).

MS ES$^+$: 699 $(M+H)^+$

^{1}HNMR (DMSOd_6,TFA): 2.31 (m, 2H); 2.98 (m, 2H); 3.10-37.5 (m, 16H); 3.86 (m, 4H); 3.99 (s, 5H); 4.31 (t, 2H); 7.33 (s, 1H); 7.39 (t, 1H); 7.50 (m, 1H); 7.65 (s, 1H); 7.92 (s, 1H); 7.97 (dd, 1H); 9.10 (s, 1H).

Ejemplo 342. Preparación de Compuesto 519 en Tabla 17

Una reacción análoga a la descrita en ejemplo 256, pero comenzando con pirrolidine (235 mg, 3.3 mmol) produjo el compuesto 519 en Tabla 17 (55 mg, 44 %).

MS ES$^+$: 571 $(M+H)^+$

^{1}HNMR (DMSOd_6,TFA): 1.90 (m, 2H); 2.06 (m, 2H); 2.27 (m, 2H); 3.09 (m, 2H); 3.36 (t, 2H); 3.66 (m, 2H); 3.98 (s, 5H); 4.29 (t, 2H); 7.29 (s, 1H); 7.39 (t, 1H); 7.50 (m, 1H); 7.64 (s, 1H); 7.90 (s,1H); 7.96 (dd, 1H); 9.09 (s, 1H).

Ejemplo 343. Preparación de Compuesto 520 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con 2-metllaminoetanol (248 mg, 3.3 mmol) produjo el compuesto 520 en Tabla 17 (34 mg, 29 %).

MS ES$^+$: 541 $(M+H)^+$

^{1}HNMR (DMSOd_6,TFA): 2.30 (m, 2H); 3.57 (s, 3H); 3.16-3.45 (m, 4H); 3.75 (t, 2H); 3.98 (s, 3H); 3.99 (s, 2H); 4.29 (t, 2H); 6.89 (t, 1H); 7.29 (s, 1H); 7.30-7.40 (m, 2H); 7.62 (d, 1H); 7.63 (s, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 344. Preparación de Compuesto 521 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con 1,2-diamino-2-metIlpropanO (291 mg, 3.3 mmol) produjo el compuesto 521 en Tabla 17 (10 mg, 8 %).

MS ES^+ : 554 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.39 (s, 6H); 2.27 (m, 2H); 3.22 (m, 4H); 3.97 (s, 3H); 3.98 (s, 2H); 4.32 (t, 2H); 6.89 (m, 1H); 7.29-7.39 (m, 3H); 7.62 (d, 1H); 7.63 (s, 1H); 7.92 (s, 1H); 9.08 (s, 1H).

Ejemplo 345. Preparación de Compuesto 522 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con N,N- dimetiletilendiamina (291 mg, 3.3 mmol) produjo el compuesto 522 en Tabla 17 (26 mg, 22 %).

MS ES^+ : 554 $(M+H)^+$

^{1}HNMR ($DMSOd_6$) : 1.95 (m, 2H); 2.15 (s, 6H); 2.33 (t, 2H); 2.63 (t, 2H); 2.73 (t, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.23 (t,2H); 6.91 (m, 1H); 7.26 (s, 1H); 7.31-7.42 (m, 2H); 7.39 (s, 1H); 7.64 (d, 1H); 8.11 (s, 1H); 8.68 (s, 1H); 10.48 (s, 1H).

Ejemplo 346. Preparación de Compuesto 523 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con N,N,N'- trimetiletilendiamina (337 mg, 3.3 mmol) produjo el compuesto 523 en Tabla 17 (37 mg, 30 %).

MS ES^+ : 568 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$,TFA): 2.34 (m, 2H); 2.88 (s, 6H); 2.93 (s, 3H); 3.38 (m, 2H); 3.55 (m, 4H); 3.98 (s, 3H); 3.99 (s, 2H); 4.29 (t, 2H); 6.89 (m, 1H); 7.29-7.41 (m, 2H); 7.33 (s, 1H); 7.63 (d, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 347. Preparación de Compuesto 524 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con N-alilpiperazina (416 mg, 3.3 mmol) produjo el compuesto 524 en Tabla 17 (77 mg, 59 %).

MS ES^+: 592 $(M+H)^+$

760

^{1}HNMR (DMSOd_6,TFA): 2.34 (m, 2H); 3.00-3.08 (m, 8H); 2.86 (d, 2H); 3.92 (m, 2H); 3.98 (s, 3H); 3.99 (s, 2H); 4.31 (t, 2H); 5.53-5.66 (m, 2H); 5.60-5.87 (m, 1H); 6.89 (m, 1H); 7.31-7.40 (m, 3H); 7.62 (d, 1H); 7.63 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 348. Preparación de Compuesto 525 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con 4-hidroxipiperidina (334 mg, 3.3 mmol) produjo el compuesto 525 en Tabla 17 (21 mg, 17 %). MS ES$^+$: 567 $(M+H)^+$

^{1}HNMR (DMSOd_6,TFA): 1.59 (m, 1H); 1.85 (m, 2H); 2.01 (d, 1H); 2.28 (m, 2H); 3.03 (t, 1H); 3.21 (m, 1H); 3.28 (m,2H); 3.40 (m, 1H); 3.57 (d, 1H); 3.68 (m, 1H); 3.98 (s, 3H); 3.99 (s, 2H); 4.28 (t, 2H) ,6.90 (t, 1H); 7.29 (s, 1H); 7.30-7.40 (m, 2H); 7.63 (d, 1H); 7.64 (s, 1H) , 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 349. Preparación de Compuesto 526 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con 3-pirrolidinol (288 mg, 3.3 mmol) produjo el compuesto 526 en Tabla 17 (18 mg, 15 %). MS ES$^+$: 553 $(M+H)^+$

^{1}HNMR (DMSOd_6,TFA): 1.84-2.03 (m, 2H); 2.27 (m, 2H); 3.02-3.79 (m, 6H); 3.99 (s, 3H); 4.00 (s, 2H); 4.29 (m, 2H); 4.41-4.51 (m, 1H); 6.91 (m, 1H); 7.28 (d, 1H); 7.31-7.41 (m, 2H); 7.63 (d, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 9.09 (s, 1H).

Ejemplo 350. Preparación de Compuesto 527 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con 1-(aminoetil)pirrolidina (377 mg, 3.3 mmol) produjo el compuesto 527 en Tabla 17 (34 mg, 27 25 %). MS ES$^+$: 580 $(M+H)^+$ ^{1}HNMR (DMSOd_6): 1.68 (m, 4H); 1.97 (m, 2H); 2.47 (m, 6H); 2.70 (t, 2H); 2.77 (t, 2H); 3.91 (s, 2H); 3.97 (s, 3H); 4.24 (t, 2H); 6.91 (m, 1H); 7.27 (s, 1H); 7.30-7.42 (m, 2H); 7.39 (s, 1H); 7.64 (d,1H) , 8.12 (s, 1H); 8.68 (s, 1H); 10.49 (s, 1H).

Ejemplo 351. Preparación de Compuesto 528 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con N-acetilpiperazina (423 mg, 3.3 mmol) produjo el compuesto 528 en Tabla 17 (93 mg, 71 %).

MS ES$^+$: 594 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.99 (m,2H); 2.00 (s, 3H); 2.35 (t, 2H); 2.41 (t, 2H); 2.49 (m, 2H); 3.45 (m, 4H); 3.91 (s, 2H); 3.97 *(s,* 3H); 4.23 (t, 2H); 6.92 (m, 1H); 7.27 (s, 1H); 7.32-7.42 (m, 2H); 7.40 (s, 1H); 7.63 (d, 1H); 8.13 (brs, 1H); 8.69 (s, 1H); 10.48 (s, 1H).

Ejemplo 352. Preparación de Compuesto 529 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con 1-(2-hidroxietil)piperazina (430 mg, 3.3 mmol) produjo el compuesto 529 en Tabla 17 (91 mg, 69 %).

MS ES$^+$: 596 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H); 2.41 (m, 12H); 3.50 (q, 2H); 3.91 (s, 2H); 3.97 *(s,* 3H); 4.20 (t, 2H); 4.37 (t, 1H); 6.91 (t, 1H); 7.25 (s, 1H); 7.32-7.42 (m, 2H); 7.39 (s, 1H); 7.65 (d, 1H); 8.12 (s, 1H); 8.68 (s, 1H); 10.48 (s, 1H); 12.04 (brs, 1H).

Ejemplo 353. Preparación de Compuesto 530 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con ciclopentilamina (281 mg, 3.3 mmol) produjo el compuesto 530 en Tabla 17 (47 mg, 39 %). MS ES$^+$: 551 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.39 (m, 2H); 1.50 (m, 2H); 1.65 (m, 2H); 1.80 (m, 2H); 2.00 (m, 2H); 2.80 (t, 2H); 3.16 (m, 1H); 3.91 (s, 2H); 3.98 (s, 3H); 4.25 (t, 2H); 6.98 (t, 1H); 7.28 (s, 1H); 7.31-7.42 (m, 2H); 7.40 (s, 1H); 7.64 (d, 1H); 8.13 (s, 1H); 8.69 (s, 1H); 10.49 (s, 1H).

Ejemplo 354. Preparación de Compuesto 531 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con 4-(2-hidroxietil)piperidina (426 mg, 3.3 mmol) produjo el compuesto 531 en Tabla 17 (65 mg, 50 %). MS ES$^+$: 595 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.15 (m, 2H); 1.36 (m, 3H); 1.63 (d, 2H); 1.88 (m, 2H); 1.96 (ID., 2H); 2.44 (m, 2H); 2.87 (d, 2H); 3.44 (m, 2H); 3.91 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.33 (t, 1H); 6.91 (t, 1H); 7.25 (s, 1H); 7.32-7.42 (m, 2H); 7.40 (s, 1H); 7.63 (d, 1H); 8.12 (brs, 1H); 8.68 *(s,* 1H); 10.48 (s, 1H); 12.03 (s, 1H).

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Ejemplo 355. Preparación de Compuesto 532 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con 3-hidroxipiperidina (334 mg, 3.3 mmol) produjo el compuesto 532 en Tabla 17 (72 mg, 58 %).

MS ES^+ : 567 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.09 (m, 1H); 1.43 (m, 1H); 1.63 (m, 1H); 1.78 (m, 2H); 1.87 (m, 1H); 1.96 (t, 2H); 2.47 (m, 2H); 2.69 (m, 1H); 2.85 (brd, 1H); 3.49 (m, 1H); 3.91 (s, 2H); 3.98 (s, 3H); 4.20 (t, 2H); 4.60 (d, 1H), 6.91 (t, 1H); 7.26 (s, 1H); 7.31-7.42 (m,2H); 7.40 (s, 1H); 7.64 (d, 1H); 8.13 (brs, 1H); 8.68 (s, 1H); 10.48 (s, 1H); 12.02 (brs, 1H).

Ejemplo 356. Preparación de Compuesto 533 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con 4-hidroximetilpiperidina (380 mg, 3.3 mmol) produjo el compuesto 533 en Tabla 17 (56 mg, 44 %).

MS ES^+ : 581 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.14 (m, 2H); 1.34 (m, 1H); 1.65 (d, 2H); 1.88 (t, 2H); 1.97 (m, 2H); 2.45 (t, 2H); 2.90 (d, 2H); 3.25 (t, 2H); 3.91 (s, 2H); 3.97 (s, 3H); 4.20 (t, 2H); 4.41 (t, 1H); 6;93 (t, 1H); 7.25 (s, 1H); 7.32-7.42 (m, 2H); 7.40 (s, 1H); 7.63 (d, 1H); 8.12 (brs, 1H); 8.68 (s, 1H); 10.48 (s, 1H); 12.03 (brs, 1H).

Ejemplo 357. Preparación de Compuesto 534 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con 1-amino-2-propanol 25 (248 mg, 3.3 mmol) produjo el compuesto 534 en Tabla 17 (36 mg, 30 %).

MS ES^+ : 541 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.06 (d, 3H); 1.95 (m, 2H); 2.48 (m, 2H); 2.72 (t, 2H); 3.69 (m, 1H); 3.90 (s, 2H); 3.97 (s, 3H); 4.23 (t, 2H); 4.47 (brs, 1H); 6.91 (t, 1H); 7.26 (s, 1H); 7.32-7.41 (m,2H); 7.39 (s, 1H); 7.63 (d, 1H); 8.11 (s, 1H); 8.67 (s, 1H); 10.48 (s, 1H).

Ejemplo 358. Preparación de Compuesto 535 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con (R)-(-)-2-pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 535 en Tabla 17 (66 mg, 53 %).

MS ES^+ : 567 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.57 (m, 1H); 1.67 (m, 2H); 2.82 (m, 1H); 1.96 (m, 2H); 2.18 (m, 1H); 2.45 (m, 2H); 2.98 (m, 1H); 3.10 (m, 1H); 3.20 (m, 1H); 3.41 (m, 1H); 3.91 (s, 2H); 3.98 (s, 3H); 4.22 (t, 2H); 4.35 (brs, 1H); 6.91 (t, 1H); 7.26 (s, 1H); 7.31-7.42 (m, 2H); 7.39 (s, 1H); 7.64 (d, 1H); 8.13 (s, 1H); 8.68 (s, 1H); 10.48 (s, 1H); 12.01 (brs, 1H).

Ejemplo 359. Preparación de Compuesto 536 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con (S)-(+)-2-pirrolidinmetanol (334 mg, 3.3 mmol) produjo el compuesto 536 en Tabla 17 (59 mg, 48 %).

MS ES^+ : 567 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA) : 1.78 (m, 1H); 1.90 (m, 1H); 2.03 (m, 1H); 2.13 (m, 1H); 2.31 (m,2H); 3.23 (m, 2H); 3.61 (m, 4H); 3.77 (q, 1H); 3.98 (s, 3H); 3.99 (s, 2H); 4.29 (t, 2H); 6.89 (t, 1H); 7.29 (s, 1H); 7.30-7.40 (m, 2H); 7.63 (d, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 9.08 (s, 1H).

Ejemplo 360. Preparación de Compuesto 537 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con t-butil-1-pIperazinecarboxilato (615 mg, 3.3 mmol) y tratando la mezcla de reacción cruda con ácido clorhídrico en 1,4-dioxano (4M, 2 ml) produjo el compuesto 537 en Tabla 17 (35 mg, 27 %).

MS ES^+: 552 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.96 (m, 2H); 2.33 (brs, 4H); 2.42 (t, 2H); 2.73 (t, 4H); 3.89 (s, 2H); 3.95 (s, 3H); 4.19 (t, 2H); 6.89 (t, 1H); 7.24 (s, 1H); 7.32-7.42 (m, 2H); 7.37 (s, 1H); 7.62 (d, 1H); 8.10 (s, 1H); 8.66 (s, 1H); 10.47 (s, 1H).

Ejemplo 361. Preparación de Compuesto 538 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con 1-(2-morfolinoetil)piperazina (519 mg, 3.3 mmol) produjo el compuesto 538 en Tabla 17 (50 mg, 37%).

MS ES^+ : 665 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 2.33 (m, 2H); 2.99 (t, 2H); 3.05-3.75 (m, 16H); 3.86 (brs, 4H); 3.99 (s, 3H); 4.00 (s, 2H); 4.29 (t, 2H); 6.90 (t, 1H); 7.32 (s, 1H); 7.41-7.31 (m, 2H); 7.62 (d, 1H); 7.64 (s, 1H); 7.92 (s, 1H); 9.09 (s, 1H).

Ejemplo 362. Preparación de Compuesto 539 en Tabla 17

Una reacción análoga a la descrita en ejemplo 257, pero comenzando con 2-amino-2-metil-1-propanol (294 mg, 3.3 mmol) produjo el compuesto 539 en Tabla 17 (40 mg, 33 %). MS ES^+ : 555 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 0.96 (s, 6H); 1.91 (m, 2H); 2.67 (t, 2H); 3.19 (s, 2H); 3.90 (s, 2H); 3.97 (s, 3H); 4.24 (t, 2H); 4.53 (brs, 1H); 6.91 (m, 1H); 7.26 (s, 1H); 7.36 (m, 2H); 7.38 (s, 1H); 7.63 (d, 1H); 8.11 (s, 1H); 8.67 (s, 1H); 10.48 (s, 1H).

Ejemplo 363. Preparación de Compuesto 540 en Tabla 18

4-((2-amino-1,3-tiazol-5-il)acético ácido)-6-metoxi-7-(3-morfolinopropoxi)quinazolina (125 mg, 0.27 mmol) en DMF (2.5 ml) se hizo reaccionar con N-etilanilina (84.3 µl, 0.707 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (136 mg, 0.37 mmol) y DIEA (95 µl, 0.54 mmol) a 50°C durante 18 horas. La mezcla de la reacción se enfrió, se agregaron bicarbonato de sodio (sat., 1 ml) [y] 3 g de alúmina, la mezcla se evaporó a sequedad, y el residuo se purificó por cromatografía sobre alúmina, eluyente CH_2Cl_2, CH_2Cl_2/MeOH 99/1 a 95/5 para producir el compuesto del título (68 mg, 44 %).

MS ES^+ : 563.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$,TFA): 1.05 (t, 3H); 2..31 (t, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.65 (m, 6H); 3.97 (s, 3H); 4.03 (d, 2H); 4.29 (t, 2H); 7.31 (s, 1H); 7.38 (s, 1H); 7.40 (m, 2H); 7.46 (m, 1H); 7.53 (m,2H); 7.87 (s, 1H); 9.06 (s, 1H).

Ejemplo 364. Preparación de Compuesto 541 en Tabla 18

Una reacción análoga a la descrita en ejemplo 363, pero comenzando con 3-cloro-4-fluoro-N-metilanilina (97 mg, 0.35 mmol) produjo el compuesto del título (98 mg, 60 %).

MS ES$^+$: 601.5, 603.5 $(M+H)^+$ ^{1}HNMR (DMSOd_6,TFA): 2.31 (t, 2H); 3.15(t, 2H); 3.21 (s, 3H); 3.35 (t, 2H); 3.54 (d, 2H); 3.7 (m, 4H); 3.97 (s, 3H); 4.03 (d,2H); 4.29 (t, 2H); 7.31 (s, 1H); 7.41 (s, 1H); 7.50 (m, 2H); 7.80 (m, 1H); 7.87 (s, 1H); 9.06 (s, 1H).

N -(tert -butiloxicarbonil)- 3 -cloro-4- fluoroanilina.

3-cloro-4-fluoroanilina (2g, 13.7 mmol) en THF (12.5 ml) bajo argón, se trató con NaHMDS (1 M, 27.5 ml, 27.5 mmol) a temperatura ambiente durante 15 minutos. Di-tert-butil dicarbonato en THF (10 ml) se agregó lentamente a la mezcla de la reacción, y la mezcla se agitó a temperatura ambiente durante 45 minutos. El solvente se evaporó, se diluyó HCl (0.1 N), y la mezcla se extrajo con acetato de etilo, se secó, se purificó por cromatografía de gel de sílice, éter/éter de petróleo 10-20/90-80 para producir el compuesto del título (2.77 g, 82 %). ^{1}HNMR ($CDCl_3$): 1.49 (s, 9H); 6.42 (s, 1H); 7.01 (t, 1H); 7.01 (m, 1H); 7.54 (m, 1H).

3 -cloro-4- fluoro-N –metilanilina.

A una solución de N-(tert-butiloxicarbonil)-3-cloro-4-fluoroanilina (250 mg, 1.02 mmol) en THF (4 ml) a O°C se agregó hidruro de sodio (60 %, 45 mg, 1.12 mmol), y la mezcla se agitó durante 20 minutos. Yoduro de metilo (70 µl, 1.12 mmol) se adicionó a la mezcla que se agitó a temperatura ambiente durante 4 horas. El solvente se evaporó, se adicionó una solución saturada de cloruro de sodio, y la mezcla se extrajo con CH_2Cl_2, se secó, y se purificó por cromatografía de gel de sílice, éter / éter de petróleo, 8/2 para producir un compuesto (235 mg). Este compuesto se disolvió en CH_2Cl_2 (2 ml) y TFA (2 ml), se añadió H_2O (200 µl), la mezcla se agitó durante 1 hora a temperatura ambiente, el solvente se evaporó, para producir el compuesto del título (256 mg, 89 %). ^{1}HNMR ($CDCl_3$): 2.98 (s, 3H); 7.3 (m, 3H).

Ejemplo 365. Preparación de Compuesto 542 en Tabla 18

Una reacción análoga a la descrita en ejemplo 363, pero comenzando con etil-2-(3-cloro-4-fluoroanilin)acetato (151 mg, 0.65 mmol) produjo el compuesto del título (10 mg, 4.5 %). MS ES$^+$: 673.6 $(M+H)^+$ ^{1}HNMR (DMSOd_6,TFA): 1.18 (t, 3H); 2.30 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.83 (s, 1H); 3.97 (s, 3H); 4.03 (m, 4H); 4.13 (s, 2H); 4.29 (t, 2H); 4.41 (s, 1H); 7.30 (s, 1H); 7.44 (s, 1H); 7.55 (m, 2H); 7.78 (m, 1H); 7.87 (s, 1H); 9.06 (s, 1H).

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Ejemplo 366. Preparación de Compuesto 543 en Tabla 18

Una reacción análoga a la descrita en ejemplo 363, pero comenzando con 2-anilinoacetonitrilo (371 mg, 2.72 mmol) produjo el compuesto del título (110 mg, 18 %).

MS ES^+ : 574.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$,TFA): 2.31 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.77 (s, 1H); 3.97 (s, 3H); 4.04 (d, 2H); 4.30 (t, 2H); 4.81 (s, 2H); 7.31 (s, 1H); 7.43 (s, 1H); 7.57 (m, 5H);7.88 (s, 1H); 9.09 (s, 1H).

Ejemplo 367. Preparación de Compuesto 544 en Tabla 18

Una reacción análoga a la descrita en ejemplo 363, pero comenzando con 3-anilinoacetonitrilo (335 mg, 2.18 mmol) produjo el compuesto del título (100 mg, 18 %).

MS ES^+ : 588.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$,TFA): 2.29 (t, 2H); 2.75 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (m, 4H); 3.95 (t, 2H); 3.97 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 7.29 (s, 1H); 7.42 (s, 1H); 7,48 (m, 3H); 7.55 (m, 2H); 7.87 (s, 1H); 9.08 (s, 1H).

Ejemplo 368. Preparación de Compuesto 545 en Tabla 18

Una reacción análoga a la descrita en ejemplo 363, pero comenzando con N-(2-tert-butiletil)-3-cloro-4-fluoroanilina (346 mg, 1.42 mmol) produjo el compuesto del título (147 mg, 30 %). MS ES^+ : 687.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$,TFA): 1.08 (s, 9H); 2.31 (t, 2H); 3.14 (t, 2H); 4.3-4.5 (m, 4H); 3.55 (d, 2H); 3.68 (m, 6H); 3.97 (s, 3H); 4.03 (d, 2H); 4.29 (t, 2H); 7.30 (s, 1H); 7.41 (s, 1H); 7.51 (m, 2H); 7.78 (m, 1H); 7.87 (s, 1H); 9.06 (s, 1H).

N-(2- hidroxietil)-3-cloro-4- fluoroanilina.

etil-2-(3-cloro-4-fluoroanilin)acetato (J. Med. Chem. 1965, 405-407) (2 g, 8.6 mmol) en THF (15 ml) éter (10 ml) se trató con Li Al H4 (460 mg, 12.1 mmol) a 40°C durante 4 horas. A continuación la mezcla se vertió en hielo, se trató con NaOH (2N, 10 ml),se extrajo con acetato de etilo, se secó, se evaporó para producir el compuesto del título (1.48 g, 90 %).

^{1}HNMR (CDCL3) : 1.67 (s, 1H); 3.24 (t, 2H); 3.84 (t, 2H); 3.92 (s, 1H); 6.47 (m, 1H); 6.64 (m, 1H); 6.95 (t, 1H).

N -(2-tert-butoxietil)- 3-chloro-4- fluoroanilina.

N-2-hidroxietil-3-chloro-4-fluoroanilina (1.48 g, 7.81 mmol) en CH_2Cl_2 (20 ml) se hizo reaccionar con N,N-diisopropil O-tert-butil-isourea (6.25 g, 31.2 mmol) a temperatura ambiente de un día para otro. El producto se purificó por cromatografía de gel de sílice, eluyente, éter / éter de petróleo 5/95, 10/90 para producir el compuesto del título (1.15 g, 60 %).

^{1}HNMR ($CDCl_3$) : 1.20 (s, 9H); 3.18 (t, 2H); 3.55 (t, 2H); 4.00 (s, 1H); 6.44 (m, 1H); 6.62 (m, 1H); 6.93 (t, 1H).

Ejemplo 369. Preparación de Compuesto 546 en Tabla 18

Una reacción análoga a la descrita en ejemplo 363, pero comenzando con N-alilanilina (0.3 ml, 2.18 mmol) produjo el compuesto del título (252 mg, 50 %). MS ES$^+$: 575.7 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.31 (t,2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (m, 4H); 3.97 (s, 3H); 4.03 (d, 2H); 4.28 (m,4H); 5.12 (m, 2H); 5.82 (m, 1H); 7.30 (s, 1H); 7.38 (m, 3H); 7.40 (s, 1H); 7.51 (m, 2H); 7.87 (s, 1H); 9.07 (s, 1H).

Ejemplo 370. Preparación de Compuesto 547 en Tabla 18

Una reacción análoga a la descrita en ejemplo 363, pero comenzando con N-etil-3,4-(metillendioxi)anilina (320 ~1, 2.18 mmol) produjo el compuesto del título (351 mg, 66 %). MS ES$^+$: 607.7 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$,TFA): 1.04 (t, 3H); 2.31 (t, 2H); 3.16 (t, 2H); 3.34 (t, 2H); 3.54 (d, 2H); 3.68 (m, 6H); 3.97 (s, 3H); 4.09 (d, 2H); 4.29 (t, 2H); 6.12 (s, 2H); 6.83 (d, 1H); 7.02 (m, 2H); 7.30 (s, 1H); 7.42 (s, 1H); 7.86 (s, 1H); 9.06 (s, 1H).

Ejemplo 371. Preparación de Compuesto 548 en Tabla 18

Una reacción análoga a la descrita en ejemplo 363, pero comenzando con etil-4-(N-butilamino)benzoato (482 mg, 2.18 mmol) produjo el compuesto del título (58 mg, 10 %). MS ES$^+$: 663.7 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$,TFA): 0.85 (t, 3H); 1.32 (m, 7H); 2.31 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.70 (m, 6H); 3.97 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 4.35 (s, 2H); 7.30 (s, 1H); 7.41 (s, 1H); 7.54 (d, 2H); 7.87 (s, 1H); 8.07 (d, 2H); 9.07 (s, 1H).

Ejemplo 372. Preparación de Compuesto 549 en Tabla 18

Una reacción análoga a la descrita en ejemplo 363, pero comenzando con N-etil-m-toluidina (294 mg, 2.18 mmol) produjo el compuesto del título (294 mg, 2.18 %). MS ES^+ : 577.7 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$,TFA): 1.05 (t, 9H); 2.31 (t, 2H); 2.38 (s, 3H); 3.16 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.67 (m, 6H); 3.97 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 7.18 (m, 2H); 7.28 (d, 1H); 7.30 (s, 1H); 7.39 (s, 1H); 7.42 (d, 1H); 7.86 (s, 1H); 9.07 (s, 1H).

Ejemplo 373. Preparación de Compuesto 550 en Tabla 18

Compuesto 545 (120 mg) en CH_2Cl_2 (2 ml) se trató con TFA (3 ml) y H_2O (200 µl) a temperatura ambiente durante 3 horas. El solvente se evaporó para producir el compuesto del título(45 mg, 41%).

MS ES^+ : 631.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$,TFA): 2.29 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.51 (t, 2H); 3.54 (d, 2H); 3.70 (m, 6H); 3.97 (s, 3H); 4.03 (d, 2H); 4.30 (t, 2H); 7.30 (s, 1H); 7.42 (s, 1H); 7.54 (m, 2H); 7.78 (d, 1H); 7.87 (s, 1H); 9.06 (s, 1H).

Ejemplo 374. Preparación de Compuesto 551 en Tabla 19

Ácido 4-((2-amino-4-metil-1,3-tiazol-5-il)acético)-6-metoxi-7-(3-morfolinopropoxi)quinazolina (118 mg, 0.25 mmol) en DMF (1.5 ml) se hizo reaccionar con anilina (32 mg, 0.35 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (142 mg, 0.375 mmol) y DIEA (65 mg, 0.5 mmol) a 65° de un día para otro. Se enfrió la mezcla, se agregó bicarbonato de sodio, y la mezcla resultante se evaporó. El residuo se disolvió en CH_2Cl_2 / MeOH 92/8 y se purificó por cromatografía de gel de sílice sobre alúmina, eluyente CH_2Cl_2, CH_2Cl_2 / MeOH 98/2 a 95/5, se realizó una segunda purificación sobre gel de sílice, eluyente CH_2Cl_2 / MeOH 95/5 a 90/10 para producir el compuesto del título (86 mg, 62 %). MS ES^+: 549.6 $(M_+H)^+$ ^{1}HNMR ($DMSOd_6$,TFA): 2.31 (t, 2H); 2.34 (s, 3H); 3.15 (t, 2H); 3.34 (t, 2H); 3.54 (d, 30 2H); 3.72 (t, 2H); 3.90 (s, 2H); 3.98 (s, 3H); (4.03); (d, 2H); 4.30 (t, 2H); 7.08 (t, 2H); 7.29 (s, 1H); 7.31 (t, 2H); 7.62 (d, 2H); 7.85 (s, 1H); 9.05 (s, 1H).

4-(etil(2-amino-4-metil-1,3-tiazol-5-il)acetato)-6-metoxi-7-(3-morflinopropoxi)quinazolina.

N'-(2-ciano-4-metoxi-5-(3-morfolinopropoxi)fenil)-N,N-dimetilimidoformamida (1.38 g, 4 mmol) en ácido acético se hizo reaccionar con etil-2-amino-4-metil-l,3-tiazol-5-il)acetato a reflujo durante 3.5 horas. La mezcla se enfrió, se evaporó, se agregó HCl (1N) y la mezcla se extrajo con acetato de etilo. Se agregó cuidadosamente bicarbonato de sodio a la fase acuosa, la cual se extrajo con acetato de etilo. Las fracciones orgánicas se secaron, se evaporaron, el residuo se purificó por cromatografía sobre alúmina, eluyente CH_2Cl_2, CH_2Cl_2 / AcOEt 1/1, CH_2Cl_2 / AcOEt / MeOH 50/45/5 para producir el material inicial como un sólido amarillo (1.12 g, 52 %).

MS ES^+: 502.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 1.24 (t, 3H); 2.28 (m, 5H); 3.15 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3;92 (s, 2H); 3.98 (s, 3H); 4.04 (d, 2H); 4.15 (q, 2H); 4.30 (t, 2H); 7.30 (s, 1H); 7.86 (8, 1H); 9.05 (s, 1H).

Ácido 4-((2-amino-4-metil-1,3-tiazol-5-il)acético)-6-metoxi-7-(3-morfolinopropoxi)quinazolina.

4-(etil(2-amino-4-metil-1,3-tiazol-5-il)acetato)-6-metoxi-7-(3-morfolinopropoxi)quinazolina (1.1 g, 2.2 mmol) en etanol (11 ml) trató con NaOH (2N, 5.5 ml, 11 mmol) a temperatura ambiente durante 1 hora. La mezcla se acidificó luego con HCl (2N) a pH 3. Se evaporó la solución, el sólido se suspendió en CH_2Cl_2 (8 ml) MeOH (6 ml), y se adicionó DIEA (852 mg, 6.6 mmol). La mezcla se agitó durante 10 minutos, se filtró. El filtrado se concentró, se agregó etanol y el sólido se recuperó para producir el compuesto del título (980 mg, 94 %).

MS ES^+: 474.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$,TFA): 2.28 (m, 5H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.70 (t, 2H); 3.83 (s, 2H); 3.98 (s, 3H); 4.04 (d, 2H); 4.30. (t, 2H); 7.30 (s, 1H); 7.86 (s, 1H); 9.05 (s, 1H).

Ejemplo 375. Preparación de Compuesto 552 en Tabla 19

Una reacción análoga a la descrita en ejemplo 374, pero comenzando con 3-cloro-4-fluoroanilina (51 mg, 0.35 mmol) produjo el compuesto del título (60 mg, 40 %). MS ES^+: 601.5 $(M+H)^+$

^{1}HNMR (DMSOd$_6$,TFA): 2.30 (t, 2H); 2.33 (s, 3H); 3.16 (t, 2H); 3.36 (t, 2H); (3.55) (d, 2H); 3.69 (t, 2H); 3.90 (s, 2H); 3.98 (s, 3H); 4.04 (d, 2H); 4.30 (t, 2H); 7.28 (s, 1H); 7.39 (t, 1H); 7.49 (m, 1H); 7.86 (s, 1H); 7.96 (m, 1H); 9.05 (s, 1H).

Ejemplo 376. Preparación de Compuesto 553 en Tabla 19

Una reacción análoga a la descrita en ejemplo 374, pero comenzando con 2-aminopiridina (33 mg, 0.35 mmol) produjo el compuesto del título (45 mg, 32 %). MS ES$^+$: 550.6 (M+H)$^+$ ^{1}HNMR (DMSOd$_6$,TFA): 2.31 (t, 2H); 2.35 (s, 3H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 10 2H); 3.69 (t, 2H); 3.98 (s, 3H); 4.04 (m, 4H); 4.30 (t, 2H); 7.30 (m, 2H); 7.87 (s, 1H); 7.95 (d, 1H); 8.05 (m, 1H); 8.40 (d, 1H); 9.04 (s, 1H).

Ejemplo 377. Preparación de Compuesto 554 en Tabla 19

Una reacción análoga a la descrita en ejemplo 374, pero comenzando con 3,4 difluoroanilina 15 (50 mg, 0.39 mmol) produjo el compuesto del título (120 mg, 74 %). MS ES$^+$: 585.6 (M+H)$^+$ ^{1}HNMR (DMSOd$_6$,TFA): 2.30 (t, 2H); 2.33 (s, 3H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.67 (t, 2H); 3.90 (s, 2H); 3.98 (s, 3H); 4.05 (d, 2H); 4.31 (t, 2H); 7.28 (s, 1H); 7.32 (m, 1H); 7.40 (q, 1H); 7.80 (m, 1H); 7.86 (s, 1H); 9.05 (s, 1H).

Ejemplo 378. Preparación de Compuesto 555 en Tabla 20

N'-(2-ciano-5-((2S)-2-hidroxi-3-piperidinilpropoxi)-4-metoxifenil)-N,N-dimetilimidoformamida (381 mg, 0.96 mmol) en ácido acético (6 ml) se irradió en un horno microondas en presencia de N-(4-fluoro-3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (275 mg, 0.96 mmol) a reflujo durante 0.5 hora. El solvente se evaporó, y el residuo se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH sat. NH_3 95/5 a 93/7 para producir el compuesto del título (230 mg, 40 %).

MS ES$^+$: 601.5 (M+H)$^+$ ^{1}HNMR (DMSOd$_6$,TFA): 1.42 (m, 1H); 1.6-1.9 (m, 5H); 3.02 (m, 2H); 3.28 (m, 2H); 3.52 30 (m,2H); 3.99 (s, 5H); 4.19 (d, 2H); 4.43 (m, 1H); 7.35 (s, 1H); 7.40 (t, 1H); 7.48 (m, 1H); 7.64 (s, 1H); 7.91 (s, 1H); 7.95 (m, 1H); 9.08 (s, 1H).

N'-(2-ciano-5-((2S)-2-hidroxi-3-piperidinilpropoxi)-4-metoxifenil)-N,N,-dimetilimidoformamida.

(2-tritilamino-1,3-tiazol-5-il)acético (1.96 g, 4.9 mmol) en DMF (25 ml) se hizo reaccionar con 3-cloro-4-fluoroanilina (1.07 g, 7.3 mmol) en presencia de hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (2.42 g, 6.37 mmol) y DIEA (1.7 ml, 9.8 mmol) a 50°C durante 18 horas. Se evaporó DMF, el residuo se absorbió en CH_2Cl_2 / EtOAc, se lavó con una solución saturada de bicarbonato de sodio. Se recuperó el sólido que se precipitó en la fase orgánica, se evaporó la fase orgánica, se añadió MeOH al residuo para producir un sólido, se recuperó en consecuencia una segunda cosecha del compuesto del título para producir en conjunto (1.38 g, 53 %). ^{1}HNMR ($DMSOd_6$): 3.56 (s, 2H); 6.61 (s, 1H); 7.28 (m, 17H); 7.88 (m, 1H); 8.41 (s, 1H).

N-(4-fluoro-3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida.

N-(4-fluoro-3-clorofenil)-2-(2-tritilamino-1,3-tiazol-5-il)acetamida (12.28 g, 23 mmol) se disolvió en TFA (100 ml) y agua (10 ml). La mezcla se agitó a temperatura ambiente durante 45 minutos. Se agregó agua (300 ml) a la mezcla de la reacción, se recuperó un sólido pro filtración, se lavó con agua y éter. El sólido se disolvió en MeOH, y la solución se trató con amoníaco (pH 8), luego se evaporó parcialmente MeOH, se agregó agua (300 ml) y se recuperó un precipitado del compuesto del título, se secó (5.37 g, 81 %). ^{1}HNMR ($DMSOd_6$): 3.64 (s, 2H); 6.76 (m, 3H); 7.38 (t, 1H); 7.48 (m, 1H); 7.92 (m, 1H).

Ejemplo 379. Preparación de Compuesto 556 en Tabla 20

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con N'-(2-ciano-5-((2S)-2-hidroxi-3-pirrolidinilpropoxi)-4-metoxifenil)-N,N,-dimetilimido- formamida (267 mg, 0.77 mmol) produjo el compuesto del título (213 mg, 52 %). MS ES$^+$: 587.5 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.68 (m, 4H); 2.5 (m, 5H); 2.66 (m, 1H); 3.88 (s, 2H); 3.96 (s, 3H); 4.00 (m, 1H); 4..07 (m, 1H); 4.20 (m, 1H); 4.95 (m, 1H); 7.26 (s, 1H); 7.36 (s, 1H); 7.37 (m, 1H); 7.47 (m, 1H); 7.95 (m, 1H); 8.11 (s, 1H); 8.66 (s, 1H).

N'-(2-ciano-5-((2S)-2-hidroxi-3-pirrolinilpropoxi)-4-metoxifenil)-N,N-dimetilimidoformamida.

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con pirrolidina (1.4 ml, 30 16 mmol) produjo el compuesto del título (2.8 g, 74 %).

MS ES$^+$: 347.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.67 (m, 4H); 1.45 (m, 4H); 1.63 (m, 2H); 2.95 (8, 3H); 3.05 (8, 3H); 3.73 (8, 3H); 3.95 (m, 2H); 4.04 (m, 1H); 4.93 (m, 1H); 6.73 (8, 1H); 7.08 (s, 1H); 7.89 (s, 1H).

Ejemplo 380. Preparación de Compuesto 557 en Tabla 20

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con N'-(2-ciano-5-((2S)-2-hidroxi-3-(4-hidroxipiperidinil)propoxi)-4-metoxi-fenil)-N,N- dimetilimidoformamida (195 mg, 0.52 mmol) produjo el compuesto del título (88 mg, 30 %).

MS ES^+ : 617.5, 619.5 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H); 1.70 (m, 2H); 2.13 (m, 2H); 2.43 (m, 2H); 2.77 (m, 2H); 3.43 (m, 1H); 3.88 (s, 2H); 3.96 (s, 3H); 4.03 (m, 2H); 4.19 (m, 1H); 4.52 (d, 1H); 4.87 (m, 1H); 7.27 (s, 1H); 7.39 (m, 2H); 7.49 (m, 1H); 7.99 (m, 1H); 8.67 (s, 1H).

N'-(2-ciano-5-((2S)-2-hidroxi-3-(4-hidroxipiperidinil)propoxi)-4-metoxifenil)-N,N- dimetilimidoformamida.

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con 4-hidroxipiperidina (131 mg, 1.27 mmol) produjo el compuesto del título (200 mg, 58 %).

MS ES^+ : 377.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.39 (m, 2H); 1.68 (m, 2H); 2.10 (m, 2H); 2.40 (m, 2H); 2.75 (m,2H); 2.95 (s, 3H); 3.05 (s, 3H); 3.21 (s, 3H); 3.31 (m, 1H); 3.95 (m, 2H); 4.00 (m, 1H); 4.52 (m, 1H); 4.82 (m, 1H); 6.73 (s, 1H); 7.08 (s, 1H); 7.88 (s, 1H).

Ejemplo 381. Preparación de Compuesto 558 en Tabla 20

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con N'-(2-ciano-5-((2S)-2-hidroxi-3-(4-tert-butiloxicarbonilpiperazinil)propoxi) -4- metoxifenil)-N,N-dimetilimidoformamida (355 mg, 0.77 mmol) produjo el compuesto del título (70 mg, 17 %).

MS ES^+ : 602.4 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 2.42 (m, 6H); 2.73 (d, 4H); 3.88 (s, 2H); 3.96 (s, 3H); 4.04 (m, 2H); 4.19 (m, 1H); 4.90 (m, 1H); 7.28 (s, 1H); 7.37 (m, 2H); 7.47 (m, 1H); 7.94 (m, 1H); 8.11 (s, 1H); 8.66 (s, 1H)

.

N'-(2-ciano-5-((2S)-2-hidroxi-3-(4-tert-butiloxicarbonilpiperazinil)propoxi) -4-metoxifenil)- N,N -dimetilimidoformamida.

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con tert- butiloxicarbonilpiperazina (284 mg, 1.53 mmol) produjo el compuesto del título (444 mg, 88 %).

MS ES^+ : 462.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.39 (s, 9H); 2.40 (m, 6H); 2.95 (s, 3H); 3.04 (s, 3H); 3.30 (m, 4H); 3.72 (s, 3H); 3.95 (m, 2H); 4.02 (m, 1H); 4.91 (d, 1H); 6.74 (s, 1H); 7.09 (s, 1H); 7.88 (s, 1H).

Ejemplo 382. Preparación de Compuesto 559 en Tabla 20

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con N'-(2-ciano-5-((2S)-2-hidroxi-3-ciclopentilaminopropoxi)-4-metoxifenil)-N,N- dimetilimidoformamida (290 mg, 0.77 mmol) produjo el compuesto del título (226 mg, 54 %). MS ES^+ : 601.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.32 (m, 2H), 1.48 (m, 2H); 1.62 (m, 2H); 1.73 (m, 2H); 2.63 (m, 1H); 2.71 (m, 1H); 3.05 (m, 1H); 3.89 (s, 2H); 3.98 (m, 4H); 4.09 (m, 1H); 4.17 (m, 1H); 5.03 15 (m, 1H); 7.27 (s, 1H); 7.40 (m, 2H); 7.51 (m, 1H); 7.97 (m, 1H); 8.12 (s, 1H); 8.67 (s, 1H).

N'-(2-ciano-5 -((2S)-2-hidroxi-3-ciclopentiaminopropoxi)-4-metoxifenil)-N,N- dimetlimidoformamida.

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con ciclopentilamina 20 (2.7 ml, 27 mmol) produjo el compuesto del título (1.6 g, 82 %). MS ES^+ : 361.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.30 (m, 2H); 1.48 (m, 2H); 1.60 (m, 2H); 1.72 (m, 2H); 2.56 (m, 1H); 2.67 (m, 1H); 2.97 (s, 3H); 3.01 (m, 1H); 3.07 (s, 3H); 3.75 (s, 3H); 3.89 (m, 1H); 4.00 (m, 2H); 5.01 (m, 1H); 6.75 (s, 1H); 7.10 (s, 1H); 7.91 (s, 1H).

Ejemplo 383. Preparación de Compuesto 560 en Tabla 20

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con N'-(2-ciano-5-((2S)-2-hidroxi-3-((2-hidroxi-1,1-dimetiletil)amino)propoxi-4-metoxifenil)-N,N-dimetilimidoformamida (350 mg, 0.77 mmol) produjo el compuesto del título (147 mg, 34 %). MS ES^+: 305.4 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 0.97 (s, 3H); 0.98 (s, 3H); 2.63 (m, 2H); 3.19 (dd, 2H); 3.89 (m, 3H); 3.98 (s, 3H); 4.10 (m, 1H); 4.18 (m, 1H); 4.56 (m, 1H); 7.29 (s, 1H); 7.39 (m, 2H); 7.50 (m, 1H); 7.97 (m, 1H); 8.13 (s, 1H); 8.68 (s, 1H).

N'-(2-ciano-5-((2S)-2-hidroxi-3-((2-hidroxi-1,1-dimetiletil)amino)propoxi)-4- metoxifenil)-N,N-dimetilimidoformamida.

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con 2-amino-2-metil-1-propanol (1.8 ml, 18.2 mmol) produjo el compuesto del título (1.25 g, 93 %).

^{1}HNMR ($DMSOd_6$): 0.93 (s, 3H); 0.94 (s, 3H); 2.58 (m, 2H); 3.19 (m, 2H); 3.73 (s, 3H); 3.80 (m, 1H); 3.97 (m, 1H); 4.03 (m, 1H); 4.50 (m, 1H); 4.95 (m, 1H); 6.75 (s, 1H); 7.10 (s, 1H); 7.91 (s, 1H).

Ejemplo 384. Preparación de Compuesto 561 en Tabla 20

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con N-(3,4-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) y ácido acético (3 ml) produjo el compuesto del título (263 mg, 60 %).

MS ES^+ : 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.37 (m, 2H); 1.50 (m, 4H); 2.41 (m, 6H); 3.88 (s, 2H); 3.96 (s, 3H); 4.03 (m, 2H); 4.18 (d, 1H); 4.88 (m, 1H); 7.28 (s, 1H); 7.40 (s, 1H); 7.40 (m, 2H); 7.80 (m, 1H); 8.11 (s, 1H); 8.66 (s, 1H).

N -(3, 4-difluorofenil)-2-(2-amino-1 ,3-tiazol-5- il)acetamida.

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con N-(3,4-difluorofenil)-2-(2-tritilamino-1,3-tiazol-5-il)acetamida (1,75 g, 3.42 mmol) produjo el compuesto del título (642 mg, 70 %).

^{1}HNMR ($DMSOd_6$): 3.62 (s, 2H); 6.73 (s, 1H); 6.74 (s, 2H); 7.28 (m, 1H); 7.37 (q, 1H); 7.77 (m, 1H).

N -(3 ,4-difluorofenil)-2-(2-tritilamino-1 ,3-tiazol-5-il)acetamida.

Una reacción análoga a la descrita en Ejemplo 255, pero comenzando con 3,4-difluoroanilina (0.97 ml, 9.75 mmol) produjo el compuesto del título (1.75 g, 46 %).

MS ES^+ : 512.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 3.54 (s, 2H); 6.58 (s, 1H); 7.25 (m, 17H); 7.71 (m, 1H); 8.39 (s, 1H).

Ejemplo 385. Preparación de Compuesto 562 en Tabla 20

Una reacción análoga a la descrita en ejemplo 379, pero comenzando con N-(3,4-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (226 mg, 53 %).

MS ES^+ : 571.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.70 (m, 4H); 2.52 (m, 5H); 2.68 (m, 1H); 3.89 (s, 2H); 3.98 (s, 3H); 4.06 (m, 2H); 4.21 (m, 1H); 4.95 (m, 1H); 7.28 *(s,* 1H); 7.33 (m, 1H); 7.39 *(s,* 1H); 7.40 (m, 1H); 7.81 (m, 1H); 8.12 *(s,* 1H); 8.68 *(s,* 1H).

Ejemplo 386. Preparación de Compuesto 563 en Tabla 20

Una reacción análoga a la descrita en ejemplo 380, pero comenzando con N-(3,4-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (220 mg, 49 %).

MS ES^+ : 601.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H); 1.70 (m, 2H); 2.12 (m, 2H); 2.40 (m, 2H); 2.78 (m, 2H); 3.43 (m, 1H); 3.88 (s, 2H); 3.96 (s, 3H); 4.03 (m, 2H); 4.18 (m, 1H); 4.51 (d, 1H); 4.87 (m, 1H); 7.27 (s, 1H); 7.32 (m, 1H); 7.38 (s, 1H); 7.40 (m, 1H); 7.80 (m, 1H); 8.11 (s, 1H); 8.67 *(s,* 1H).

Ejemplo 387. Preparación de Compuesto 565 en Tabla 20

Una reacción análoga a la descrita en ejemplo 382, pero comenzando con N-(3,4-difluorofenil)-2-(2(amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (233 mg, 53 %).

MS ES^+ : 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.32 (m, 2H); 1.47 (m, 2H); 1.61 (m, 2H); 1.72 (m, 2H); 2.63 (m, 1H); 2.72 (m, 1H); 3.05 (m, 1H); 3.89 (s, 2H); 3.97 (m, 4H); 4.09 (m, 1H); 4.16 (m, 1H); 5.05 (m, 1H); 7.27 (s, 1H); 7.34 (m, 1H); 7.38 (s, 1H); 7.42 (m, 1H); 7.82 (m, 1H); 8.12 (s, 1H); 8.67 (s, 1H).

Ejemplo 388. Preparación de Compuesto 566 en Tabla 20

Una reacción análoga a la descrita en ejemplo 379, pero comenzando con N-(3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (238 mg, 56 %).

MS ES^+ : 569.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.70 (s, 1H); 2.52 (m, 5H); 2.68 (m, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4.06 (m, 2H); 4.21 (m, 1H); 4.97 (m, 1H); 7.14 (d, 1H); 7.27 (s, 1H); 7.37 (m, 2H); 7.48 (d, 1H); 7.85 (m, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

N -(3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida.

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con N-(3-clorofenil)-2-(2-tritilamino-1,3-tiazol-5-il)acetamida (3.62 g, 7.1 mmol) produjo el compuesto del título (1.6 g, 84%).

^{1}HNMR ($DMSOd_6$): 3.63 (s, 2H); 6.74 (m, 3H); 7.11 (m, 1H); 7.33 (t, 1H); 7.42 (d, 1H); 7.79 (m, 1H).

N -(3-clorofenil)- 2-(2-tritilamino-1,3-tiazol-5 -il)acetamida.

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con 3-cloroanilina (1.4 ml, 13 mmol) produjo el compuesto del título (3.62 g, 71 %).

^{1}HNMR ($DMSOd_6$): 3.55 (s, 2H); 6.59 (s, 1H); 7.21 (m, 18H); 7.76 (m, 1H); 8.39 (s, 1H).

Ejemplo 389. Preparación de Compuesto 567 en Tabla 20

Una reacción análoga a la descrita en ejemplo 380, pero comenzando con N-(3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.75 mmol) produjo el compuesto del título (156 mg, 35 %).

MS ES^+ : 599.4, 601.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.40 (m, 2H); 1.70 (m, 2H); 2.12 (m, 2H); 2.42 (m, 2H); 2.77 (m, 2H); 3.42 (m, 1H); 3.89 (s, 2H); 3.96 (s, 3H); 4.02 (m, 2H); 4.18 (m, 1H); 4.52 (d, 1H); 4.89 (m, 1tl); 7.12 (d, 1H); 7.26 (s, 1tl); 7.35 (t, 1tl); 7.38 (s, 1H); 7.46 (d, 1H); 7.84 (m, 1H); 8.11 (s, 1H); 8.67 (s, 1H).

Ejemplo 390. Preparación de Compuesto 568 en Tabla 20

Una reacción análoga a la descrita en ejemplo 382, pero comenzando con N-(3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.75 mmol) produjo el compuesto del título (255 mg, 58 %).

MS ES^+ : 583.5, 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.32 (m, 2H); 1.48 (m, 2H); 1.62 (m, 2H); 1.73 (m, 2H); 2.63 (m, 1H); 2.72 (m, 1H); 3.04 (m, 1H); 3.90 (s, 2H); 3.97 (m, 4H); 4.09 (m, 1H); 4.16 (m, 1H); 5.05 (m, 1H); 7.12 (d, 1H); 7.27 (s, 1H); 7.37 (t, 1H); 7.39 (s, 1H); 7.48 (m, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

Ejemplo 391. Preparación de Compuesto 569 en Tabla 20

Una reacción análoga a la descrita en ejemplo 383, pero comenzando con N-(3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida *(200* mg, 0.74 mmol) produjo el compuesto del título (130 mg, 30 %).

MS ES^+ : 587.5, 589.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 0.97 (s, 6H); 2.63 (m,2H); 3.19 (m, 2H); 3.90 (m, 3H); 3.98 (s, 3H); 4.10 (m, 1H); 4.18 (m, 1H); 4.55 (m, 1H); 5.03 (m, 1H); 7.13 (d, 1H); 7.29 (s, 1H); 7.37 (t, 1H); 7.39 (s, 1H); 7.48 (d, 1H); 7.86 (m, 1H); 8.13 (s, 1H); 8.68 (s, 1H).

Ejemplo 392. Preparación de Compuesto 570 en Tabla 20

Una reacción análoga a la descrita en ejemplo 381, pero comenzando con N-(3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.75 mmol) produjo el compuesto del título (211 mg,48%).

MS ES^+ : 584.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.37 (m, 6H); 2.70 (m, 4H); 3.89 (s, 2H); 3.96 (s, 3H); 4.05 (m,2H); 4.19 (m, 1H); 4.90 (m, 1H); 7.12 (d, 1H); 7.27 (s, 1H); 7.35 (t, 1H); 7.37 (s, 1H); 7.47 (d, 1H); 7.84 (m, 1H); 8.10 (s, 1H); 8.66 (s, 1H).

Ejemplo 393. Preparación de Compuesto 571 en Tabla 20

Una reacción análoga a la descrita en ejemplo 388, pero comenzando con N'-(2-ciano-5-((2S)-2-hidroxi-3-metoxi)propoxi-4-metoxifenil)-N,N-dimetil imidoformamida (252 mg, 0.82 mmol) produjo el compuesto del título (200 mg, 50 %). MS ES^+ : 530.4, 532.4 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 3.22 (s, 3H); 3.42 (m, 2H); 3.91 (s, 2H); 3.98 (s, 2H); 4.10 (m, 3H); 5.21 (d, 1H); 7.13 (d, 1H); 7.26 (s, 1H); 7.37 (t, 1H); 7.39 (s, 1H); 7.48 (d, 1H); 7.85 (m, 1H); 8.13 (m, 1H); 8.69 (s, 1H).

N'-(2-ciano-5 -((2S)-2-hidroxi-3-metoxi)propoxi-4-metoxi-fenil)-N,N-dimetilimidoformamida.

N'-(2-ciano-5-(2S)-oxiranlLmetoxi-4-metoxifenil)-N,N-dimetilimidofomamida (1 g, 3.6 mmol) en metanol (80 ml) se trató con metóxido de sodio (10 g, 218 mmol) a reflujo en un horno microondas durante 0.5 horas. El solvente se evaporó y la mezcla se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH 95/5 para producir el compuesto del título (896 mg, 80 %).

^{1}HNMR ($DMSOd_6$): 2.97 (s, 1H); 3.07 (s, 1H); 3.29 (s, 1H); 3.38 (m, 2H); 3.75 (s, 3H); 3.98 (m, 3H); 5.16 (d, 1H); 6.75 (s, 1H); 7.10 (s, 1H); 7.93 (s, 1H).

Ejemplo 394. Preparación de Compuesto 572 en Tabla 20

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con N-(3-clorofenil)-2-(2-amino-13-tiazol-5-il)acetamida (200 mg, 0.75 mmol) produjo el compuesto del título (268 mg, 61 %).

MS ES^+ : 583.5 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.38 (m, 2H); 1.50 (m, 4H); 2.43 (m, 6H); 3.91 (s, 2H); 3.98 (s, 3H); 4.05 (m, 2H); 4.21 (m, 1H); 4.88 (m, 1H); 7.14 (d, 1H); 7.29 (s, 1H); 7.37 (t, 1H); 7.39 (s, 1H); 7.48 (d, 1H); 7.85 (m, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

Ejemplo 395. Preparación de Compuesto 573 en Tabla 20

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con N-(3,5-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (157 mg, 36 %).

MS ES$^+$: 585.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.37 (m, 2H); 1.50 (m, 4H); 2.40 (m, 6H); 3.90 (s, 2H); 3.96 (s, 3H); 4.05 (m, 2H); 4.19 (m, 1H); 4.88 (m, 1H); 6.92 (m, 1H); 7.28 (s, 1H); 7.34 (m, 2H); 7.38 (s, 1H); 8.11 (s, 1H); 8.67 (s, 1H).

N-(3 ,5-difluorofenil)-2-(2-amino-1 ,3-tiazol-5-il) acetamida.

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con N-(3,5-difluorofenil)-2-(2-tritilamino-1,3-tiazol-5-il)acetamida (11.4 g, 28.5 mmol) produjo el compuesto del título (4.75 g, 62 %).

^{1}HNMR ($DMSOd_6$): 3.64 (s, 2H); 6.74 (s, 1H); 6.76 (s, 2H); 6.89 (m, 1H); 7.29 (m, 2H).

N -(3,5 -difluorofenil)-2-(2-tritilamino-1,3-tiazol-5-il)acetamida.

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con 3,5-difluoroanilina (1.68 g, 13 mmol) produjo el compuesto del título (3.53 g, 69 %).

^{1}HNMR ($DMSOd_6$): 3.56 (s, 2H); 6.59 (s, 1H); 6.90 (m, 1H); 7.28 (m, 17H); 8.40 (s, 1H).

Ejemplo 396. Preparación de Compuesto 574 en Tabla 20

Una reacción análoga a la descrita en ejemplo 379, pero comenzando con N-(3,5-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (200 mg, 47 %).

MS ES$^+$: 571.5 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.65 (m, 4H); 2.50 (m, 5H); 2.65 (m, 1H); 3.91 (s, 1H); 3.96 (s, 3H); 4.04 (m, 2H); 4.20 (m, 1H); 4.95 (m, 1H); 6.92 (m, 1H); 7.26 (s, 1H); 7.34 (m, 2H); 7.38 (s, 1H); 8.11 (s, 1H); 8.66 (s, 1H).

Ejemplo 397. Preparación de Compuesto 575 en Tabla 20

Una reacción análoga a la descrita en ejemplo 383, pero comenzando con N-(3,5-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (177 mg, 40 %).

MS ES$^+$: 589.4 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 0.96 (s, 3H); 0.97 (s, 3H); 2.64 (m, 2H); 3.19 (dd, 2H); 3.92 (m, 3H); 3.98 (s, 3H); 4.09 (m, 1H); 4.20 (m, 1H); 4.56 (m, 1H); 5.05 (m, 1H); 6.94 (m, 1H); 7.29 (s, 1H); 7.35 (m, 2H); 7.39 (s, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

Ejemplo 398. Preparación de Compuesto 576 en Tabla 20

Una reacción análoga a la descrita en ejemplo 381, pero comenzando con N-(3,5-difluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (40 mg, 9 %).

MS ES^+ : 628.5 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 2.05 (s, 3H); 2.40 (m, 4H); 2.57 (m, 2H); 2.69 (m, 4H); 3.91 (s, 2H); 3.97 (s, 3H); 4.35 (m, 2H); 5.31 (m, 1H); 6.93 (m, 1H); 7.33 (s, 1H); 7.35 (m, 2H); 7.39 (s, 1H); 8.13 (s, 1H); 8.68 (s, 1H).

Ejemplo 399. Preparación de Compuesto 577 en Tabla 20

Una reacción análoga a la descrita en ejemplo 381, pero comenzando con N-(3,5-ditluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.74 mmol) produjo el compuesto del título (192 mg, 44 %).

MS ES^+ : 586.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.42 (m, 6H); 2.74 (m, 4H); 3.92 (s, 2H); 3.98 (s, 3H); 4.09 (m, 2H); 4.20 (m, 1H); 4.92 (m, 1H); 6.93 (m, 1H); 7.29 (s, 1H); 7.35 (m, 2H); 7.39 (s, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

Ejemplo 400. Preparación de Compuesto 578 en Tabla 20

Una reacción análoga a la descrita en ejemplo 379, pero comenzando con N-(3-fluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.8 mmol) produjo el compuesto del título (156 mg, 35 %).

MS ES^+ : 553.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.70 (m, 4H); 2.5 (m, 5H); 2.67 (m, 1H); 3.90 (s, 2H); 3.98 (s, 3H); 4.06 (m, 2H); 4.20 (m, 1H); 4.97 (m, 1H); 6.92 (m, 1H); 7.28 (m, 1H); 7.35 (m, 2H); 7.39 (s, 1H); 7.63 (m, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

N -(3- fuorofenil)-2-(2-amino-1,3-tiazol- 5-il)acetamida.

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con N-(3-fuorofenil)-2-(2-tritilamino-1,3-tiazol-5-il)acetamida (14.6 g, 38.4 mmol) produjo el compuesto del título (6.21 g, 65 %).

^{1}HNMR ($DMSOd_6$): 3.65 (s, 2H); 6.76 (m, 3H); 6.89 (t, 1H); 7.35 (m, 2H); 7.59 (d, 1H).

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con 3-fluoroanilina produjo el compuesto del título (14.6 g, 79 %).

^{1}HNMR ($DMSOd_6$): 3.56 (s, 2H); 6.61 (s, 1H); 6.89 (t, 1H); 7,25 (m, 17H); 7.56 (d, 1H); 8.41 (s, 1H).

Ejemplo 401. Preparación de Compuesto 579 en Tabla 20

Una reacción análoga a la descrita en ejemplo 378, pero comenzando con N-(3-fluororfenil)-2-(2-amino-1,3-tiazol-5-il)acetamide (200 mg, 0.8 mmol) produjo el compuesto del título (214 mg, 47 %).

MS ES^+ : 567.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 1.38 (m, 2H); 1.52 (m, 4H); 2.42 (m, 6H); 3.91 (s, 2H); 3.98 (s, 3H); 4.04 (m, 2H); 4.20 (m, 1H); 4.89 (m, 1H); 6.91 (m, 1H); 7.29 (s, 1H); 7.37 (m, 2H); 7.39 (s, 1H); 7.63 (m, 1H); 8.13 (s, 1H); 8.68 (s, 1H).

Ejemplo 402. Preparación de Compuesto 580 en Tabla 20

Una reacción análoga a la descrita en ejemplo 381, pero comenzando con N-(3-fluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.8 mmol) produjo el compuesto del título (210 mg, 46%).

MS ES^+ : 568.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.38 (m, 6H); 2.70 (m, 4H); 3.89 (s, 2H); 3.96 (s, 3H); 4.02 (m, 2H); 4.19 (m, 1H); 4.98 (m, 1H); 6.89 (m, 1H); 7.27 (s, 1H); 7.32 (m, 2H); 7.37 (s, 1H); 7.61 (m, 1H); 8.10 (s, 1H); 8.66 (s, 1H).

Ejemplo 403. Preparación de Compuesto 581 en Tabla 20

Una reacción análoga a la descrita en ejemplo 381, pero comenzando con N-(3-fluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.8 mmol) produjo el compuesto del título (35 mg, 7 %).

MS ES^+ : 610.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$): 2.03 (s, 3H); 2.38 (m, 4H); 2.57 (m, 2H); 2.69 (m, 4H); 3.88 (s, 2H); 3.95 (s, 3H); 4.34 (m, 2H); 5.30 (m, 1H); 6.89 (m, 1H); 7.31 (s, 1H); 7.34 (m, 2H); 7.37 (s, 1H); 7.62 (m, 1H); 8.11 (s, 1H); 8.66 (s, 1H).

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Ejemplo 404. Preparación de Compuesto 582 en Tabla 20

Una reacción análoga a la descrita en ejemplo 382, pero comenzando con N-(3-fluorofenil)-2-(2-amino-1,3-tiazol-5-il)acetamida (200 mg, 0.8 mmol) produjo el compuesto del título (196 mg, 43 %).

MS ES^+ : 567.5 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.30 (m, 2H); 1.47 (m, 2H); 1.61 (m,2H); 1.73 (m, 3H); 2.62 (m, 1H); 2.71 (m,1H); 3.0 (m, 1H); 3.89 (m, 1H); 3.97 (s, 3H); 4.07 (m, 1H); 4.13 (m, 1H); 5.03 (m, 1H); 6.90 (m, 1H); 7.25 (s, 1H); 7.35 (m, 2H); 7.37 (s, 1H); 7.62 (m, 1H); 8.10 (s, 1H); 8.66 (s, 1H).

Ejemplo 405. Preparación de Compuesto 583 en Tabla 21

Ácido 4-((2-amino-1,3-tiazol-5-il)acético)-6,7-dimetoxiquinazolina (173 mg, 0.5 mmol) en NMP (2 ml) se hizo reaccionar con 3,5-difluoroanilina (98 mg, 0.75 mmol) en la presencia de hexafluorofosfato de 0-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (285 mg, 0.75 mmol) y DIEA (130 µl, 0.75 mmol) a 50°C durante 20 horas. La mezcla se enfrió, se agregó dimetilamina (2M MeOH, 2 ml), y la solución resultante se agitó a temperatura ambiente durante 15 horas, se evaporó MeOH, y se adicionó agua (20 ml) a la mezcla, se recuperó el precipitado, se lavó con agua, y se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH 50/40/10 para producir el compuesto del título (22 mg, 10 %).

^{1}HNMR ($DMSOd_6$): 3.90 (s, 2H); 3.95 (s, 6H); 6.93 (t, .1H); 7.26 (s, 1H); 7.34 (d, 2H); 7.39 (s, 1H); 8.12 (s, 1H); 8.68 (s, 1H).

Ácido 4-((2-amino-1,3-tiazol-5-il)acético)-6,7-dimetoxiquinazolina.

4-(metil(2-amino-1,3-tiazol-5-il)acetato)-6,7-dimetoxiquinazolina (3.92 g, 10.9 mmol) en etanol 50 ml se trató con hidróxido de sodio (2N, 27 ml, 54.5 mmol) durante 45 minutos. El solvente se evaporó, el residuo se disolvió en CH_2Cl_2 / MeOH trietilamina (3 eq.) se añadió, se retiró el sólido por filtración, el filtrado se evaporó y trituró con etanol para producir el compuesto del título como un sólido (1.88 g, 50 %). ^{1}HNMR ($DMSOd_6$): 3.83 (s, 2H); 3.96 (s, 6H); 7.27 (s, 1H); 7.35 (s, 1H); 8.13 (s, 1H); 8.69 (s, 1H).

4-(metil(2-amino-1,3-tiazol-5-il)acetato)-6,7-dimetoxiquinazolina.

N'-(2-ciano-4,5-dimetoxifenil)-N,N-dimetilimidoformamida (3.5 g, 15 mmol) en ácido acético (35 ml) se hizo reaccionar con metil (2-amino-1,3-tiazol-5-il)acetato (3.22 g, 18.7 mmol)

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a reflujo durante 4 horas. El solvente se evaporó y el residuo se purificó por cromatografía de gel de sílice, eluyente CR_2Cl_2 / MeOH 95/5 para producir el compuesto del título (3.92 g, 73 %).

^{1}HNMR ($DMSOd_6$): 3.69 (s, 3H); 3.95 (s, 2H); 3.96 (s, 6H); 7.27 (s, 1H); 7.38 (s, 1H); 8.12 (s, 1H); 8.69 (s, 1H).

Ejemplo 406. Preparación de Compuesto 584 en Tabla 21

Una reacción análoga a la descrita en ejemplo 405, pero comenzando con 3-cloroanilina (80 µl, 0.75 mmol) produjo el compuesto del título (81 mg, 26 %). MS ES$^+$: 456.4, 458.4 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 3.9.1 (s, 2H); 3.96 (s, 6H); 7.14 (d, 1H); 7.28 (s, 1H); 7.37 (t, 1H); 7.48 (d, 1H); 7.85 (m, 1H); 8.13 (s, 1H); 8.69 (s, 1H).

Ejemplo 407. Preparación de Compuesto 585 en Tabla 21

Una reacción análoga a la descrita en ejemplo 405, pero comenzando con 3-cloro-4-fluoroanilina 15 (110 mg, 0.75 mmol) produjo el compuesto del título (93.7 mg, 40 %). MS ES$^+$: 474.4, 476.4 $(M+H)^+$ ^{1}HNMR: 3.90 (s, 2H); 3.97 (s, 3H); 7.28 (s, 1H); 7.40 (m, 1H); 7.40 (s, 1H); 7.50 (m, 1H); 7.96 (m, 1H); 8.14 (s, 1H); 8.70 (s, 1H).

Ejemplo 408. Preparación de Compuesto 586 en Tabla 21

Una reacción análoga a la descrita en ejemplo 405, pero comenzando con 3,4-difluoroanilina (75 mg, 0.75 mmol) produjo el compuesto del título (130 mg, 60 %). MS ES$^+$: 458.5 $(M+H)^+$ ^{1}HNMR: 3.89 (s, 2H); 3.97 (s, 6H); 7.28 (s, 1H); 7.33 (m, 1H); 7.40 (s, 1H); 7.41 (m, 1H); 7.82 (m, 1H); 8.14 (s, 1H); 8.69 (s, 1H).

Ejemplo 409. Preparación de Compuesto 587 en Tabla 22

Ácido 4-((2-amino-1,3-tiazol-5-il)(hidroxi)acético)-6-metoxi-7-(3-morfolinopropoxi)quinazolina (143 mg, 0.3 mmol) en DMF (4 ml) se hizo reaccionar con anilina (36 mg, 0.39 mmol), 1-(3-dimetilaminopropil)-3-etilcarbodiimida clorhidrato (63 mg, 0.33 mmol), 2-hidroxipiridina N-óxido (33 mg, 0.3 mmol) y DIEA (36 mg, 0.3 mmol) a 90°C durante 1 hora. Se enfrió la mezcla, se diluyó CH_2Cl_2 (8 ml) y se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2/ MeOH 90/10 a 85/15. Las fracciones combinadas

que contenían el producto se evaporaron, el residuo se disolvió en MeOH, se agregó agua y se recuperó el precipitado, se disolvió en MeOR / CH_2Cl_2, se secó, se concentró para producir el compuesto del título (145 mg, 88 %). MS ES^+: 551.6 $(M+H)^+$ ^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H); 3.15 (t, 2H); 3.34 (t, 2H); 3.55 (d, 2H); 3.71 (t, 2H); 3.98 (s, 3H); 4.03 (d, 2H); 4.31 (t, 2H); 5.47 (s, 1H); 7.11 (t, 1H); 7.31 (s, 1H); 7.33 (t, 2H); 7.70 (s, 1H); 7.73 (d, 2H); 7.92 (s, 1H); 9.12 (s, 1H).

4-(2-amino-1,3-tiazol-5- il)-6- metoxi-7-(3-morfolinopropoxi)quinazolina.

N'-(2-ciano-4-metoxi-5-(3-morfolinopropoxi)fenil)-N,N-dimetilimidoformamida (692 mg, 2 mmol) se hizo reaccionar con amino-1,3-tiazol (240 mg, 2.4 mmol) en ácido acético (6.9 ml) a reflujo durante 4 horas. La mezcla se concentró, el residuo se disolvió en AcOEt, se lavó con bicarbonato de sodio acuoso, se secó la fase orgánica, se concentró, el aceite residual se trituró en éter para producir un sólido (560 mg, 70 %). MS ES^+: 402.6 $(M+H)^+$ ^{1}HNMR (DMSOd_6, TFA): 2.29 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 3.99 (s, 3H); 4.04 (d, 2H); 4.31 (t, 2H); 7.32 (s, 1H); 7.47 (d, 1H); 7.75((d, 1H); 7.95 (s, 1H); 9.11 (s, 1H).

Ácido 4-((2-amino-1,3-tiazol-5-il)(hidroxi)acético)-6-metoxi-7-(3-morfolinopropoxi)quinazolina.

20 4-(2-amino-1,3-tiazol-5-il)-6-metoxi-7-(3-morfolinopropoxi)quinazolina (1.6 g, 4 mmol) en agua (16 ml), MeOH (16 ml), se hizo reaccionar con ácido glioxílico (740 mg, 8 mmol) a pH 11.5 (NaOH 6N) y 45-50°C durante 6 horas. Se evaporó metanol, y el pH de la fase acuosa se ajustó a 3 (HCl 6N), y la solución se vertió en una columna (isolute®) de intercambiador fuerte de cationes, se lavó con agua (120 ml), metanol (120 ml) y se eluyó con CH_2Cl_2 / MeOH, NH_3 (3N) 1/1 200 ml para producir el compuesto del título (1.58 g, 83 %). ^{1}HNMR (DMSOd_6, TFA): 2.31 (t, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.98 (s, 3H); 4.03 (d, 2H); 4.30 (t, 2H); 5.38 (s, 1H); 7.32 (s, 1H); 7.68 (s, 1H); 7.91 (8, 1H); 9.12 (s, 1H).

Ejemplo 410. Preparación de Compuesto 588 en Tabla 22

Una reacción análoga a la descrita en ejemplo 409, pero comenzando con 3,4-difluoroanilina (34 mg, 0.26 mmol) produjo el compuesto del título (30 mg, 26%).

amino-1,3-tiazol-5-il)-2-hidroxiacetamida (82 mg, 0.3 mmol) en ácido acético (260 mg) a 105°C durante 40 minutos. La mezcla se evaporó y purificó por cromatografía de gel de sílice, eluyenye CH_2Cl_2 / MeOH (NH3 3N) 9/1 para producir el compuesto del título (42 mg, 26 %).

MS ES^+: 567.5 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.4 (m, 2H); 1.51 (m, 4H); 1.95 (t, 2H); 2.40 (m, 6H); 3.95 (s, 3H); 4.19 (t, 2H); 5.41 (d, 1H); 6.78 (d, 1H); 6.91 (m, 1H); 7.25 (s, 1H); 7.35 (q, 1H); 7.50 (s, 1H); 7.55 (d, 1H); 7.71 (m, 1H); 8.10 (s, 1H); 8.68 (s, 1H).

N'-(2-ciano-4-metoxi-5-(3-piperidinilpropoxi)-4-metoxifenil)-N,N-dimetetilimidoformamida.

N'-(2-ciano-4-metoxi-5-(3-cloropropoxi)-4-metoxifenil)-N,N-dimetilimidoformamida (3 g, 10 mmol) en acetonitrilo (50 ml) se hizo reaccionar con piperidina (10 ml, 100 mmol) en presencia de KI (300 mg, 1.8 mmol) y K_2CO_3 (2.1 g, 0.015 mmol) a 75° C bajo argón durante 3 horas. El solvente se evaporó, y el residuo se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH, NH_3 3N 95/5 para producir el compuesto del título (3.48 g, 100 %). MS ES^+: 345.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.4 (m, 2H); 1.50 (m, 4H); 1.88 (m, 2H); 2.35 (m, 6H); 2.95 (s, 3H); 3.05 (s, 3H); 3.72 (s, 3H); 4.05 (t, 2H); 6.72 (s, 1H); 7.07 (s, 1H); 7.89 (s, 1H).

N -(3-fluorofenil)-2-(2-amino-1,3-tiazol-5'-il)-2-hidroxiacetomida.

Una reacción análoga a la descrita en Ejemplo 289, pero comenzando con N-(3-fluorobenzil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)-2-hidroxiacetamida (2.55 g, 0.69 mmol) produjo el compuesto del título (1.37 g, 75 %).

MS ES^+: 268.5 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 5.16 (d, 1H); 6.45 (d, 1H); 6.90 (m, 4H); 7.34 (q, 1H); 7.49 (d, 1H); 7.70 (m, 1H).

N-(3-fluorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)-2-hidroxiacetamida.

Una reacción análoga a la descrita en ejemplo 411, pero comenzando con N-(3-fluorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il) (oxo)acetamida (2.92 g, 8 mmol) produjo el compuesto del título (2.59 g, 88 %).

^{1}HNMR ($DMSOd_6$): 1.48 (s, 9H); 5.34 (d, 1H); 6.74 (d, 1H); 6.90 (m, 1H); 7.33 (m, 2H); 7.54 (d, 1H); 7.70 (m, 1H).

N-(3- fluorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il) (oxo) acetamida.

Una reacción análoga a la descrita en ejemplo 411, pero comenzando con 3-fluoroanilina (1.6 g, 14.4 mmol) produjo el compuesto del título (4.06 g, 93 %). ^{1}HNMR ($DMSOd_6$): 1.54 (s, 9H); 7.01 (m, 1H); 7.42 (m, 1H); 7.69 (m, 1H); 7.80 (m, 1H); 8.6 (s, 1H).

Ejemplo 413. Preparación de Compuesto 591 en Tabla 22

Una reacción análoga a la descrita en ejemplo 412, pero comenzando con N-(3-clorofenil)-2-(2-amino-1,3-tiazol-5-il)-2-hidroxiacetamida (99 mg, 0.35 mmol) produjo el compuesto del título (47 mg, 23 %).

MS ES^+ : 583.4 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$): 1.38 (m, 2H); 1.51 (m, 4H); 1.95 (m, 2H); 2.38 (m, 6H); 3.95 (s, 3H); 4.19 (t, 2H); 5.40 (d, 1H); 6.79 (d, 1H); 7.14 (d, 1H); 7.24 (s, 1H); 7.35 (t, 1H); 7.50 (s, 1H); 7.67 (d, 1H); 7.95 (s; 1H); 8.10 (s, 1H); 8.68 (s, 1H).

N -(3-clorofenil)-2-(2-amino-1,3-tiazol-5- il)- 2-hidroxiacetamida.

Una reacción análoga a la descrita en ejemplo 412, pero comenzando con N-(3-clorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)-2-hidroxiacetamida (2.13 g, 5.5 mmol) produjo el compuesto del título (1.02 g, 65 %). ^{1}HNMR ($DMSOd_6$): 5.15 (d, 1H); 6.45 (d, 1H); 6.90 (m, 3H); 7.12 (dd, 1H); 7.33 (t, 1H); 20 7.62 (d, 1H); 7.89 (m, 1H).

N-(3-clorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)-2-hidroxiacetamida.

Una reacción análoga a la descrita en ejemplo 412, pero comenzando con N-(3-clorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il)(oxo)acetamida (2.5 g, 6.5 mmol) produjo el compuesto del título (2.23 g, 89 %).

^{1}HNMR ($DMSOd_6$): 1.48 (s, 9H); 5.34 (d, 1H); 6.74 (d, 1H); 7.14 (m, 1H); 7.34 (m, 2H); 7.65 (m, 1H); 7.92 (m, 1H).

N-(3-clorofenil)-2-(2-tert-butoxicarbonilamino-1,3-tiazol-5-il) (oxo) acetamida.

Una reacción análoga a la descrita en ejemplo 412, pero comenzando con 3-cloroanilina (1.84 g, 14 mmol) produjo el compuesto del título (3.6 g, 79 %). ^{1}HNMR ($DMSOd_6$): 1.54 (s, 9H); 7.24 (d, 1H); 7.43 (t, 1H); 7.79 (d, 1H); 8.03 (s, 1H); 8.61 (s, 1H).

de bicarbonato de sodio (2 ml) y la mezcla se agitó durante 0.5 hora Se recuperó un sólido por filtración, se lavó con agua, se secó para producir el compuesto del título (15 mg, 16 %).

MS ES^+ : 521 $(M_+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (m, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d,2H); 3.69 (t, 2H); 4.03 (d, 2H); 4.05 (s, 3H); 4.32 (t, 2H); 7.43 (m,2H); 7.53 (t, 1H); 7.94 (d, 1H); 8.21 (m, 2H); 8.35 (t, 1H); 8.49 (d, 1H); 9.30 (s, 1H).

Ejemplo 416. Preparación de Compuesto 594 en Tabla 23

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con 4-metilanilina (19 mg, 0.18 mmol) produjo el compuesto del título (69 mg, 72 %).

MS ES^+ : 535 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.34 (s, 3H); 2.40 (t, 2H); 3.11 (t, 2H); 3.38 (t, 2H); 3.60 (d, 2H); 3.90 (t, 2H); 4.03 (d, 2H); 4.05 (s, 3H); 4.35 (t, 2H); 7.15 (d, 2H); 7.27 (d, 1H); 7.52 (s, 1H); 7.62 (d, 2H); 7.85 (d, 1H); 8.15 (s, 1H); 8.87 (s, 1H).

Ejemplo 417. Preparación de Compuesto 595 en Tabla 23

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con 2-metilanilina (19 mg, 0.18 mmol) produjo el compuesto del título (28 mg, 29 %). MS ES^+ : 535 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2/28 (s, 3H); 2.32 (t, 2H); 3.18 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 4.05 (d, 2H); 4.07 (s, 3H); 7.30 (m, 4H); 7.35 (d, 1H); 7.41 (s, 1H); 7.96 (d, 1H); 8.22 (s, 1H); 9.26 (s, 1H).

Ejemplo 418. Preparación de Compuesto 596 en Tabla 23

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con 3-metoxianilina (22 mg, 0.18 mmol) produjo el compuesto del título (14 mg, 14 %).

MS ES^+ : 550.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.17 (t,2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 3.78 (s, 3H); 4.04 (d, 2H); 4.06 (s, 3H); 4.33 (t, 2H); 6.7 (d, 1H); 7.28 (s, 1H); 7.35 (s, 30 1H); 7.36 (d, 1H); 7.41 (s, 1H); 7.45 (s, 1H); 8.01 (d, 1H); 8.22 (s, 1H); 9.27 (s, 1H).

Ejemplo 419. Preparación de Compuesto 597 en Tabla 23

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con 2-hidroximetil-anilina (22 mg, 0.18 mmol) produjo el compuesto del título (7 mg, 7 %). MS ES^+ : 550.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (m, 2H); 3.18 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.06 (m, 5H); 4.32 (t, 2H); 4.65 (s, 2H); 7.22 (t, 1H); 7.32 (t, 1H); 7.37 (d, 1H); 7.40 (s, 1H); 7.46 (d, 1H); 7.72 (d, 1H); 7.81 (d, 1H); 8.22 (s, 1H); 9.27 (s, 1H).

Ejemplo 420. Preparación de Compuesto 598 en Tabla 23

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con 3-nitroanilina (25 mg, 0.18 mmol) produjo el compuesto del título (6 mg, 6 %). MS ES^+ : 565.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.18 (t, 2H); 3.38 (t, 2H); 3.58 (d, 2H); 3.70 (t, 2H); 4.05 (d, 2H); 4.07 (s, 3H); 4.33 (t, 2H); 7.39 (d, lH); 7.42 (s, 1H); 7.68 (t, 1H); 7.98 (d, 1H); 8.08 (d, 1H); 8.20 (m, 1H); 8.23 (s, 1H); 8.77 (s, 1H); 9.3 (s, 1H).

Ejemplo 421. Preparación de Compuesto 599 en Tabla 23

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con 4-trifluoromethiloaniline (29 mg, 0.18 mmol) produjo el compuesto del título (8 mg; 8 %).

MS ES^+ : 588.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (m, 2H); 3.19 (t, 2H); 3.41 (t, 2H); 3.61 (d, 2H); 3.75 (t, 2H); 4.05 (d, 2H); 4.08 (s, 1H); 4.37 (t, 2H); 7.39 (d, lh); 7.43 (s, 1H); 7.72 (d, 2H); 8.03 (d, 2H); 8.10 (d, 1H); 8.23 (s, 1H); 9.29 (s, 1H).

Ejemplo 422. Preparación de Compuesto 600 en Tabla 23

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con 3-cloroanilina (23 mg, 0.18 mmol) produjo el compuesto del título (21 mg, 21 %).

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (m, 2H); 3.19 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 4.03 (d, 2H); 4.07 (s, 3H); 4.34 (t, 2H); 7.17 (d, 1H); 7.37 (t, 1H); 7.40 (m, 2H); 7.70 (d, 1H); 7.95 (m, 1H); 8.02 (d, 1H); 8.22 (s, 1H); 9.29 (s, 1H).

Ejemplo 423. Preparación de Compuesto 601 en Tabla 23

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con 2-metoxianilina (22 mg, 0.18 mmol) produjo el compuesto del título (32 mg, 32 %). ^{1}HNMR ($DMSOd_6$, TFA): 2.35 (t, 2H); 3.18 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 3.87 (s, 3H); 4.05 (d, 2H); 4.06 (s, 3H); 4.34 (t, 2H); 6.99 (t, 1H); 7.11 (d, 1H); 7.20 (s, 1H); 7.33 (d, 1H); 7.40 (s, 1H); 7.73 (dd, 1H); 7.97 (d, 1H); 8.22 (s, 1H); 9.27 (s, 1H).

Ejemplo 424. Preparación de Compuesto 602 en Tabla 23

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con 3-(2-hidroxietil) anilina (25 mg, 0.18 mmol) produjo el compuesto del título (27 mg, 26 %).

MS ES^+ : 564.7 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 1.37 (d, 3H); 2.32 (t, 2H); 3.19 (t, 2H); 3.38 (t, 2H); 3.58 (d, 2H); 3.62 (t, 2H); 4.06 (d, 2H); 4.08 (s, 3H); 4.36 (t, 2H); 4.76 (q, 1H); 7.08 (d, 1H); 7.29 (t, 1H); 7.35 (d, 1H); 7.42 (s, 1H); 7.70 (d, 1H); 7.76 (s, 1H); 8.05 (d, 1H); 8.23 (s, 1H); 9.28 (s, 1H).

Ejemplo 425. Preparación de Compuesto 603 en Tabla 23

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con 3-fluoro-4-metoxianilina (25 mg, 0.18 mmol) produjo el compuesto del título (14 mg, 14 %).

MS ES^+ : 568.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.19 (t, 2H); 3.38 (t, 2H); 3.57 (d, 2H); 3.72 (t, 2H); 3.85 (s, 3H); 4.04 (d, 2H); 4.07 (s, 3H); 4.35 (t, 2H); 7.17 (t, 1H); 7.36 (d, 1H); 7.42 (s, 1H); 7.47 (dd, 1H); 7.73 (dd, 1H); 7.98 (d, 1H); 8.24 (s, 1H); 9.27 (s, 1H).

Ejemplo 426. Preparación de Compuesto 604 en Tabla 23

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con 2-metil-4-fluoroanilina (23 mg, 0.18 mmol) produjo el compuesto del título (27 mg, 27 %). MS ES^+ : 552.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.28 (s, 3H); 2.31 (t,2H); 3.18 (t, 2H); 3.38 (t, 2H); 3.57 (d, 2H); 3.71 (t, 2H); 4.05 (d, 2H); 4.07 (s, 3H); 7.07 (dt, 1H); 7.15 (dd, 1H); 7.35 (d, 1H); 7.36 (m, 1H); 7.41 (s, 1H); 7.95 (d, 1H); 8.23 (s, 1H); 9.26 (s, 1H).

Ejemplo 427. Preparación de Compuesto 605 en Tabla 23

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con 2-fluoro-5-metilanilina (23 mg, 0.18 mmol) produjo el compuesto del título (9 mg, 9 %).

MS ES^+ : 552.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 2.33 (m, 5H); 3.19 (t, 2H); 3.38 (t, 2H); 3.56 (d, 2H); 3.71 (t, 2H); 4.04 (d, 2H); 4.07 (s, 3H); 4.35 (t, 2H); 7.09 (m, 1H); 7.18 (m, 1H); 7.35 (d, 1H); 7.40 (s, 1H); 7.41 (m, 1H); 8.0 (d, 1H); 8.23 (s, 1H); 9.27 (s, 1H).

Ejemplo 428. Preparación de Compuesto 606 en Tabla 23

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con 10 3-cianoanilina (21 mg, 0.18 mmol) produjo el compuesto del título (9 mg, 9 %). MS ES^+ : 545.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (t,2H); 3.21 (t, 2H); 3.39 (t, 2H); 3.60 (d, 2H); 3.72 (t, 2H); 4.07 (d, 2H); 4.10 (s, 3H); 4.37 (t, 2H); 7.40 (d, 1H); 7.44 (s, 1H); 7.62 (s, 1H); 7.63 (m, 1H); 8.06 (m, 1H); 8.06 (d, 1H); 8.26 (s, 1H); 8.30 (s, 1H); 9.32 (s, 1H).

Ejemplo 429. Preparación de Compuesto 607 en Tabla 23

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con isoamilamina (16 mg, 0.18 mmol) produjo el compuesto del título (15 mg, 17 %).

MS ES^+ : 514.7 $(M+H)^+$

^{1}HNMR ($CDCl_3$): 0.96 (d, 6H); 1.77 (m, 5H); 2.11 (m, 2H); 2.5 (m, 4H); 2.56 (t, 2H); 3.73 (m, 4H); 4.03 (s, 3H); 4.22 (t, 2H); 6.05 (t, 1H); 6.88 (d, 1H); 7.24 (s, 1H); 7.39 (d, 1H); 7.58 (s, 1H); 8.70 (s, 1H).

Ejemplo 430. Preparación de Compuesto 608 en Tabla 23

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con 2-cloroanilina (23 mg, 0.18 mmol) produjo el compuesto del título (5 mg, 5 %). MS ES^+ : 554.5, 556.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.19 (t, 2H); 3.39 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 4.04 (d, 2H); 4.07 (s, 3H); 4.34 (t, 2H); 7.32 (t, 1H); 7.36 (d, 1H); 7.41 (s, 1H); 7.41 (t, 1H); 7.57 (d, 1H); 7.63 (d, 1H); 8.0 (d, 1H); 8.23 (s, 1H); 9.27 (s, 1H).

Ejemplo 431. Preparación de Compuesto 609 en Tabla 24

Una reacción análoga a la descrita en ejemplo 415, pero comenzando con ácido 5-((6-metox-7-(3-morfolinopropoxi)quinazolin-4-il)amino)tiofen-3-carboxílico (80 mg, 0.18 mmol) y anilina (20 µl, 0.22 mmol)) produjo el compuesto del título (28 mg, 30 %). MS ES$^+$: 520 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.18 (t, 2H); 3.38 (t,2H); 3.56 (d, 2H); 3.71 (t, 2H); 4.05 (d, 2H); 4.06 (s, 3H); 4.34 (t, 2H); 7.12 (t, 1H); 7.37 (t, 2H); 7.40 (s, 1H); 7.76 (d, 1H); 7.79 (d, 2H); 8.18 (s, 1H); 8.21 (d, 1H); 9.17 (s, 1H).

Ácido 5-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)amino)tiofen-3-carboxílico.

Etil-5-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)amino tiofen-3-carboxilato (1.05 g, 2.2 mmol) en metanol (10 ml) se trató con hidróxido de sodio (2N, 10 ml) a 75°C durante 1.5 hora. Metanol se evaporó, HCl (2N) se agregó (pH 3), se filtró el sólido, se volvió a disolver en CH_2Cl_2 / MeOH 1/1, se añadió DIEA (1.5 ml, 8.8 mmol), el sólido se retiró por filtración, el filtrado se concentró, y el residuo se disolvió en etanol, se obtuvo el material del título como un sólido (0.7 g, 71 %).

MS ES$^+$: 445 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 2.36 (t,2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.79 (t, 2H); 4.03 (d, 2H); 4.08 (s, 3H); 4.35 (t, 2H); 7.45 (s, 1H); 7.81 (s, 1H); 8.03 (s, 1H); 8.50 (s, 1H); 9.15 (s, 1H).

Etil-5-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)aminotiofen-3-carboxilato.

4-cloro-6-metoxi-7-(3-morfolinopropoxi)quinazolina (1 g, 3 mmol) en isopropanol (25 ml) e isopropanol HCl (0.5 ml) se hizo reaccionar con etil 5-aminotiofen-3-carboxilato (0.6 g, 3.3 mmol) a 110°C durante 1 hora. La mezcla se enfrió, se diluyó con EtOAc, se filtró para producir el compuesto del título (1.58 g, 99 %).

MS ES$^+$: 473 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 1.33 (t, 3H); 2.33 (t,2H); 3.17 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.75 (t, 2H); 4.03 (d, 2H); 4.06 (s, 3H); 4.30 (q, 2H); 4.33 (t,2H); 7.42 (s, 1H); 7.73 (s, 1H); 8.09 (s, 1H); 8.35 (s, 1H); 9.15 (s, 1H).

Ejemplo 432. Preparación de Compuesto 610 en Tabla 24

Una reacción análoga a la descrita en ejemplo 431, pero comenzando con 4-fluoroanilina (24 mg, 0.18 mmol) produjo el compuesto del título (20 mg, 22 %).

MS ES$^+$: 538.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.20 (t, 2H); 3.40 (t, 2H); 3.60 (d, 2H); 3.72 (t, 2H); 4.04 (d, 2H); 4.07 (s, 3H); 4.34 (t, 2H); 7.9 (s, 1H); 7.20 (m, 2H); 7.41 (s, 1H); 7.76 (d, 1H); 7.82 (m, 1H); 8.19 (s, 1H); 8.21 (d, 1H); 9.17 (s, 1H).

Ejemplo 433. Preparación de Compuesto 611 en Tabla 24

Una reacción análoga a la descrita en ejemplo 431, pero comenzando con 3-hidroxianilina (24 mg, 0.18 mmol) produjo el compuesto del título (15 mg, 17 %).

MS ES$^+$: 536.6 $(M+H)^+$

Ejemplo 434. Preparación de Compuesto 612 en Tabla 24

Una reacción análoga a la descrita en ejemplo 431, pero comenzando con 3-(metiltio)anilina (30 mg, 0.18 mmol) produjo el compuesto del título (23 mg, 24 %).

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.04 (m, 5H); 4.33 (t, 2H); 7.24 (t, 1H); 7.32 (t, 1H); 7.41 (s, 1H); 7.43 (m, 2H); 7.72 (d, 2H); 8.16 (m, 2H); 9.17 (s, 1H).

Ejemplo 435. Preparación de Compuesto 613 en Tabla 24

Una reacción análoga a la descrita en ejemplo 431, pero con 4-fluoro-3-cloroanilina (32 mg, 0.18 mmol) produjo el compuesto del título (21 mg, 21 %). MS ES$^+$: 577 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.19 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.71 (t, 2H); 4.06 (m, 5H); 4.34 (t, 2H); 7.41 (m, 2H); 7.75 (m, 2H); 8.11 (m, 1H); 8.18 (s, 1H); 8.21 B(s, 1H); 9.18 (s, 1H).

Ejemplo 436. Preparación de Compuesto 614 en Tabla 24

Una reacción análoga a la descrita en ejemplo 431, pero comenzando con 2,4- difluorobencilamina (31 mg, 0.18 mmol) produjo el compuesto del título (22 mg, 22 %). MS ES$^+$: 570.5 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 2.34 (t, 2H); 3.19 (t, 2H); 3.39 (t, 2H); 3.58 (d, 2H); 3.72 (t, 2H); 4.06 (m, 5H); 4.34 (t, 2H); 4.51 (s, 2H); 7.06 (t, 1H); 7.15 (t, 1H); 7.40 (s, 1H); 7.48 (m, 1H); 7.69 (d, 1H); 8.03 (d, 1H); 8.17 (s, 1H); 9.14 (s, 1H).

Ejemplo 437. Preparación de Compuesto 615 en Tabla 24

Una reacción análoga a la descrita en ejemplo 431, pero comenzando con 3-fluoroanilina (24 5 mg, 0.18 mmol) produjo el compuesto del título (27 mg, 29 %). MS ES^+ : 538.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (t, 2H); 3.18 (t, 2H); 3.38 (t, 2H); 3.58 (d, 2H); 3.72 (d, 2H); 4.04 (d, 2H); 4.07 (s, 3H); 4.35 (t, 2H); 6.91 (m, 1H); 7.42 (m, 2H); 7.59 (d, 1H); 7.78 (d, 1H); 7.79 (m, 1H); 8.19 (s, 1H); 8.24 (d, 1H); 9.18 (s, 1H).

Ejemplo 438. Preparación de Compuesto 616 en Tabla 25

Ácido 2-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)amino)imidazol-5-carboxílico (200 mg, 0.47 mmol) en DMF (3 ml) se hizo reaccionar con anilina (43 µl, 0.47 mmol) en presencia de hexafluorofosfato de 0-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (178 mg, 0.47 mmol) y DIEA (120 µl, 0.7 mmol) a 40°C durante 3 horas. Se agregó una solución de dimetilamina en metanol (2M, 1 ml) y se practicó agitación durante 3 horas. El solvente se evaporó, y la mezcla se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2/ MeOH NH_3 (sat.) 95/5 para producir el compuesto del título (80 mg, 34 %).

MS ES^+ : 504.1 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.29 (t, 2H); 3.18 (t, 2H); 3.35 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 3.96 (s, 3H); 4.04 (d, 2H); 4.27 (t, 2H); 7.15 (t, 1H); 7.25 (s, 1H); 7.40 (t, 2H); 7.74 (d, 2H); 7.81 (s, 1H); 8.09 (s, 1H); 8.75 (s, 1H).

Ejemplo 439. Preparación de Compuesto 617 en Tabla 25

Una reacción análoga a la descrita en ejemplo 438, pero comenzando con 4-fluoroanilina (60 µl, 0.58 mmol) produjo el compuesto del título (120 mg, 39 %). MS ES^+: 522.1 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.29 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.55 (d, 1H); 3.69 (t, 2H); 3.96 (s, 3H); 4.04 (d, 2H); 4.27 (t, 2H); 7.22 (m, 3H); 7.74 (m, 2H); 7.82 (s, 1H); 8.07 (s, 1H); 8.76 (s, 1H).

Ejemplo 440. Preparación de Compuesto 618 en Tabla 25

Una reacción análoga a la descrita en ejemplo 438, pero comenzando con alilamina 50 µl, 0.7 mmol) produjo el compuesto del título (133 mg, 40 %).

MS ES^+ : 468.1 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 2.28 (t, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.94 (m, 5H); 4.04 (d, 2H); 4.26 (t, 2H); 5.14 (dd, 1H); 5.23 (dd, 1H); 5.88 (m, 1H); 7.23 (s, 1H); 7.77 (s, 1H); 7.86 (s, 1H); 8.71 (s, 1H).

Ácido 2-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)amino)imidazol-5-carboxílico.

Etil-2((4-imino-6-metoxi-7-(3-morfolinoropoxi)quinazolin-3-(4H)-il)imidazol-5-carboxilato (650 mg, 1.42 mmol) en metanol (14 ml) se trató con hidróxido de sodio (2N, 14 ml) a 80°C durante 1.5 hora. Metanol se evaporó, se agregó ácido clorhídrico (6N) (pH 2.5), el precipitado se recuperó por filtración, se secó para producir el compuesto del título (650 mg, 100 %).

^{1}HNMR ($DMSOd_6$, TFA): 2.35 (t, 2H); 3.13 (t, 2H); 3.32 (t, 2H); 3.5 (d, 2H); 3.95 (m, 7H); 4.28 (t, 2H); 7.42 (s, 1H); 7.8 (s, 1H); 7.86 (s, 1H); 8.72 (s, 1H).

Ejemplo 441. Preparación de Compuesto 619 en Tabla 26

4-cloro-6-metoxi-7-(3-morfolinopropoxi)quinazolina (265 mg, 0.79 mmol) en 2-propanol (14 ml) se hizo reaccionar con clorhidrato de 4-amino-N-feniltiofen-3-carboxamida (210 mg, 0.82 mmol) a 100°C durante 2 horas. El solvente se evaporó y el residuo se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH, NH_3 sat. 95/5 para producir el compuesto del título (330 mg, 81 %).

MS ES^+ : 520.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 2.30 (t, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 4.03 (s, 3H); 4.04 (d, 2H); 4.32 (t, 2H); 7.13 (t, 1H); 7.35 (t, 2H); 7.39 (s, 1H); 7.69 (d, 2H); 7.79 (s, 1H); 8.13 (d, 1H); 8.58 (d, 1H); 8.95 (s, 1H).

4-(tert-butoxicarbonilamino-N-feniltiofen-3-carboxamida.

Ácido 4-(tert-butoxicarbonilamino)tiofen-3-carboxílico obtenido por un procedimiento de la literatura, Tetrahedron Letters 1997, 2637, (385 mg, 1.58 mmol) en DMF (5 ml) se hizo reaccionar con anilina (140 µl, 1.58 mmol) en presencia de hexafluorofosfato de 0-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (602 mg, 1.58 mmol) a 40°C durante 7 horas. El solvente se evaporó,

y el residuo se purificó por cromatografía de gel de sílice, eluyente éter de petróleo / AcOEt: 80/20 para producir el compuesto del título (348 mg, 70 %). ^{1}HNMR ($CDCl_3$): 1.50 (s, 9H); 7.19 (t, 1H); 7.39 (t, 2H); 7.54 (d, 2H); 7.69 (s, 2H); 7.71 (s, 1H); 9.45 (s, 1H).

4-amino-N-feniltiofen-3-carboxamida.

4-(tert-butoxicarbonilamino)-N-feniltiofen-3-carboxamida (300 mg, 0.94 mmol) en CH_2Cl_2 (3 ml) se trató con TFA (0.36 ml, 4.71 mmol) a temperatura ambiente durante 2.5 horas. El solvente se evaporó, el residuo se disolvió en metanol / HCl, se agregó a la solución, el precipitado se recuperó para producir el compuesto del título (210 mg, 87 %) el cual se empleó en el siguiente paso.

Ejemplo 442. Preparación de Compuesto 620 en Tabla 26

Una reacción análoga a la descrita en ejemplo 441, pero comenzando con 4-amino-N-aliltiofen-3-carboxamida (218 mg, 1.06 mmol) produjo el compuesto del título (366 mg, 75 %).

MS ES$^+$: 484.6 $(M+H)^+$ ^{1}HNMR (DMSOd_6, TFA): 2.28 (t,2H); 3.15 (t,2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.68 (t, 2H); 3.95 (d, 2H); 4.03 (m, 5H); 4.32 (t, 2H); 5.14 (dd, 1H); 5.24 (dd, 1H); 5.91 (m, 1H); 7.41 (s, 1H); 7.59 (s, 1H); 8.28 (d, 1H); 8.51 (d, 1H); 9.04 (s, 1H). 4-tert-butoxicarbonilamino)- N-aliltiofen-3-carboxamida.

Una reacción análoga a la descrita en ejemplo 319, pero comenzando con alilamina (150 µl, 2.06 mmol) produjo el compuesto del título (385 mg, 66 %). ^{1}HNMR ($CDCl_3$): 1.51 (s, 9H); 4.04 (m, 2H); 5.21 (dd, 1H); 5.29 (dd, 1H); 5.92 (m, 1H); 6.1 (m, 1H); 7.54 (d, 1H); 7.64 (m, 1H); 9.64 (s, 1H).

4-amino-N-aliltiofen-3-carboxamida.

Una reacción análoga a la descrita en ejemplo 441, pero comenzando con 4-tert-butoxicarboxilamino-N-aliltiofen-3-carboxamida (320 mg, 1.13 mmol) produjo el compuesto del título (218 mg, 94 %) el cual se usó en el estado actual en el siguiente paso.

Ejemplo 443. Preparación de Compuesto 621 en Tabla 27

4-cloro-6-metoxi-7-(3-morfolinopropoxi)quinazaolina (100 mg, 0.29 mmol) en isopropanol (5 ml). se hizo reaccionar con metil-4-amino-tiofen-4-carboxilato clorhidrato (63.6 mg, 0.33 mmol) a reflujo durante 1 hora. Se agregó acetato de etilo a la mezcla de reacción, se recuperó el sólido por filtración, se secó, para producir el compuesto del título (140 mg, 89, %).

MS ES^+ : 459.1 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.39 (t, 2H); 3.19 (t, 2H); 3.40 (t, 2H); 3.58 (d, 2H); 3.77 (m, 5H); 4.06 (m, 5H); 4.37 (t, 2H); 7.42 (s, 1H); 7.95 (s, 1H); 8.01 (d, 1H); 8.49 (d, 1H); 8.93 (s, 1H).

Ejemplo 444. Preparación de Compuesto 624 en Tabla 28

4-cloro-6-metoxi-7-(3-morfolinopropoxi)quinazolina (110 mg, 0.3 mmol) en 2-pentanol (5 ml) e isopropanol / HCl (55 µl) se hizo reaccionar con 2-amino-5-isopropiltiofen-3-carboxamida (60 mg, 0.33 mmol) a 100°C durante 1 hora, éter y acetato de etilo se agregaron a la mezcla, el precipitado se filtró para producir el compuesto del título (155 mg, 93 %).

MS ES^+ : 486.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.38 (d, 6H); 2.38 (t, 2H); 3.20 (m, 3H); 3.38 (t, 2H); 3.57 (d, 2H); 3.82 (t, 2H); 4.05 (d, 2H); 4.08 (s, 3H); 4.39 (t, 2H); 7.40 (s, 1H); 7.47 (s, 1H); 7.52 (s, 1H); 9.23 (s, 1H).

Ejemplo 445. Preparación de Compuesto 623 en Tabla 28

Una reacción análoga a la descrita en ejemplo 444, pero comenzando con alil-5-aminotiofen-2-carboxilato (67 mg, 0.33 mmol) a 100° C durante 2 horas produjo el compuesto del título (151 mg, 85 %).

MS ES^+ : 485.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.38 (t,2H); 3.18 (t, 2H); 3.38 (t, 2H); 3.57 (d, 2H); 3.80 (t, 2H); 4.06 (d, 2H); 4.12 (s, 3H); 4.38 (t, 2H); 4.84 (d, 2H); 5.33 (d, 1H); 5.45 (d, 1H); 6.10 (m, 1H); 7.48 (s, 1H); 7.65 (d, 1H); 7.84 (d, 1H); 8.64 (s, 1H); 9.30 (s, 1H).

Ejemplo 446. Preparación de Compuesto 624 en Tabla 28

Una reacción análoga a la descrita en ejemplo 444, pero comenzando con 2-aminotiofen-3-carboxamida (46 mg, 0.33 mmol) produjo el compuesto del título (154 mg, 99 %).

MS ES^+ : 444.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.34 (t, 2H); 3.15 (t, 2H);.3.36 (t, 2H); 3.54 (d, 2H); 3.76 (t, 2H); 4.02 (d, 2H); 4.05 (s, 3H); 4.36 (t, 2H); 7.32 (d, 1H); 7.41 (s, 1H); 7.48 (s, 1H); 7.66 (d, 1H); 9.23 (s, 1H).

Ejemplo 447. Preparación de Compuesto 625 en Tabla 28

Una reacción análoga a la descrita en ejemplo 444, pero comenzando con 2-amino-5-etiltiofen-3-carboxamida (55 mg, 0.33 mmol) produjo el compuesto del título (147 mg, 90 %).

MS ES^+ : 472.5 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.34 (t, 3H); 2.38 (t, 2H); 2.86 (q, 2H); 3.18 (t,2H); 3.38 (t,2H); 3.57 (d, 2H); 3.80 (t, 2H); 4.05 (d,2H); 4.07 (s, 3H); 4.38 (t, 2H); 7.40 (s, 1H); 7.43 (s, 1H); 7.52 (s, 1H); 9.21 (s, 1H).

Ejemplo 448. Preparación de Compuesto 626 en Tabla 29

Metil-2-ciano-4-metoxi-5-(3-morfolinopropoxi)fenilimidoformato (100 mg; 0.3 mmol) en DMF (1.5 ml) se hizo reaccionar con 2-amino-4-fenil-1,3-tiazol (58 mg; 0.33 mmol) en presencia de hidruro de sodio (13.2 mg; 0.33 mmol) a 75°C durante 1.5 horas. Se agregó ácido acético (1.5 eq.) y el solvente se.evaporó para producir 6-metoxi-7-(3-momorfolinopropoxi)-3-(4-fenil-1,3-tiazol-2-il)quinazolin-4(3H)-imina como un intermedio que se volvió a disolver en DMF (1.5 ml) y se agregó acetato de amonio (95 mg; 0.9 mmol). La mezcla se agitó a 75°C durante 1 hora, el solvente se evaporó y el residuo se purificó por cromatografía de gel de sílice, CH_2Cl_2/MeOH 95/5 → 90/10 para producir el compuesto del título (44 mg, 31 %).

^{1}HNMR ($DMSOd_6$, TFA): 2.30 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H) 20; 4.05 (m, 5H); 4.33 (t, 2H); 7.42 (m, 2H); 7.51 (t, 2H); 7.90 (s, 1H); 8.00 (d, 2H); 8.35 (s, 1H); 9.27 (s, 1H).

Ejemplo 449. Preparación de Compuesto 627 en Tabla 29

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con 2-amino-4-metil-5-acetil-1,3-tiazol (103 mg, 0.66 mmol), calentando a 75°C durante 1 hora en el primer paso, y agitando el intermedio en las condiciones anteriores a temperatura ambiente durante 1 hora, produjo el compuesto (71 mg, 52 %).

MS ES^+ : 458 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 2.55 (s, 3H); 2.67 (s, 3H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.0 *(s,* 3H); 4.03 (d, 2H); 4.32 (t, 2H); 7.37 (s, 1H); 7.99 (s, 1H); 9.26 (s, 1H).

Ejemplo 450. Preparación de Compuesto 628 en Tabla 29

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con etil-2-amino-4-trifluorometil-1,3-tiazol-5-carboxilato (79 mg, 0.33 mmol) produjo el compuesto del título (81 mg, 50 %).

MS ES^+ : 542 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.34 (t, 3H); 2.32 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.03 (s, 3H); 4.04 (d, 2H); 4.36 (m, 4H); 7.47 (s, 1H); 8.41 (s, 1H); 9.34 (s, 1H).

Ejemplo 451. Preparación de Compuesto 629 en Tabla 29

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con etil-2-amino-4-fenil-1,3-tiazol-5-carboxilato (82 mg, 0.33 mmol) produjo el compuesto del título (133 mg, 81 %).

MS ES^+ : 550 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.25 (t, 2H); 2.32 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.02 (s, 1H); 4.04 (d, 2H); 4.26 (q, 2H); 4.35 (t, 2H); 7.45 (s, 1H); 7.50 (m, 3H); 7.79 (m, 2H); 8.33 (s, 1H); 9.37 (s, 1H).

Ejemplo 452. Preparación de Compuesto 630 en Tabla 29

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con 4,5,6,7-tetrahydro-1,3-benzotiazol-2-amina (51 mg, 0.33 mmol) produjo el compuesto del título (97 mg, 71 %).

MS ES^+ : 456 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.83 (m, 4H); 2.29 (t, 2H); 2.61 (m, 2H); 2.67 (m, 2H); 3.15 (t, 25 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.97 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 7.28 (s, 1H); 7.84 (s, 1H); 9.0 (s, 1H).

Ejemplo 453. Preparación de Compuesto 631 en Tabla 29

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con N-(4-(2-amino-1,3-tiazol-4-il)fenil)acetamida (77 mg, 0.33 mmol) produjo el compuesto del título (58 mg, 36 %).

MS ES^+ : 535 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.09 (s, 3H); 2.32 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 4.05 (s, 3H); 4.06 (d, 2H); 4.35 (t, 2H); 7.40 (s, 1H); 7.72 (d, 2H); 7.77 (s, 1H); 7.92 (d, 2H); 8.33 (s, 1H); 9.25 (s, 1H).

Ejemplo 454. Preparación de Compuesto 632 en Tabla 29

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con 5-fenil-4-(trifluorometil)-1,3-tiazol-2-amina (81 mg, 0.33 mmol) produjo el compuesto del título (144 mg, 88 %).

MS ES$^+$: 546 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.32 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.04 (d, 2H); 4.05 (s, 3H); 4.36 (t, 2H); 7.49 (s, 1H); 7.54 (s, 5H); 8.46 (s, 1H); 9.30 (s, 1H).

Ejemplo 455. Preparación de Compuesto 633 en Tabla 29

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con 4-(trifluorometil)-1,3-tiazol-2-amina (55 mg, 0.33 mmol) produjo el compuesto del título (62 mg, 44 %).

MS ES$^+$: 470 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 2.32 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.04 (s, 3H); 4.05 (d, 2H); 4.36 (t, 2H); 7.49 (s, 1H); 8.23 (s, 1H); 8.44 (s, 1H); 9.34 (s, 1H).

Ejemplo 456. Preparación de Compuesto 634 en Tabla 29

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con 4-tert-butil-1,3- tiazol-2-amina (52 mg, 0.33 mmol) produjo el compuesto del título (90 mg, 65 %).

MS ES$^+$: 458 $(M+H)^+$

^{1}HNMR (DMSOd_6, TFA): 1.46 (s, 9H); 2.32 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.00 (s, 3H); 4.03 (d, 2H); 4.32 (d, 2H); 7.38 (s, 1H); 7.95 (s, 1H); 9.18 (s, 1H).

Ejemplo 457. Preparación de Compuesto 635 en Tabla 29

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con 30 4,5-dimetil-1,3-tiazol-2-amina (42 mg, 0.33 mmol) produjo el compuesto del título (61 mg, 47 %).

MS ES^+ : 430 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 2.25 (s, 3H); 2.30 (m, 5H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.96 (s, 3H); 4.04 (d, 2H); 4.28 (t, 1H); 7.28 (s, 1H); 7.82 (s, 1H); 8.98 (s, 1H).

Ejemplo 458. Preparación de Compuesto 636 en Tabla 29

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con 4-metil-1,3-tiazol-2-amina (38 mg, 0.33 mmol) produjo el compuesto del título (40 mg, 32 %). MS ES^+ : 415 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H); 2.34 (s, 3H); 3.15 (t, 2H); 3.37 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3.99 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 7.03 (s, 1H); 7.29 (s, 1H); 7.87 (s, 1H); 9.05 (s, 1H).

Ejemplo 459. Preparación de Compuesto 637 en Tabla 29

1-(2-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)amino)-4-metil-1,3-tiazol-5- il)etanona (50 mg, 0.11 mmol) en etanol (4 ml) y pyridina (1 ml) se hizo reaccionar con hidroxilamina clorhidrato (19.5 mg, 0.27 mmol) a reflujo durante 3 horas. El solvente se evaporó, se agregó agua al residuo y se recuperó un sólido, se lavó con agua para producir el compuesto del título (14 mg, 27 %)

MS ES^+ : 473 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.25 (s, 3H); 2.30 (t, 2H); 2.53 (s, 3H); 3.17 (t, 2H); 3.38 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 3.99 (s, 3H); 4.05 (d, 2H); 4.32 (t, 2H); 7.32 (s, 1H); 7.88 (s, 1H); 9.12 (s, 1H).

Ejemplo 460. Preparación de Compuesto 638 en Tabla 29

Ácido 2-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)amino)-1,3-tiazol-5-carboxílico (89 mg, 0.2 mmol) en DMF (1.5 ml) se trató con difenilfosforil azida (66 mg, 0.24 mmol) y trietilamina (26 mg, 0.26 mmol). La solución se agitó a temperatura ambiente durante 1 hora y a 45°C durante 1 hora. Se adicionó tert-butanol (1 ml), y la mezcla se calentó a 90°C durante 2 horas. Se diluyó la mezcla con acetato de etilo, bicarbonato de sodio acuoso, se recuperó la fase orgánica, se secó sobre $MgSO_4$, se filtró, concentró y purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2 / MeOH 95/5 a 85/15 para producir el compuesto del título cómo un sólido amarillo (25 mg, 24 %).

MS ES$^+$: 517 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.50 (s, 9H); 2.31 (t, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.69 (t,2H); 3.97 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 7.13 (s, 1H); 7.26 (s, 1H); 7.94 (5, 1H); 9.11 (s, 1H).

Ejemplo 461. Preparación de Compuesto 639 en Tabla 29

Una reacción análoga a la descrita en ejemplo 459, pero comenzando con 0-metilhidroxilamina clorhidrato (18 mg, 0.22 mmol) y calentando a reflujo durante 72 horas produjo el compuesto del título (39 mg, 63 %).

MS ES$^+$: 487 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.26 *(s,* 3H); 2.31 (t, 2H); 3.53 (s, 3H); 3.16 (t, 2H); 3.35 (t, 2H); 3.54 (d, 2H); 3.76 (s, 2H); 3.94 *(s,* 3H); 3.99 (s,3H); 4.02 (d, 2H); 4.33 (t, 2H); 7.35 (s, 1H); 7.89 *(s,* 1H); 9.11 (s, 1H).

Ejemplo 462. Preparación de Compuesto 640 en Tabla 29

Una reacción análoga a la descrita en ejemplo 459, pero comenzando con 0-fenilhidroxilamina clorhidrato (32 mg, 0.22 mmol) produjo el compuesto del título (8 mg, 12 %).

MS ES$^+$: 549 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.28 (t, 2H); 3.12 (t, 2H); 3.32 (t, 2H); 3.52 (d, 2H); 3.65 (t, 2H); 3.96 (s, 3H); 4.0 (d, 2H); 4.27 (t, 2H); 7.06 (t, 1H); 7.20 (d, 2H); 7.28 (s, 1H); 7.34 (t, 2H); 7.91 *(s,* 1H); 9.17 (s, 1H).

Ejemplo 463. Preparación de Compuesto 641 en Tabla 29

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con 2-amino-5-(4-metoxifenil)-1,3-tiazol, HBr (86 mg, 0.33 mmol) produjo el compuesto del título (105 mg, 77 %).

MS ES$^+$: 508.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.33 (t, 2H); 3.20 (t, 2H); 3.40 (t, 2H); 3.60 (d, 2H); 3.73 (t,2H); 3.86 (s, 3H); 4.08 (s, 3H); 4.09 (d, 2H); 4.36 (t, 2H); 7.10 (d, 2H); 7.44 (s, 1H); 7.76 (s, 1H); 7.96 (d, 2H); 8.33 (s, 1H); 9.26 (s, 1H).

Ejemplo 464. Preparación de Compuesto 642 en Tabla 29

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con 2-amino-5-FenIL)-1,3-tiazol (58 mg, 0.33 mmol) produjo el compuesto del título (120 mg, 84 %).

MS ES^+ : 478.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H); 4.01 (s, 3H); 4.05 (d, 2H); 4.32 (t, 2H); 7.34 (s, 1H); 7.41 (t, 1H); 7.51 (t,2H); 7.72 (d, 2H); 7.97 (s, 1H); 8.24 (s, 1H); 9.16 (s, 1H).

Ejemplo 465. Preparación de Compuesto 643 en Tabla 29

Metil-2-ciano-4-metoxi-5-(3-morfolinopropoxi)fenil-imidoformato (300 mg, 0.9 mmol) en DMF (4.5 ml) se hizo reaccionar con 2-amino-5-etil-1,3-tiazol (127 mg, 0.99 mmol) en presencia de hidruro de sodio (39.6 mg, 0.99 mmol) a 75°C durante 2 horas. Se añadió ácido acético (77 µl, 1.35 mmol) a la mezcla a temperatura ambiente, seguido por $MeOH/Me_2NH$ (2M) (90 µl, 0.18 mmol) y la mezcla se agitó a 75°C durante 1 hora. El solvente se evaporó y la mezcla se purificó por cromatografía de gel de sílice, eluyente CH_2Cl_2/MeOH 95/5 → 90/10 para producir el compuesto del título (193 mg, 50 %).

MS ES^+ : 430.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 1.29 (t, 3H); 2.32 (t, 2H); 2.81 (q, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 3.98 (s, 3H); 4.05 (d, 2H); 4.30 (t, 2H); 7.30 (s, 1H); 7.50 (s, 1H); 7.87 (s, 1H); 9.04 (s, 1H).

Ejemplo 466. Preparación de Compuesto 644 en Tabla 29

Una reacción análoga a la descrita en ejemplo 465, pero comenzando con 2-amino-5-isopropil)-1,3-tiazol (141 mg, 0.99 mmol) produjo el compuesto del título (107 mg, 26 %). MS ES^+: 444.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 1.33 (d, 6H); 2.32 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3.98 (s, 3H); 4.04 (d, 2H); 4.30 (t, 2H); 7.29 (s, 1H); 7.49 (s, 1H); 7.87 (s, 1H); 9.05 (s, 1H).

803
804

Ejemplo 467. Preparación de Compuesto 645 en Tabla 29

Una reacción análoga a la descrita en ejemplo 465, pero comenzando con 2-amino-5-bencil)-51,3-tiazol (188 mg, 0.99 mmol) produjo el compuesto del título (370 mg, 84 %).

MS ES^+ : 492.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t,2H); 3.16 (t, 2H); 3.35,(t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 3.98 (s, 3H); 4.04 (d, 2H); 4.18 (s, 2H); 4.29 (t, 2H); 7.27 (s, 1H); 7.28 (m, 1H); 7.35 (m, 4H); 7.61 (s, 1H); 7.88 (s, 1H); 9.02 (s, 1H).

Ejemplo 468. Preparación de Compuesto 646 en Tabla 29

Una reacción análoga a la descrita en ejemplo 465, pero comenzando con 2-amino-5-metil)-1,3-tiazol (113 mg, 0.99 mmol) produjo el compuesto del título (300 mg, 80 %).

MS ES^+ : 416.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H); 2.42 (s, 3H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.97 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 1.30 (s, 1H); 7.48 (s, 1H); 7.86 (s, 1H); 9.03 (s, 1H).

Ejemplo 469. Preparación de Compuesto 647 en Tabla 29

Una reacción análoga a la descrita en ejemplo 465, pero comenzando con 2-amino-5-butil)-1,3-tiazol (155 mg, 0.99 mmol) produjo el compuesto del título (385 mg, 93 %).

MS ES^+ : 458.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 0.93 (t, 3H); 1.36 (m, 2H); 1.64 (m, 2H); 2.29 (t, 2H); 2.79 (t, 2H); 3.16 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.97 (s, 3H); 4.04 (d, 2H); 4.29 (t, 2H); 7.29 (s, 1H); 7.51 (s, 1H); 7.86 (s, 1H); 9.03 (s, 1H).

Ejemplo 470. Preparación de Compuesto 648 en Tabla 29

Una reacción análoga a la descrita en ejemplo 465, pero comenzando con 2-amino-5-formil-1,3-tiazol (499.4 mg, 3.9 mmol) produjo el compuesto del título (244 mg, 39 %).

MS ES^+ : 430.6 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.17 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 4.03 (s, 3H); 4.06 (d, 2H); 4.35 (t, 2H); 7.45 (s,1H); 8.12 (s, 1H); 8.71 (s, 1H); 9.32 (s, 1H).

Ejemplo 471. Preparación de Compuesto 649 en Tabla 29

Una reacción análoga a la descrita en ejemplo 459, pero comenzando con 2-((6-metoxi-7-(3-morfolinopropoxi)quinazolin-4-il)amino-1,3-tiazol-5-carbaldehído (100 mg, 0.23 mmol) y calentando a 80°C durante 4 horas, produjo el compuesto del título (21 mg, 20 %).

MS ES^+: 445.6 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.31 (t, 2H); 3.17 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.70 (t, 2H) 4.00 (s, 3H); 4.05 (d, 2H); 4.32 (t, 2H); 7.36 (s, 1H); 7.92 (s, 1H); 7.98 (s, 1H); 8.33 (s, 1H); 9.20 (s, 1H).

Ejemplo 472. Preparación de Compuesto 650 en Tabla 30

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con 2-amino-5-tert-butil-1,3,4-tiadiazol (52 mg, 0.33 mmol) produjo el compuesto del título (80 mg, 58 %).

MS ES^+: 458 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.45 (s, 9H); 2.32 (t, 2H); 3.16 (t, 2H); 3.36 (t, 2H); 3.56 (d, 2H); 3.69 (t, 2H); 4.00 (s, 3H); 4.03 (d, 2H); 4.32 (t, 2H); 7.38 (s, 1H); 7.95 (s, 1H); 9.18 (s, 1H).

Ejemplo 473. Preparación de Compuesto 651 en Tabla 30

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con 20 2-amino-5- cyclopropyl-1,3,4-tiadiazol (47 mg, 0.33 mmol) produjo el compuesto del título (105 mg, 83 %).

MS ES^+ : 443 $(M+H)^+$ ^{1}HNMR ($DMSOd_6$, TFA): 1.08 (m, 2H); 1.23 (m, 3H); 2.32 (t, 2H); 3.15 (t, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.68 (t, 2H); 3.99 (s, 3H); 4.04 (d, 2H); 4.32 (t, 2H); 7.38 (s, 1H); 7.93 (s, 1H); 9.14 (s, 1H).

Ejemplo 474. Preparación de Compuesto 652 en Tabla 30

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con 2-amino-5-etiltio-1,3,4-tiadiazol (53 mg, 0.33 mmol) produjo el compuesto del título (103 mg, 75 %).

MS ES^+ : 463 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 1.41 (t, 3H); 2.31 (t, 2H); 3.15 (t, 2H); 3.31 (q, 2H); 3.35 (t, 2H); 3.55 (d, 2H); 3.69 (t, 2H); 4.00 (s, 3H); 4.04 (d, 2H); 4.33 (t, 2H); 7.41 (s, 1H); 8.08 (s, 1H); 9.19 (s, 1H).

Ejemplo 475. Preparación de Compuesto 653 en Tabla 30

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con 2-amino-5-fenil-1,3,4-tiadiazol (91 mg, 0.33 mmol) produjo el compuesto del título (110 mg, 76 %). MS ES^+ : 479 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.16 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.69 (t, 2H); 4.03 (s, 3H); 4.05 (d, 2H); 4.34 (t, 2H); 7.42 (s, 1H); 7.61 (m, 3H); 7.99 (m, 2H); 8.06 (s, 1H); 9.25 (s, 1H).

Ejemplo 476. Preparación de Compuesto 654 en Tabla 30

Una reacción análoga a la descrita en ejemplo 448, pero comenzando con N-fenil-4H-1,2,4- triazol-3,5-diamina (58 mg, 0.33 mmol) produjo el compuesto del título (70 mg, 49 %). MS ES^+ : 477 $(M+H)^+$

^{1}HNMR ($DMSOd_6$, TFA): 2.32 (t, 2H); 3.16 (t, 2H); 3.37 (t, 2H); 3.57 (d, 2H); 3.70 (t, 2H); 4.02 (s, 3H); 4.05 (d, 2H); 4.34 (t, 2H); 6.92 (t, 1H); 7.30 (t, 1H); 7.42 (s, 1H); 7.58 (d, 2H); 8.19 (s, 1H); 8.95 (s, 1H).

Datos Biológicos

Los compuestos de la invención inhiben la actividad serina/treonina cinasa de la cinasa aurora2 y, en consecuencia, inhiben el ciclo celular y la proliferación de la célula. Estas propiedades pueden evaluarse por ejemplo, empleando uno o más de los procedimientos expuestos a continuación:

a) **Prueba de inhibición de cinasa aurora2**

Este ensayo determina la capacidad de un compuesto de prueba para inhibir actividad serina/treonina cinasa. El ADN que codifica aurora2 puede obtenerse por síntesis genética total o por clonado. Este ADN puede expresarse entonces en un sistema apropiado de expresión para obtener polipéptido con actividad serina/treonina cinasa. En el caso de aurora2, la secuencia codificadora se aisló de cADN mediante reacción en cadena la polimerasa (PCH) y se clonó en los sitios de endonucleasa de restricción BamHl y Notl del vector de expresión del baculovirus pFastBac HTc (GibcoBRL/Life

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REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN X **MODELO DE UTILIDAD**	( )	( )
- Indicación de que se solicita la concesión de una patente.	( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
- Descripción de la invención.	( )	( )
- Dibujos de ser estos pertinentes.	( )	( )
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) **INCOMPLETA**	( )	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) **INCOMPLETA**	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) **INCOMPLETA**	( )	( )

Firma Responsable:

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