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DIVISION DE NUEVAS CREACIONES

CONTESTACION A REPAROS - OBSERVACIONES
APORTACION DE NUEVA DOCUMENTACION A
UNA SOLICITUD DE PATENTE DE INVENCION O
MODELO DE UTILIDAD O DISEÑO INDUSTRIAL

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TITULO

COMPUESTOS DE DIHIDROPIRIMIDINA HETEROCICLICOS

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BRISTOL - MYERS SQUIBB COMPANY

INDICE DE DOCUMENTOS QUE SE ACOMPAÑAN

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☐	de Estados Unidos de la solicitud 60/236,037,	☐	
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February 08, 2001

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111

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COMMISSIONER OF PATENTS AND TRADEMARKS

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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

Transmitted herewith for filing under 37 CFR §1.53(c) is the PROVISIONAL APPLICATION for patent of

INVENTOR(S)

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TITLE OF THE INVENTION (280 characters max)

HETEROCYCLIC DIHYDROPYRIMIDINE COMPOUNDS

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ENCLOSED APPLICATION PARTS (check all that apply)

- ☒ Specification (Including Any Claims and Abstract) - 243 pages
- ☐ Drawings sheets
- ☐ Other (specify):

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Respectfully submitted

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Date: 9/28/00

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HETEROCYCLIC DIHYDROPYRIMIDINE COMPOUNDS

Field of the Invention

The present invention relates to heterocyclic dihydropyrimidine compounds, to methods of using such compounds in the treatment of arrhythmia and I_{Kur} –associated disorders, and to pharmaceutical compositions containing such compounds

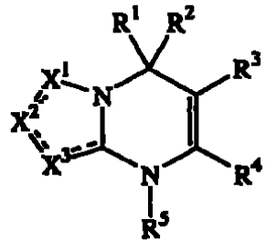
Background of the Invention

Atrial fibrillation and flutter are the most common arrhythmias encountered in clinical practice. Although some presently available antiarrhythmic drugs can convert sustained fibrillation to sinus rhythm, they are only effective in acute atrial fibrillation and even then their efficacy is low Furthermore, these drugs are of limited use because of a variety of potentially adverse effects, including ventricular proarrhythmia. Thus, there is presently an unmet medical need for safe and efficacious treatment of atrial fibrillation and other supraventricular arrhythmias.

The ultrarapid delayed rectifier potassium current (I_{Kur}) is a rapidly activating sustained current that has been identified in human atrial myocytes but is apparently absent from human ventricular myocytes (Konarzewska et al , *Circulation J Physiol 491*, 13 (1996)) Considerable molecular biological, pharmacological and biophysical data indicates that I_{Kur} is encoded by the potassium channel gene Kv1.5 I_{Kur} plays a significant role in the repolarization of the atrial action potential and selective inhibition of this current in human atrial myocytes prolongs action potential duration by greater than 50% (Wang et al , *Circ. Res* , *73*, 1061 (1993)) Prolongation of the action potential consequently prolongs atrial effective refractory period, that is, inhibition of I_{Kur} produces a class III antiarrhythmic effect Importantly, an inhibitor of I_{Kur} may have utility against atrial fibrillation without having the attendant ventricular proarrhythmic risk associated with other class III agents that have potassium channel targets expressed in both atrium and ventricle.

Summary of the Invention

The present invention provides heterocyclic dihydropyrimidine compounds of the following formula I, including enantiomers, diastereomers, and salts thereof for the treatment of arrhythmia and I_{Kur} –associated disorders



(I)

where

X^1, X^2 and X^3 are independently selected from N, NR^6, $(CR^7)_q$, $(CHR^7)_q$ or C=O, wherein the bonds connecting X^1, X^2 and X^3 to adjacent atoms may be single or double bonds forming a 5 to 7-membered saturated, partially unsaturated or aromatic ring;

R^1 R^2 R^3 R^4, R^5, R^6 and R^7 are the same or different and are independently selected from groups of the formula $-(CH_2)_n-(Z^1)_m-(CH_2)_p-Z^2$; or

R^1 R^2 R^3, R^4 and R^5 may, in one or more pairs of two (such as R^1 and R^2 R^1 and R^3 R^2 and R^3, R^3 and R^4 or R^4 and R^5), together with the atoms to which they are bonded, form a carbocyclic, substituted carbocyclic, heterocyclic or substituted heterocyclic group, or

R^6 and R^7 may in one or more pairs of two (such as R^6 and R^7, R^6 and R^6, or R^7 and R^7), together with the atoms to which they are bonded, form a carbocyclic, substituted carbocyclic, heterocyclic or substituted heteroryclic group,

Z^1 is $-CZ^3Z^4-$ -O-, $-NZ^3-$, -S-, -SO-, $-SO_2-$, -C(O)- $-C(O)Z^3-$ $-C(O)NZ^4$, -C(S)-, $-C(=NOZ^3)-$ alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbocyclo substituted carbocyclo, aryl, substituted aryl heterocyclo, or substituted heterocyclo;

Z^2 is hydrogen $-OZ^5$ $-OC(O)Z^5$, $-NZ^5-C(O)-Z^6$, $-NZ^5-CO_2-Z^6$, $-NZ^5(C=O)-NZ^6Z^7$, $-NZ^5Z^6$, $-NO_2$, halo, -CN, $-C(O)Z^5$, $-CO_2Z^5$ $-C(S)Z^5$, $-(C=NOZ^5)Z^6$

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-C(O)NZ^{5}Z^6; -C(S)NZ^{5}Z^6, -SZ^5, -SOZ^5, -SO$_2$Z^5, -SO$_2$NZ^{5}Z^6 alkyl substituted alkyl, alkenyl, substituted alkenyl, alkynyl substituted alkynyl carbocyclo, substituted carbocyclo, aryl, substituted aryl heterocyclo (such as heteroaryl) or substituted heterocyclo;

Z^3, Z^4, Z^5, Z^6 and Z^7 are independently hydrogen, halo alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbocyclo; substituted carbocyclo, aryl, substituted aryl heterocyclo or substituted heterocyclo, or

Z^3, Z^4, Z^5, Z^6 and Z^7 may, in one or more pairs of two (such as Z^3 and Z^4, Z^5 and Z^6 or Z^6 and Z^7), together with the atoms to which they are bonded, form a carbocyclic, substituted carbocyclic, heterocyclic or substituted heterocyclic group,

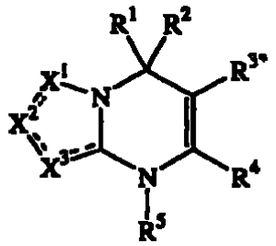
n and p are independently selected from integers from 0 to 10 wherein, when m is 0 p is also 0;

m is an integer selected from 0 or 1, and

q is an integer selected from 1 to 3

The present invention provides novel methods for the prevention and treatment of arrhythmia and I_{Kur} -associated disorders employing one or more compounds of the formula I, enantiomers, diastereomers or pharmaceutically acceptable salts thereof In particular the present invention provides a novel method for the selective prevention and treatment of supraventricular arrhythmias

In addition, compounds within the formula I, as well as enantiomers, diastereomers and salts thereof are novel compounds, including compounds of formula I* and salts thereof



(I*)

where

X^1, X^2, X^3, R^1, R^2, R^4 and R^5 are as defined above,

R^{3*} is $-OZ^5$, $-OC(O)-Z^5$, $-NZ^5-C(O)_z-Z^6$, $-NZ^5(C=O)-NZ^6Z^7$, $-NZ^5Z^6$, $-(C=NOZ^5)Z^6$, $-C(O)NZ^{5*}Z^{6*}$, $-C(S)NZ^{5*}Z^{6*}$, $-SZ^5$, $-SOZ^5$ $-SO^2Z^5$ $-SO_2NZ^5Z^6$, $-C(O)Z^{3*}-Z^{2*}$ halo alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbocyclo, substituted carbocyclo aryl, substituted aryl, heterocyclo or substituted heterocylco,

Z^{2*} is other than hydrogen when Z^{3*} is heterocyclo,

Z^{3*} is heterocyclo or substituted heterocyclo

Z^{5*} is substituted alkyl, alkenyl substituted alkenyl, alkynyl, substituted alkynyl, carbocyclo, substituted carbocyclo, aryl substituted aryl, heterocyclo; or substituted heterocyclo; and

Z^{6*} is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbocyclo, substituted carbocyclo; aryl, substituted aryl, heterocyclo, or substituted heterocyclo, provided that Z^{6*} is not hydrogen when Z^{5*} is unsubstituted cycloalkyl, unsubstituted aryl, or unsubstituted benzyl,

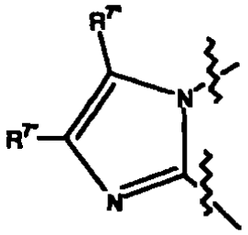
or Z^{5*} and Z^{6*} may together with the nitrogen atom to which they are bonded form a heterocyclic group or substituted heterocyclic group, provided that Z^{5*} and Z^{6*} do not together form unsubstituted piperidinyl, unsubstituted pyrrolidinyl, or unsubstituted morpholinyl and further provided that when

(i) R^1 and R^5 are each hydrogen, and

(ii) R^2 is aryl or substituted aryl, and

(iii) R^4 is heterocyclo-substituted aryl and

(iv) X^1, X^2 and X^3 form the ring



where R^{7*} is H or alkyl

Z^{5*} and Z^{6*} do not together form unsubstituted piperazinyl or N-alkyl-substituted piperazinyl

Preferred Compounds

Compounds of the formula I and salts thereof wherein one or more, and especially all, of X^1, X^2, X^3, R^1, R^2, R^3, R^4 and R^5 are selected from the following definitions are preferred compounds of the present invention

R^1 is hydrogen,

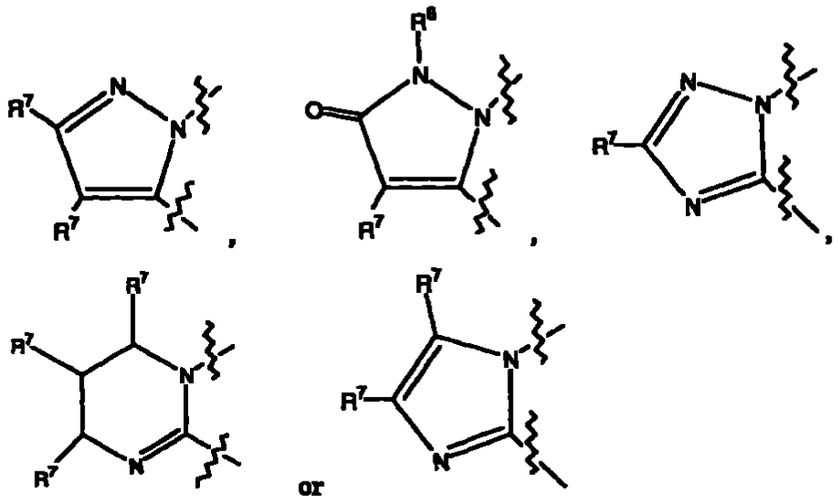
R^2 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo or substituted carbocyclo,

R^3 is $-(CH_2)_n-Z^2$ $-(CH_2)_n-C(O)Z^3-(CH_2)_p-Z^2$, or $-(CH_2)_n-C(O)NZ^4-(CH_2)_p-Z^2$,

R^4 is alkyl or substituted alkyl and

R^5 is hydrogen, or $-(CH_2)_n-Z^2$; and

X^1, X^2 and X^3, together with the atoms to which they are bonded, form a ring selected from.



where R^6 and/or R^7 are the same or different, as defined above.

Compounds of the formula I and salts thereof wherein one or more, and especially all, of X^1, X^2, X^3, R^1, R^2, R^3, R^4 and R^5 are selected from the following definitions, are more preferred compounds of the present invention

R^1 is hydrogen,

R^2 is aryl (especially where aryl is phenyl), substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo or substituted carbocyclo,

R^3 is $-(CH_2)_n-Z^2$ $-(CH_2)_n-C(O)Z^3-(CH_2)_p-Z^2$, or $-(CH_2)_n-C(O)NZ^4-(CH_2)_p-Z^2$ wherein

Z^2 is selected from $-C(O)NZ^5Z^6$, $-CO_2Z^5$, $-SO_2Z^5$, $-NZ^5Z^6$, $-NZ^5CO_2Z^6$, $-NZ^5C(O)Z^6$, $-OZ^5$, aryl, substituted aryl, heterocyclo, substituted heterocyclo, alkyl or substituted alkyl

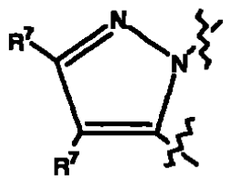
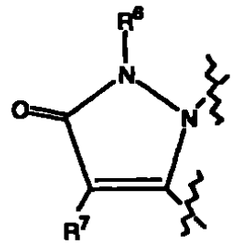
Z^3 is heterocyclo or substituted heterocyclo and

n and p are independently selected from integers 0 to 3

R^4 is alkyl, or substituted alkyl,

R^5 is hydrogen, or $-(CH_2)_n-Z^2$ wherein Z^2 is selected from $-C(O)NZ^5Z^6$, $-CO_2Z^5$, $-NZ^5Z^6$, aryl, substituted aryl, alkyl, or substituted alkyl, and

X^1 X^2 and X^3, together with the atoms to which they are bonded, form a ring selected from.

Compounds of the formula I and salts thereof wherein one or more, and especially all, of X^1, X^2, X^3, R^1, R^2, R^3, R^4 and R^5 are selected from the following definitions are most preferred compounds of the present invention.

R^1 is hydrogen,

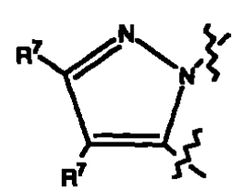
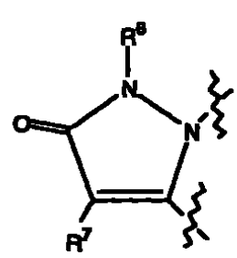
R^2 is aryl (especially where aryl is phenyl), substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo or substituted carbocyclo

R^3 is heterocyclo or substituted heterocyclo, $-C(O)NZ^5Z^6$, $-C(O)Z^3-CONZ^5Z^6$, $-C(O)Z^3-Z^2$, or $-C(O)Z^3-CO_2Z^5$ wherein Z^3 is heterocyclo or substituted heterocyclo and Z^2 is aryl or substituted aryl

R^4 is alkyl (especially lower alkyl) or substituted alkyl (especially halo-substituted alkyl)

R^5 is hydrogen, alkyl or substituted alkyl, and

X^1 X^2 and X^3, together with the atoms to which they are bonded, form a ring selected from.

wherein

R^6 is H or $C(O)Z^5$, where Z^5 is alkyl or carbocyclo, and

R^7 is independently selected from H, alkyl, substituted alkyl (especially halo-substituted), halo, or CN

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Detailed Description of the Invention

The following are definitions of terms used in this specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification, individually or as part of another group unless otherwise indicated.

The terms "alk" or "alkyl" refer to straight or branched chain hydrocarbon groups having 1 to 12 carbon atoms, preferably 1 to 8 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, pentyl, hexyl heptyl octyl, etc Lower alkyl groups, that is, alkyl groups of 1 to 6 carbon atoms, are generally most preferred. The term "substituted alkyl" refers to alkyl groups substituted with one or more groups (such as by groups described above in the definition of R^1), preferably selected from aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo, substituted carbocyclo, halo, hydroxy, alkoxy (optionally substituted) aryloxy (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), alkanoyl (optionally substituted), aryol (optionally substituted) cyano, nitro, amino substituted amino, amido, lactam, urea, urethane, sulfonyl, etc.

The term "alkenyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms, preferably 2 to 4 carbon atoms, and at least one double carbon to carbon bond (either cis or trans), such as ethenyl. The term "substituted alkenyl" refers to alkenyl groups substituted with one or more groups (such as by groups described above in the definition of R^1) preferably selected from aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo, substituted carbocyclo, halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), alkanoyl (optionally substituted), aryol (optionally substituted), cyano, nitro, amino, substituted amino, amido, lactam, urea, urethane sulfonyl, etc.

The term "alkynyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms, preferably 2 to 4 carbon atoms, and at least one triple carbon to carbon bond, such as ethynyl. The term "substituted alkynyl" refers to alkynyl groups substituted with one or more groups (such as by groups described above in the definition of R^1), preferably selected from aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo substituted carbocyclo, halo,

hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), alkanoyl (optionally substituted), aryol (optionally substituted), cyano, nitro, amino, substituted amino, amido, lactam, urea, urethane, sulfonyl, etc.

The terms "ar" or "aryl" refer to aromatic homocyclic (i.e. hydrocarbon) mono-, bi- or tricyclic ring-containing groups preferably having 6 to 12 members such as phenyl, naphthyl and biphenyl. Phenyl is a preferred aryl group. The term "substituted aryl" refers to aryl groups substituted with one or more groups (such as by groups described above in the definition of R^1), preferably selected from alkyl substituted alkyl, alkenyl (optionally substituted), aryl (optionally substituted), heterocyclo (optionally substituted), halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkanoyl (optionally substituted), aroyl, (optionally substituted), alkylester (optionally substituted), arylester (optionally substituted), cyano, nitro, amino, substituted amino, amido, lactam, urea, urethane, sulfonyl, etc., where optionally one or more pair of substituents together with the atoms to which they are bonded form a 3 to 7 member ring.

The terms "cycloalkyl" and "cycloalkenyl" refer to mono-, bi- or tri homocyclic ring groups of 3 to 15 carbon atoms which are, respectively, fully saturated and partially unsaturated. The term "cycloalkenyl" includes bi- and tricyclic ring systems that are not aromatic as a whole, but contain aromatic portions (e.g. fluorene, tetrahydronapthalene, dihydroindene, and the like). The terms "substituted cycloalkyl" and "substituted cycloalkenyl" refer, respectively, to cycloalkyl and cycloalkenyl groups substituted with one or more groups (such as by groups described above in the definition of R^1), preferably selected from aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo, substituted carbocyclo, halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted) alkylester (optionally substituted), arylester (optionally substituted) alkanoyl (optionally substituted), aryol (optionally substituted), cyano, nitro, amino, substituted amino, amido, lactam, urea, urethane, sulfonyl, etc.

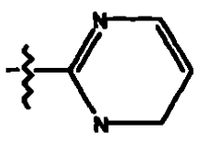
The terms "carbocyclo", "carbocyclic" or "carbocyclic group" refer to both cycloalkyl and cycloalkenyl groups. The terms "substituted carbocyclo", "substituted carbocyclic" or "substituted carbocyclic group" refer to carbocyclo or carbocyclic

groups substituted with one or more groups as described in the definition of cycloalkyl and cycloalkenyl

The terms "halogen" and "halo" refer to fluorine, chlorine, bromine and iodine.

The terms "heterocycle", "heterocyclic", "heterocyclic group" or "heterocyclo" refer to fully saturated or partially or completely unsaturated, including aromatic ("heteroaryl") or nonaromatic cyclic groups (for example, 3 to 13 member monocyclic, 7 to 17 member bicyclic, or 10 to 20 member tricyclic ring systems, preferably containing a total of 3 to 10 ring atoms) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3 or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached at any heteroatom or carbon atom of the ring or ring system. The rings of multi-ring heterocycles may be either fused, bridged and/or joined through one or more spiro unions

Exemplary monocyclic heterocyclic groups include azetidinyl, pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, 4-piperidonyl, pyridyl, pyrazinyl pyrimidinyl, pyridazinyl, triazinyl, tetrahydropyranyl, tetrazoyl, triazolyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl,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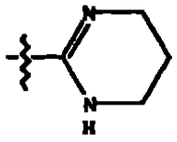
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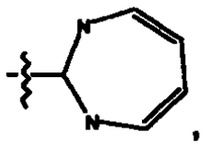
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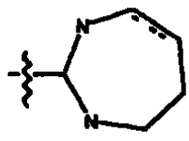
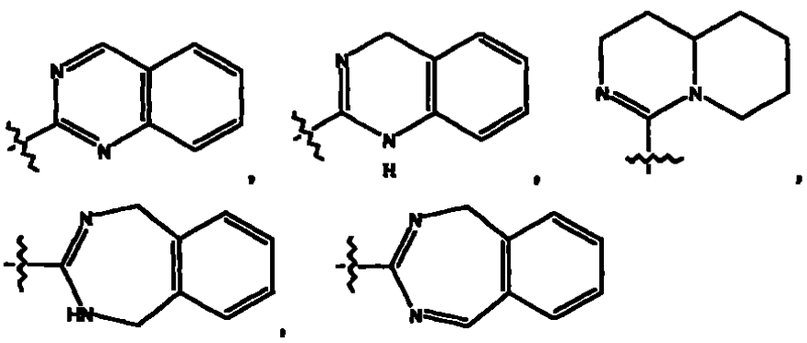


and the like

Exemplary bicyclic heterocyclic groups include indolyl, benzothiazolyl, benzoxazolyl benzothienyl, quinuclidinyl, quinolinyl, tetra-hydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, benzofuranly, dihydrobenzofuranyl chromonyl, coumarinyl, benzodioxolyl, dihydrobenzodioxolyl,

benzodioxinyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), tetrahydroquinolinyl, azabicycloalkyls (such as 6-azabicyclo[3 2.1]octane), azaspiroalkyls (such as 1,4 dioxa-8-azaspiro[4.5]decane), imidazopyridinyl (such as imidazo[1 5-a]pyridin-3-yl) triazolopyridinyl (such as 1,2,4-triazolo[4,3-a]pyridin-3-yl), and hexahydroimidazopyridinyl (such as 1,5,6 7,8,8a-hexahydroimidazo[1,5-a]pyridin-3-yl),



and the like

Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, acridinyl phenanthridinyl, xanthenyl and the like.

The terms "substituted heterocycle" "substituted heterocyclic", "substituted heterocyclic group" and "substituted heterocyclo" refer to heterocycle, heterocyclic and heterocyclo groups substituted with one or more groups (such as by groups described above in the definition of R^1), preferably selected from alkyl, substituted alkyl, alkenyl, oxo, aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo (optionally substituted), halo, hydroxy, alkoxy (optionally substituted), aryloxy (optionally substituted), alkanoyl (optionally substituted), aroyl (optionally substituted) alkylester (optionally substituted), arylester (optionally substituted), cyano, nitro, amido, amino, substituted amino, lactam, urea, urethane, sulfonyl etc. where optionally one or more pair of substituents together with the atoms to which they are bonded form a 3 to 7 member ring

The term "alkanoyl" refers to alkyl group (which may be optionally substituted as described above) linked to a carbonyl group (i.e. –C(O)-alkyl) Similarly the term

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"aroyl" refers to an aryl group (which may be optionally substituted as described above) linked to a carbonyl group (i.e., -C(O)-aryl).

Throughout the specification, groups and substituents thereof may be chosen to provide stable moieties and compounds

The compounds of formula I form salts which are also within the scope of this invention. Reference to a compound of the formula I herein is understood to include reference to salts thereof, unless otherwise indicated The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases In addition, when a compound of formula I contains both a basic moiety and an acidic moiety, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred although other salts are also useful, e.g., in isolation or purification steps which may be employed during preparation. Salts of the compounds of the formula I may be formed, for example, by reacting a compound I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

The compounds of formula I which contain a basic moiety may form salts with a variety of organic and inorganic acids Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides (formed with hydrochloric acid), hydrobromides (formed with hydrogen bromide), hydroiodides, 2-hydroxyethanesulfonates, lactates, maleates (formed with maleic acid), methanesulfonates (formed with methanesulfonic acid), 2-naphthalenesulfonates, nicotinates, nitrates, oxalates, pectinates, persulfates, 3-phenylpropionates, phosphates, picrates, pivalates, propionates, salicylates succinates sulfates (such as those formed with sulfuric acid) sulfonates (such as those mentioned herein), tartrates, thiocyanates toluenesulfonates such as tosylates, undecanoates, and the like.

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The compounds of formula I which contain an acidic moiety may form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glucamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like.

Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others

Prodrugs and solvates of the compounds of the invention are also contemplated herein The term "prodrug", as employed herein denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula I, or a salt and/or solvate thereof Solvates of the compounds of formula I are preferably hydrates

To the extent that compounds of the formula I, and salts thereof, may exist in their tautomeric form, all such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers of the present compounds, such as those which may exist due to asymmetric carbons on the various R and Z substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons) and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers The chiral centers of the present invention can have the S or R configuration as defined by the IUPAC 1974 Recommendations

The terms "including", "such as" "for example" and the like are intended to refer to exemplary embodiments and not to limit the scope of the present invention.

Schemes

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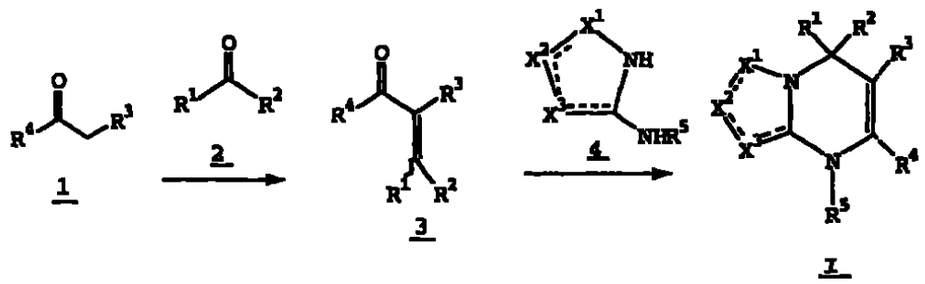
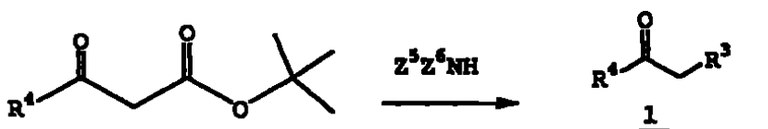
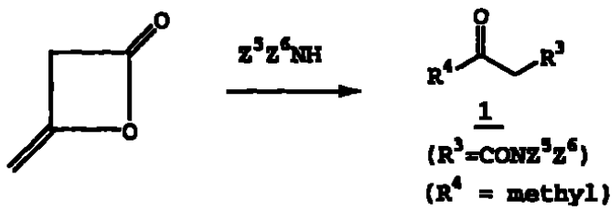
Compounds of formula I may be prepared using the sequence of steps outlined below



Compounds 1 2 and 4 used in this preparation are commercially available or are readily prepared by methods well known to those skilled in the art. For example compounds of formula 1 where $R^3 = CONZ^5Z^6$ can be prepared by the method of Witzeman (JOC 1991 56(5), 1713) which involves warming an amine and a t-butoxy-β-ketoester neat or in a suitable solvent (xylenes, toluene, etc)

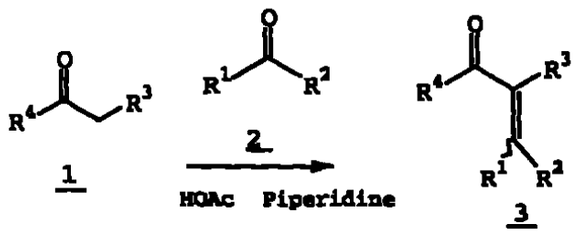


Alternately compounds of formula 1 where R^4 = methyl and $R^3 = CONZ^5Z^6$ may be prepared by reaction of an amine with diketene in a suitable solvent such as dichloromethane at temperatures between –100 –22 °C



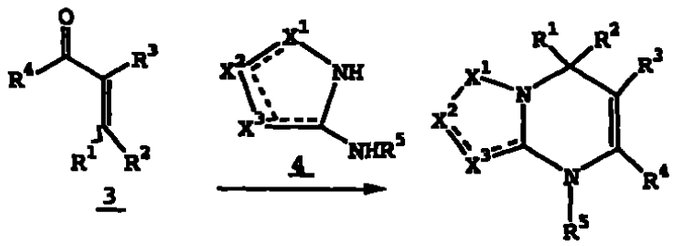
Compounds of formula 3 can be prepared by modification of the Knovenagel condensation For example condensation of a compound of formula 1 and a

compound of formula 2 at temperatures between 22-170 °C in solvents such as toluene or dimethylformamide in the presence of an acid such as acetic acid and an a base such as piperidine with removal of water generated during the reaction by the use of 4Å dry molecular sieves or a Dean-Stark trap affords compounds of formula 3 as a mixture of cis and trans stereoisomers



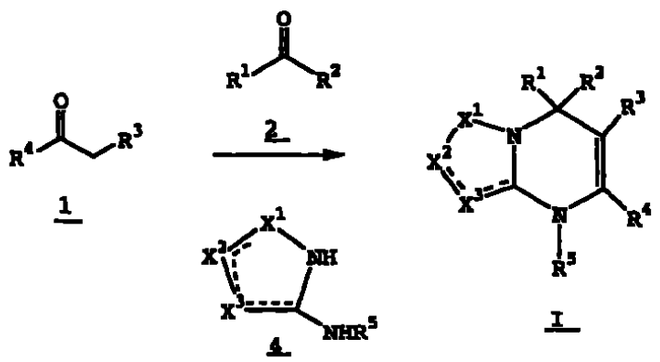
1 2 3

Compounds of formula I may also be prepared by condensation of compounds of formula 3 with compounds of formula 4 by warming at temperatures between 30-150 °C in alcoholic solvents such as ethanol or propanol or by warming between 30-150 °C in a solvent such as dimethylformamide and in the presence of a base such as sodium acetate.

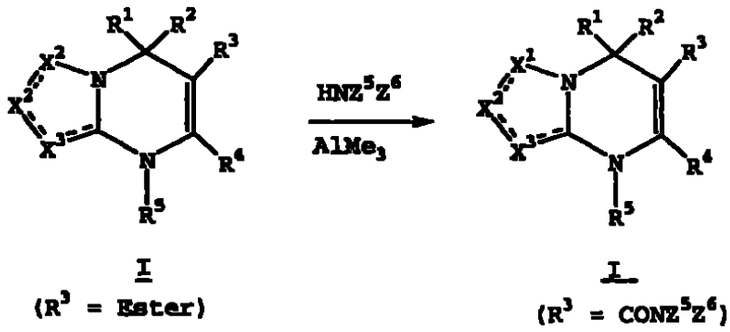


3 4 I

Compounds of formula I where R^3 = ester may be prepared by condensation of compounds of formula 1, formula 2 and heterocycles of formula 4 by warming between temperatures of 30 – 150 °C in the presence of a base such as sodium carbonate or sodium bicarbonate in a suitable solvent such as dimethylformamide.



Compounds of formula I where R^3 = amide maybe prepared by treating compounds of formula I where R^3 = ester with a suitable amine and trimethylaluminum in a solvent such as toluene at temperatures between 0-150 °C



Compounds of formula I where R^3 = amide may also be prepared by condensing compounds of formula I where R^3 = COOH with a suitable amine by amidation methods well known to those skilled in the art. For example treatment of a compound of formula I where R^3 = COOH with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI) and dimethylaminopyridine (DMAP) in a solvent such as dichloromethane affords compounds of formula I where R^3 = amide.

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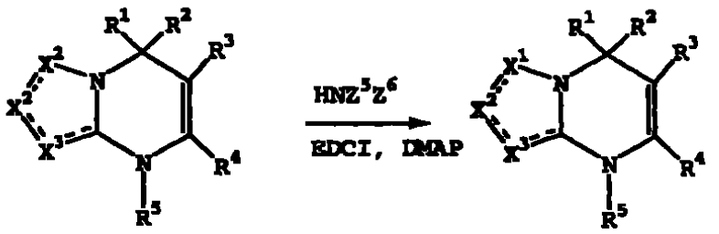
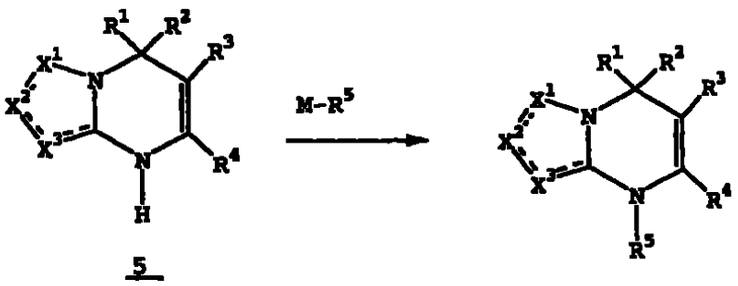


I
(R^3 = COOH)

I
(R^3 = $CONZ^5Z^6$)

Compounds of formula I where R^5 is a substituent other than hydrogen may be formed by reacting a compound of formula 5 with a reactive species M-R^5 such that a compound of formula Ia is obtained, where M is Cl, Br, OR etc , and R^5 is as defined above (other than hydrogen)



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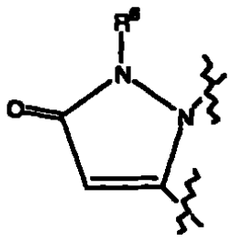
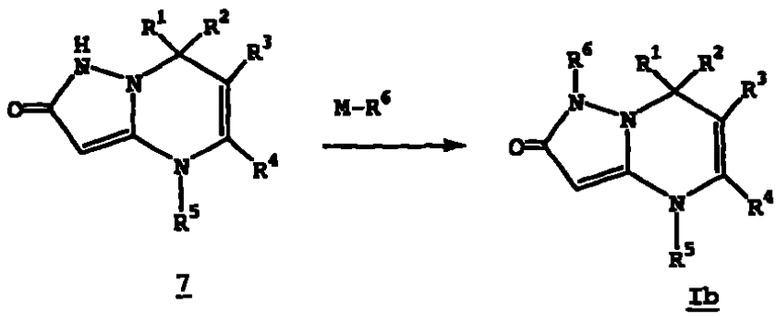
Ia

Compounds of formula I where X^1, X^2 and X^3 form a ring of the structure

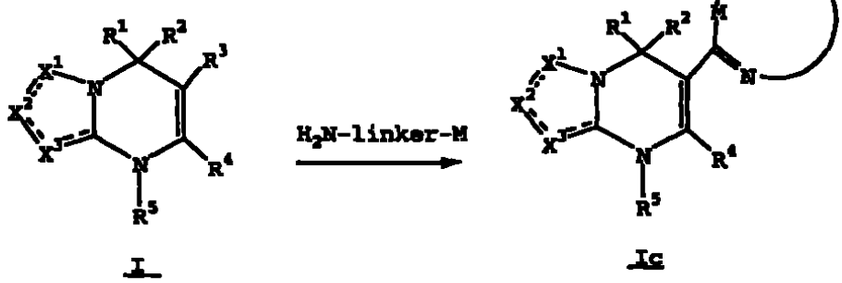


where R^6 is a substituent other than hydrogen may be formed by reacting a compound of formula 7 with a reactive species M-R^6 such that a compound of formula Ib is obtained where M is Cl, Br, OR, etc. and R^6 is as defined above.



7 Ib

Compounds of formula Ic where R^3 is a amino containing heterocycle may be formed by condensing compounds of formula I where R^3 is an acid or ester with an amine which is attached through a linker to M M may be NH_2 NHR, SH, or OH. The linker unit may be selected such that unsubstituted, substituted or fused heterocycles are formed.



I Ic

R^3 = Ester or Acid

Additional compounds within the scope of the present invention can be prepared from the compounds obtained by the above described methods through conversion of the substituent groups to other functionality by the usual methods of chemical synthesis, as illustrated in the following examples

Compounds of formula I that contain chiral centers maybe obtained in non-racemic form by non-racemic synthesis or resolution by methods well known to those skilled in the art. Compounds that are non-racemic are designated as "chiral" in the examples

In the examples described below it may be necessary to protect reactive functionality such as hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in reactions The

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introduction and removal of protecting groups are well known to those skilled in the art for example see (Green T W in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991)

Utility

The compounds of the present invention are antiarrhythmic agents which are useful in the prevention and treatment (including partial alleviation or cure) of arrhythmias The present compounds are particularly useful in the selective prevention and treatment of supraventricular arrhythmias such as atrial fibrillation, and atrial flutter By "selective prevention and treatment of supraventricular arrhythmias" is meant the prevention or treatment of supraventricular arrhythmias wherein the ratio of the prolongation of the atrial effective refractory period to the prolongation of the ventricular effective refractory period is greater than 1 1 This ratio is preferably greater than 4 1, more preferably greater than 10 1, and most preferably such that prolongation of the atrial effective refractory response period is achieved without significantly detectable prolongation of the ventricular effective refractory period.

In addition, the present compounds can block I_{Kur}, and thus may be useful in the prevention and treatment of all I_{Kur}-associated conditions An "I_{Kur}-associated condition" is a disorder which may be prevented partially alleviated or cured by the administration of an I_{Kur} blocker The Kv1 5 gene is known to be expressed in stomach tissue, intestinal/colon tissue, the pulmonary artery, and pancreatic beta cells. Thus, administration of an I_{Kur} blocker could provide useful treatment for disorders such as reflux esauphagitis, functional dispepsia, constipation, asthma, and diabetes Additionally, Kv1 5 is known to be expressed in the anterior pituntary Thus, administration of an I_{Kur} blocker could stimulate growth hormone secretion. I_{Kur} inhibitors can additionally be useful in cell proliferative disorders such as leukemia, and autoimmune diseases such as rheumatoid arthritis and transplant rejection

The present invention thus provides methods for the prevention or treatment of one or more of the aforementioned disorders, comprising the step of administering to a subject in need thereof an effective amount of at least one compound of the formula I. Other therapeutic agents such as those described below may be employed with the inventive compounds in the present methods. In the

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methods of the present invention such other therapeutic agent(s) may be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention

The present invention also provides pharmaceutical compositions comprising at least one of the compounds of the formula I or salts thereof capable of preventing or treating one or more of the aforementioned disorders in an amount effective therefor, and a pharmaceutically acceptable vehicle or diluent. The compositions of the present invention may contain other therapeutic agents as described below and may be formulated, for example by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation

The compounds of the formula I may be administered by any suitable means for example, orally, such as in the form of tablets, capsules, granules or powders, sublingually; bucally; parenterally such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g , as sterile injectable aqueous or non-aqueous solutions or suspensions), nasally such as by inhalation spray; topically, such as in the form of a cream or ointment, or rectally such as in the form of suppositories in dosage unit formulations containing non-toxic pharmaceutically acceptable vehicles or diluents The present compounds may for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. In the case where the compounds of formula I are being administered to prevent or treat arrhythmias, the compounds may be administered to achieve chemical conversion to normal sinus rhythm, or may optionally be used in conjunction with electrical cardioconversion.

Exemplary compositions for oral administration include suspensions which may contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer and

sweeteners or flavoring agents such as those known in the art, and immediate release tablets which may contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The compounds of formula I may also be delivered through the oral cavity by sublingual and/or buccal administration Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG) Such formulations may also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g., Carbopol 934) Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which may contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting and suspending agents, including synthetic mono- or diglycerides and fatty acids, including oleic acid.

Exemplary compositions for rectal administration include suppositories which may contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures but liquify and/or dissolve in the rectal cavity to release the drug.

Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene)

The effective amount of a compound of the present invention may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for an adult human of from about 0 001 to 100 mg/kg of body weight of active compound per day, which may be administered in a single dose or in the form of individual divided doses such as from 1 to 4 times per day It will be understood that the specific dose level and frequency of dosage for any particular subject may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans and domestic animals such as dogs, cats and the like, subject to the aforementioned disorders.

The compounds of the present invention may be employed alone or in combination with each other and/or other suitable therapeutic agents useful in the treatment of the aforementioned disorders, such as other antiarrhythmic agents, calcium channel blockers, cyclooxygenase inhibitors platelet aggregation inhibitors, fibrinogen antagonists, diuretics, angiotensin converting enzyme inhibitors, angiotensin II antagonists, thrombolytic agents, thromboxane receptor antagonists, prostacyclin memetics, or phospodiesterase inhibitors. Exemplary other antiarrhythmic agents include Class I agents (such as propafenone and quinidine), Class II agents (such as sotalol), and Class III agents (such as dofetilide and amiodarone) Exemplary calcium channel blockers include diltiazem, verapamil nifedipine, and amlodipine. Exemplary cyclooxygenase inhibitors include aspirin or indomethacin. Exemplary platelet aggregation inhibitors include clopidogrel, ticlopidene or aspirin. Exemplary diuretics include chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide, musolimine, bumetanide, triamtrerene, amiloride or spironolactone. Exemplary angiotensin converting enzyme inhibitors include captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril delapril pentopril, quinapril ramipril, lisinopril or salts of such compounds Exemplary

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angiotensin II antagonists include losartan, irbesartan or valsartan Exemplary thrombolytic agents include tissue plasminogen activator (tPA), recombinant tPA, streptokinase, urokinase, prourokinase, anisoylated plasminogen streptokinase activator complex (APSAC, Eminase, Beecham Laboratories) or animal salivary gland plasminogen activators. Exemplary thromboxane receptor antagonists include ifetroban

The above other therapeutic agents, when employed in combination with the compounds of the present invention may be used for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art

Assays to determine the degree of activity of a compound as an I_{Kur} inhibitor are well known in the art and are described in references such as *J Gen. Physiol.* Apr;101(4) 513-43, and *Br J Pharmacol.* 1995 May;115(2) 267-74

All documents cited in the present specification are incorporated herein by reference in their entirety

The following examples and preparations describe the manner and process of making and using the invention and are illustrative rather than limiting. It is to be understood that there may be other embodiments which fall within the spirit and scope of the invention as defined by the claims appended hereto. Abbreviations employed herein are defined below

CDI = carbonyl diimidazole

DCM = dichloromethane

DMAP = dimethylaminopyridine

DMF = dimethylformamide

DMPU = 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1 *H*)-pyrimidinone

EDCI (or EDC) = 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

M+H = monoisotopic mass plus one proton

Et = ethyl

h = hours

HPLC = high performance liquid chromatography

HOBT = hydroxybenzotriazole

LC/MS = liquid chromatography/mass spectrometry

Me = methyl

min = minutes

MS = mass spectrometry

NaOAc = sodium acetate

Ph = phenyl

PPA = poly phosphoric acid

Pr = propyl

Py = pyridine

PyBrOP = bromo-tris-pyrrolidino-phosphonium hexafluorophosphate

RT = room temperature

Rt = retention time

TEA = triethylamine

TFA = trifluoroacetic acid

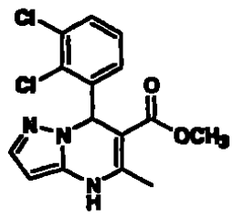
TLC = thin layer chromatography

THF = tetrahydrofuran

TMSOTf = trimethylsilyl trifluoromethanesulfonate

Example 1

7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid methyl ester



Method.

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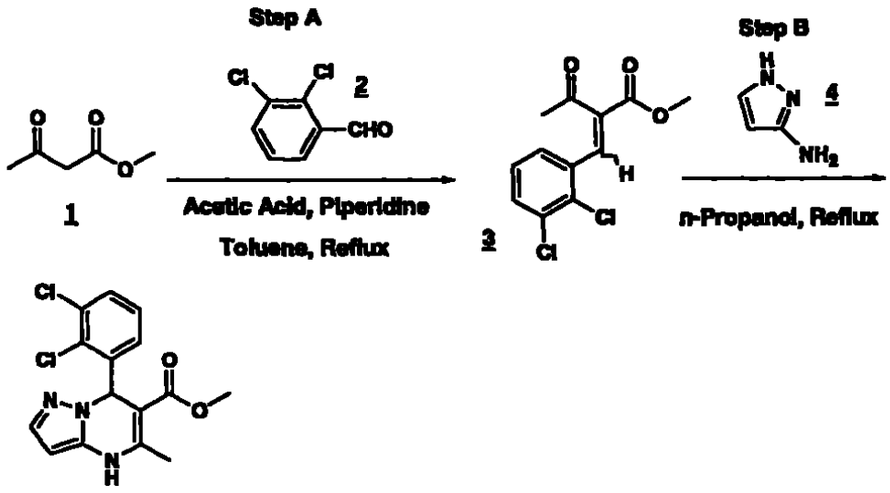


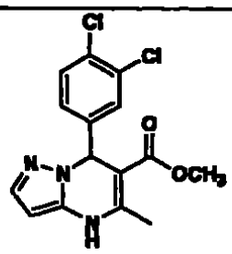
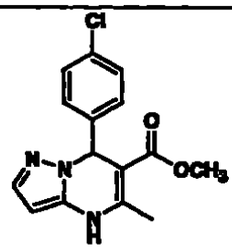
Step A A mixture of methyl acetoacetate 1 (5 mL, 46 mmol), 2,3-dichlorobenzaldehyde 2 (8 1 g, 46 mmol), piperidine (1 1 ml, 12 mmol), and acetic acid (0 6 mL, 11 mmol) in toluene (200 mL) was refluxed overnight with azeotropic removal of water via a Dean-Stark trap The mixture was cooled to room temperature, quenched with water transferred to a separatory funnel, diluted with ethyl acetate, washed with aqueous NaOH (1M), aqueous HCl (1M), water and brine and concentrated in vacuo The residue was purified by flash chromatography (silica gel, 33% Ethyl acetate/hexanes) to afford 10 8 g (85% yield) of compound 3 as a mixture of diasteromers. Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220λ, 4 min. gradient (10% MeOH/H_2O with 0 1% TFA-90% MeOH/H_2O with 0 1% TFA) 4 mL/min. Diastereomer A, Rt = 3.51 min,(53%) Diastereomer B, Rt=3 70 min (45%) MS (M+H 273)

Step B A mixture of compound 3 (5 g, 18.3 mmol), 3-aminopyrazole 4 (1 5 g, 18.3 mmol) in 1-propanol (60 mL) was refluxed for 6 h. The mixture was cooled to room temperature and concentrated and recrystallized from ethyl acetate/hexanes to give 1 25 g (20%) of the title compound as a yellow solid. The mother liquor was concentrated and purified by flash chromatography (silica gel, 5% methanol/dichloromethane) to give an additional 1 62 g (26%) of the title compound. Combined yield 2 87g (46%) Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220λ, 4 min. gradient (10% MeOH/H_2O with 0 1%

TFA-90% MeOH/H_2O with 0 1% TFA), 4 mL/min. Rt = 3 38 min, (96% pure) MS (M+H. 338) HMR ($CDCl_3$, 400 MHz) 7 98(1H, app s), 7 15(3H, m), 6 91(1H,s), 5 52(1H, app s) 3 61(3H, s), 2.39(3H,s)

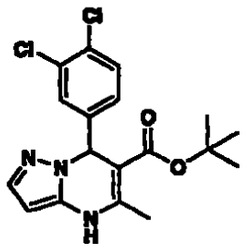
Examples 2 and 3

The compounds of Examples 2 and 3, shown in the table provided below, were prepared in a manner similar to that described in Example 1

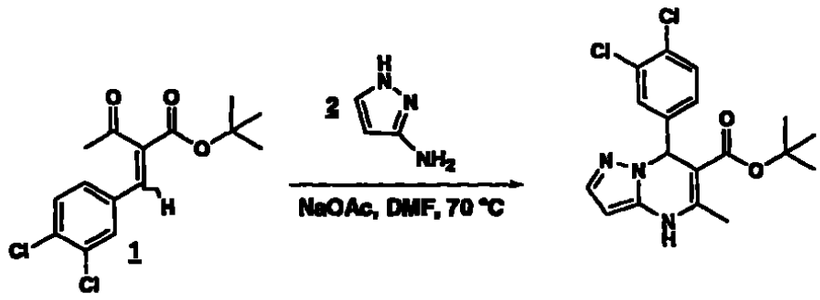
Example	Structure	Name	(M+H)
2		7-(3,4-Dichlorophenyl)-4 7 dihydro-5-methylpyrazolo[1 5-a]pyrimidine-6-carboxylic acid methyl ester	338
3		7-(4-Chlorophenyl)-4,7 dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid methyl ester	303

Example 4

7 (3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1 5-a]pyrimidine-6-carboxylic acid 1 1-dimethylethyl ester



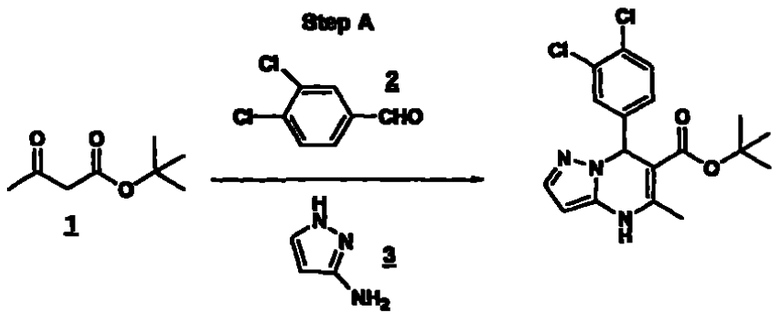
Method 1



Compound 1 Compound 1 was prepared by condensing t butoxyacetoacetate and 2,4-dichlorobenzaldehyde as described in Example 1 step A

Title Compound A mixture of compound 1 (44 4 g, 141 mmol), 3-aminopyrazole 2 (17 6 g 212 mmol) and sodium acetate (46.3 g, 564 mmol) in dimethylformamide (300 mL) was stirred at 70 °C overnight (17 h) The mixture was cooled to room temperature, transferred to a separatory funnel, diluted with water and ethyl acetate, washed with water (a small amount of methanol was added to breakup emulsions that formed) and brine, dried over anhydrous sodium sulfate and concentrated. A precipitate formed. The precipitate was collected and washed with ethyl acetate, ethyl ether and hexanes and dried to give 8.93g The mother liquor was concentrated to give a second crop of precipitate 9.32 g. LC/MS analysis indicated the precipitates were not pure The precipitates were combined, dissolved in dichloromethane and concentrated onto enough silica gel such that a free flowing powder was obtained The resulting powder was loaded onto a chromatography column prepacked with silica gel and dichloromethane. Elution with 100% dichloromethane followed by 3% methanol/dichloromethane gave 15 1 g (29% yield) of the title compound. Reverse Phase LC/MS YMC S5 ODS 4.6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient (10% MeOH/H20 with 0 1% TFA-90% MeOH/H_2O with 0 1% TFA), 4 mL/min. Rt = 4.63min, (97% pure). MS (M+H 380) HMR (CD_3OD, 400 MHz) 7.41(2H, m), 7 33(1H, d, J=2 Hz), 7.08(1H, m), 6.21(1H,s) 5 68(1H, d, J=2 Hz), 2.43(3H, s), 1.37(9H,s)

Method 2.



A mixture of t-butoxyacetoacetate 1 (22.6 g, 143 mmol), 3,4-dichlorobenzaldehyde 2 (25.0 g, 143 mmol), 3-aminopyrazole 3 (15.4 g, 185 mmol) and sodium bicarbonate (36 g, 428 mmol) in dimethylformamide (250 mL) was stirred at 70 °C overnight (18 h) The mixture was cooled to room temperature, quenched with ethyl acetate and water, transferred to a separatory funnel, washed with water and brine, dried over sodium sulfate, filtered and concentrated. The residue was recrystallized from ethyl acetate/hexanes to give 16.8g (31% yield) of the title compound as a white solid. Data for the title compound is given in method 1

Examples 5 and 6

The compounds of Examples 5 and 6, shown in the table provided below were prepared in a manner similar to that described in Example 4, Method 1

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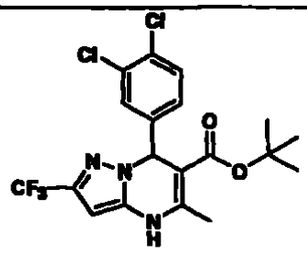
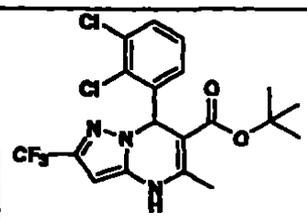
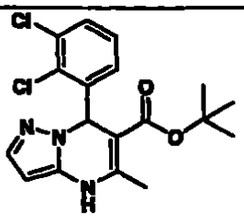
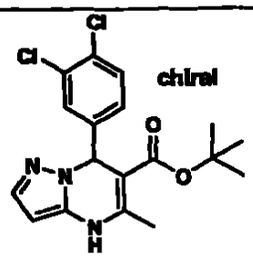
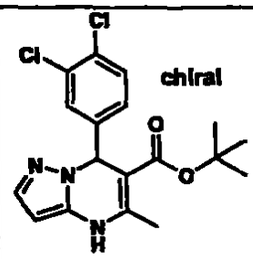
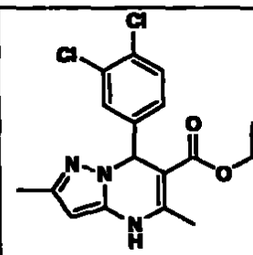
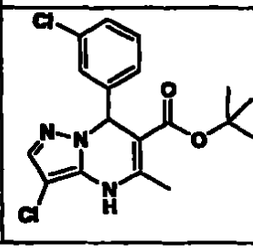
636

Example	Structure	Name	(M+H)
5		7 (3,4-Dichlorophenyl)-4 7-dihydro-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1 1-dimethylethyl ester	448
6		7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-2 (trifluoromethyl)pyrazolo[1 5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethyl ester	448

Examples 7-11

The compounds of Examples 7-11 shown in the table provided below, were prepared in a manner similar to that described in Example 4, Method 2 The compound of Example 4, method 2 could be resolved into the corresponding enantiomers A (Example 8) and B (Example 9) by preparative chiral HPLC (Chiralcel OD column (50 X 500 mm), eluting with 7% isopropanol/hexanes containing 0 1 % triethylamine amine at 50 mL/min), UV detection at 254λ. Analytical HPLC (Chiralcel OD column (4 6 X 250 mm) eluting with 10% isopropanol/hexanes containing 0 1 % triethylamine amine at 1 mL/min), UV detection at 254λ, enantiomer A (Rt= 6 98 min, 98% ee) enantiomer B (Rt= 9 22 min 98% ee).

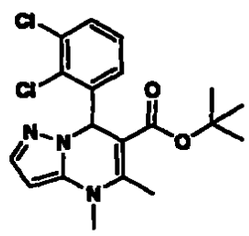
Example	Structure	Name	(M+H)
7		7-(2,3-Dichlorophenyl)-4 7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1 1-dimethylethyl ester	380

8	 chiral	7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethylester, enantiomer A	380
9	 chiral	7 (3,4-Dichlorophenyl)-4 7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethylester enantiomer B	380
10		7 (3,4-Dichlorophenyl)-4,7-dihydro-2,5-dimethylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1 1-dimethylethyl ester	394
11		3-Chloro-7-(3-chlorophenyl)-4 7-dihydro-5-methylpyrazolo[1 5-a]pyrimidine-6-carboxylic acid 1 1-dimethylethyl ester	380

Example 12

7-(2 3-Dichlorophenyl)-4 7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1 1-dimethylethyl ester

5



Method.

1

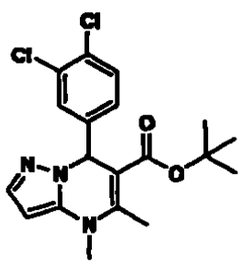
Compound 1 Compound 1 was prepared as described in Example 4, method 1

Title Compound Sodium hydride (0 186 g, 7 76 mmol) was added to a 0 °C solution of 1 (2.27 g, 5 97 mmol) in dimethylformamide (30 mL). After 10 min., methyl iodide (0.41 mL, 6.57 mmol) was added. After an additional 85 min, the mixture was quenched with saturated ammonium chloride solution, diluted with ethyl acetate, transferred to a separatory funnel, washed with saturated ammonium chloride, water and brine, dried over anhydrous sodium sulfate and concentrated onto enough silica gel such that a free flowing powder was obtained. The resulting powder was loaded onto a chromatography column prepacked with 100% dichloromethane. Elution with 0-10% ethyl acetate/dichloromethane gave 1 16 g (49%) of the tile compound as a slightly yellow solid. Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 40-100% Solvent B/A (Solvent A. 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0.1% TFA), 4 mL/min Rt = 3 46 min, (96% pure) MS (M+H 394) HMR (CD_2Cl, 400 MHz) 7 39(1H, d, J=2 Hz), 7.35(1H, m), 7 23(1H, m), 7 11(1H, m) 6 91(1H,s), 5.58(1H, d, J=2 Hz) 2 38(3H, s), 2.62(3H, s), 1 27(9H,s)

Example 13

7-(3,4-Dichlorophenyl)-4,7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1 1-dimethylethyl ester

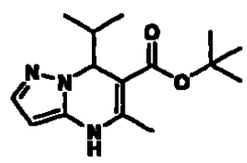
639



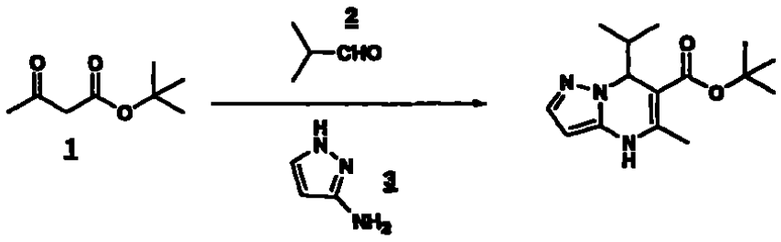
The title compound was prepared in a similar manner to that provided in Example 12 yielding a compound with (M+H) 394

Example 14

4,7-Dihydro-5-methyl 7-(1-methylethyl)pyrazolo[1 5-a]pyrimidine-6-carboxylic acid 1 1-dimethylethyl ester



Method.



A pressure tube was dried with a heat gun under nitrogen The pressure tube was charged in the following order with isobutyraldehyde 2 (0 262 g, 3 63 mmol), dimethylformamide (3 mL) t-butylacetoacetate 1 (0 574 g, 3 63 mmol), 3-aminopyrazole 3 (0.362 g, 4 36 mmol) and sodium acetate (1 22 g, 14 5 mmol) The

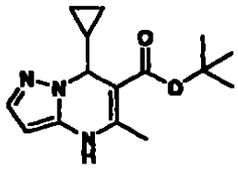
640
647

mixture was flushed with nitrogen The tube was sealed and warmed to 75 °C and stirred overnight. The mixture was cooled to room temperature, diluted with ethyl acetate to a volume of 20 mL, washed with lithium chloride (2 4M, 10 mL) and brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 1 02 of a yellow oil The oil was purified by flash chromatography (silica, 45% ethyl acetate/heptane) to give 0.42 g (41% yield) of the title compound. Reverse Phase HPLC YMC S5 ODS 4 6 x 50mm Ballistic column, UV detection at 220 λ, 4 min. gradient 0-100% Solvent B/A (Solvent A 10% MeOH/H_2O with 0.2% PPA, Solvent B 90% MeOH/H_2O with 0.2% PPA) 4mL/min Rt = 3 83 min, (100% pure) Reverse Phase LC/MS YMC S5 ODS 4 6 x 50mm Ballistic column, UV detection at 220 λ, 4 min. gradient 0-100% Solvent B/A (Solvent A 10% MeOH/H_2O with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA) 4mL/min. Rt = 3.06min. MS (EM, M+1 278) HMR ($CDCl_3$, 400MHz) 7 37(1H,d,J=2.2Hz), 6.35(1H,s), 5 55(1H,d,J=1 8Hz), 5.29(1H,d,J=2.2Hz), 2.41(3H,s), 1.50(9H,s), 1 28-1 19(1H,m), 1 07(3H,d,J=7 0Hz), 0 60(3H,d,J=7 0Hz)

641

Example 15

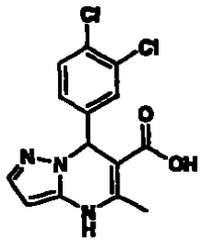
7-Cyclopropyl-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethyl ester



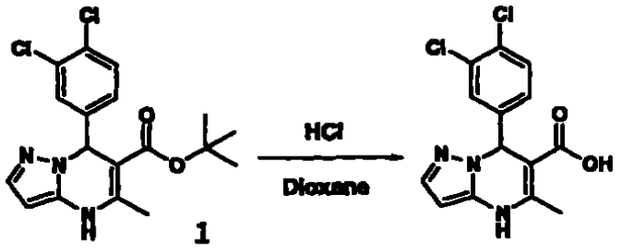
The title compound was prepared in a similar manner to that provided in Example 14 yielding a compound with (M+H) 275

Example 16

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1 5-a]pyrimidine-6-carboxylic acid



Method



1

Compound 1 Compound 1 was prepared as described in Example 4

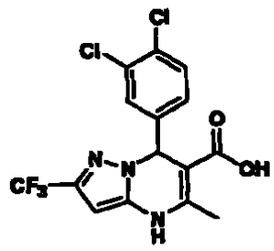
Title Compound HCl (4M in dioxane) was added to solid compound 1 (1 13 g, 2.97 mmol) at room temperature. The solid dissolves and a precipitate forms. The resulting thick reaction mixture was allowed to stir overnight and was concentrated in

642
6/9

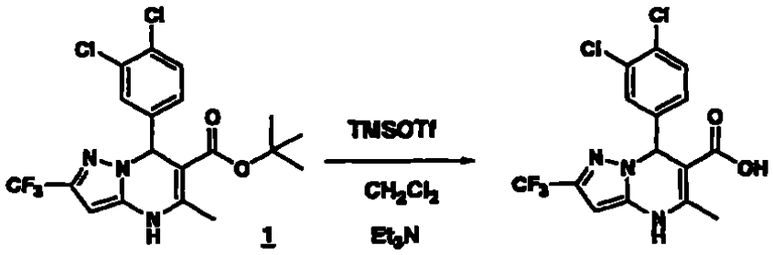
vacuo to give 1 14 g (120% contains dioxane) of the title compound as a white solid. Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 0-100% Solvent B/A (Solvent A. 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0.1% TFA), 4 mL/min. Rt = 3.54 min, (93% pure) MS (M+H 324) HMR (CD_3OD, 400 MHz) 7 96(1H, d, J=3 Hz) 7.51(2H, m), 7 21(1H, m), 6 49(1H,s), 6 11(1H, d, J=3 Hz), 2.51(3H, s) The title compound was used in subsequent reactions without further purification.

Example 17

7-(3 4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxylic acid



Method.



1

Compound 1 Compound 1 (the compound of Example 5) was prepared in a manner similar to that described in Example 4

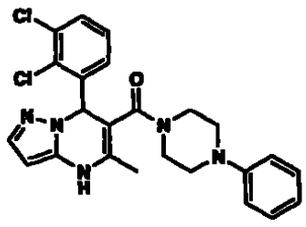
Title Compound Trimethylsilyl trifluoromethanesulfonate (0 873 mL, 4.82 mmol) was added to a room temperature solution of compound 1 (1 08 g, 2.41 mmol) in dichloromethane (50 mL) After 2h triethylamine (0 672 ml, 4 82 mmol) was added

and the reaction mixture was poured into water The organic layer was separated and dried over Na_2SO_4, concentrated, and purified by flash chromatography (50% ethylacetate/hexane → 100% ethyl acetate) to give 0 71 g (75% yield) of the title compound as a white solid MS (M+H 392)

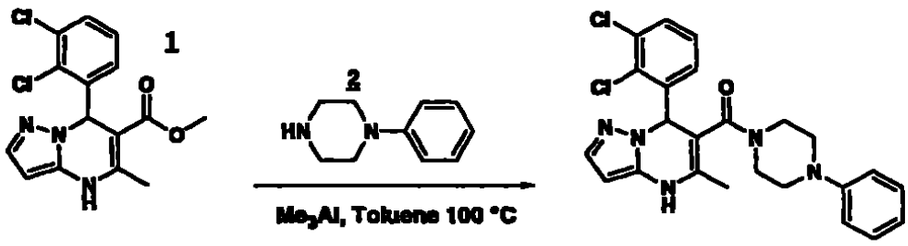
644

Example 18

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine



Method 1

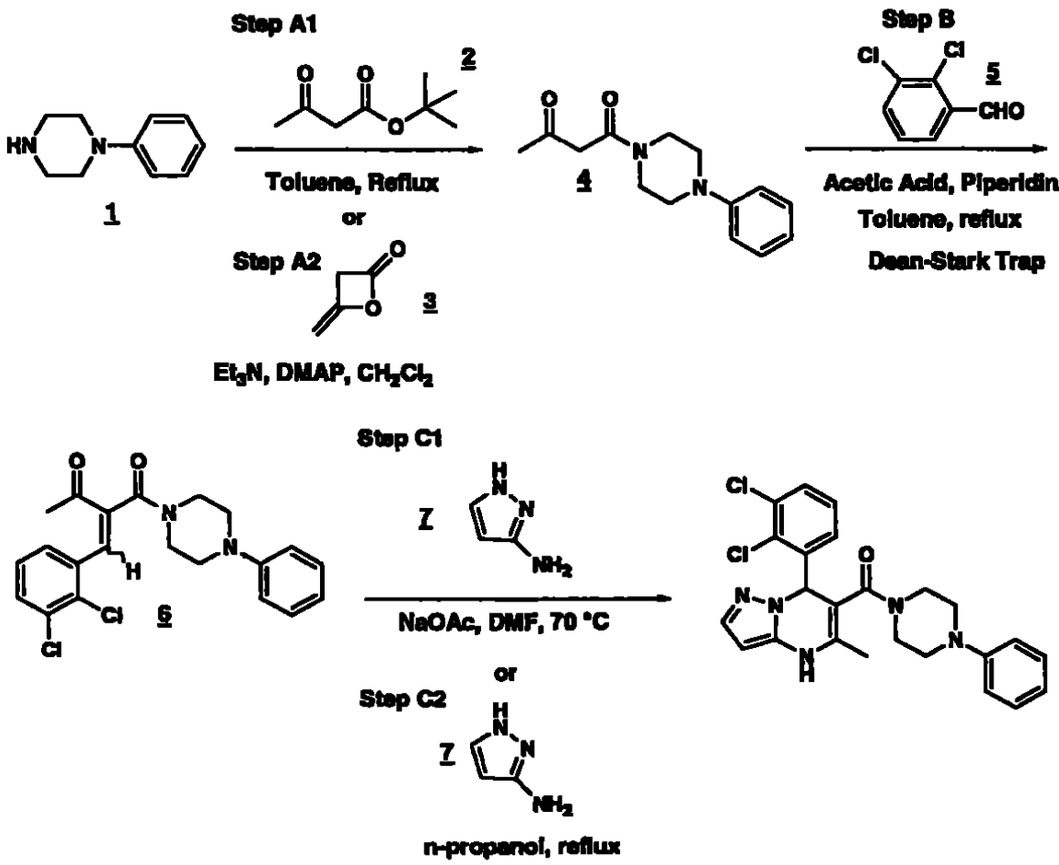


Compound 1 Compound 1 was prepared as described in Example 1

Title Compound Trimethylaluminum (1 1 mL, 2.2 mmol, 2 M in toluene) was dropwise added to a room temperature solution of 1-phenylpiperazine 2 (0.4 mL, 2.2 mmol) in toluene (7 mL) After one hour compound 1 (0.50 g, 1.5 mmol) was added and the resulting mixture was stirred at 100 °C for 18 h. The mixture was cooled to room temperature, quenched with water, diluted with ethyl acetate, transferred to a separatory funnel, washed with aqueous HCl (1M), water and brine, dried over anhydrous sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 50% ethyl acetate/hexanes followed by 5% methanol/dichloromethane to provide 0 22 g (32%) of a solid which was further purified by recrystallization from methanol/ethyl ether to give 0 15 g (22%) of the title compound. Reverse Phase LC/MS YMC S5 ODS 4.6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 0-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0 1% TFA, SolventB 90% MeOH/H_2O with 0.1% TFA), 4 mL/min Rt = 3 58 min, (92% pure) MS (M+H 468) Additional Data for the title compound is reported in Method 2, step C variation 1

645 62

Method 2



Step A Variation 1 A mixture of N-phenylpiperazine 1 (6 7 mL, 41 mmol) and t-butoxyacetoacetate 2 (6 8 mL, 45 mmol) in toluene (50 mL) was refluxed overnight. The mixture was cooled to room temperature, transferred to a separatory funnel, diluted with ethyl ether and extracted (3X) with aqueous HCl (1M) The HCl extracts were combined and washed with ethyl ether (2X), made basic (pH 9) with aqueous NaOH (50% w/w) and extracted with ethyl acetate. The ethyl acetate extracts were combined, washed with water and brine, dried over anhydrous sodium sulfate, filtered and concentrated to give 9 76 g (97 6%) of compound 4 as a thick amber oil Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV

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detection at 220 λ, 4 min gradient 0-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0 1% TFA, SolventB 90% MeOH/H_2O with 0.1% TFA), 4 mL/min. Rt = 1 65 min, (100% pure) MS (M+H 247) HMR ($CDCl_3$, 400 MHz) 7 28(2H, m) 6 91(3H, m), 3 80(2H, m), 3 78(2H, m), 3 59(4H, m), 3 19(4H, m), 2.30(3H, s).

Step A Variation 2 Diketene 3 (5.50 g, 65 5 mmol) was slowly added over 15 min to a 0 ^{0}C solution of 4-phenylpiperazine 1 (5 31 g, 32.7 mmol) in dichloromethane (50 mL) TLC after 4 h indicated compound 1 was not completely consumed Additional diketene (5 50 g, 65 5 mmol) was added. After an additional 1 5h the reaction was quenched with 1N NaOH, transferred to a separatory funnel, washed with 1H NaOH and brine, dried over sodium sulfate, concentrated onto enough silica gel such that a free flowing powder was obtained. The resulting powder was loaded onto a chromatography column prepacked with silica and 50% ethyl acetate/hexanes Elution with 50-100% ethylacetate/hexanes gave 8 2 g (100%) of compound 4 as a thick yellow oil Data for compound 4 is given above in step A variation 1

Step B A mixture of compound 4 (9 76 g, 40 mmol), 2,3-dichlorobenzaldehyde 6 (7 89 g, 45 mmol), piperidine (1 0 ml, 10 mmol), acetic acid (0 59 mL, 10 mmol) in toluene (100 mL) was refluxed overnight with azeotropic removal of water via a Dean-Stark trap The mixture was cooled to room temperature and concentrated in vacuo and was typically used in subsequent reactions without purification Compound 6 may be Purified by silica gel chromatography (30-40% ethyl acetate/hexanes) Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 0-100% Solvent B/A (Solvent A. 10% MeOH/H20 with 0 1% TFA, SolventB 90% MeOH/H_2O with 0 1% TFA), 4 mL/min. Rt = 3.83 min, (96% pure) MS (M+H 404) HMR ($CDCl_3$, 400 MHz) 7 82(1H, s), 7.55(1H, dd, J=1, 8 Hz), 7 48(1H, dd, J=1, 8 Hz), 7 23(3H, m), 6 89(1H, app t, 7 Hz), 6.81(2H, d, J=8 Hz), 3 78(2H, m), 3 34(1H, m), 3.23(2H, m), 2.96(1H, m), 2.85(1H, m), 2 50(3H, s), 2.42(1H, M)

Step C Variation 1 A mixture of compound 6 (16 g, 40 mmol), 3-aminopyrazole 7 (5 1 g 62 mmol) and sodium acetate (10 1 g, 123 mmol) in dimethylformamide (100

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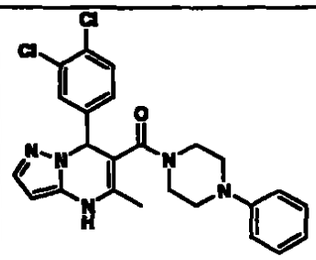
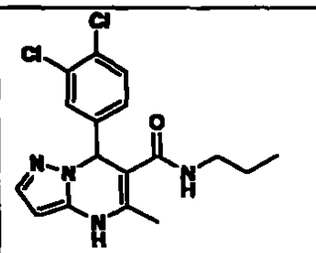
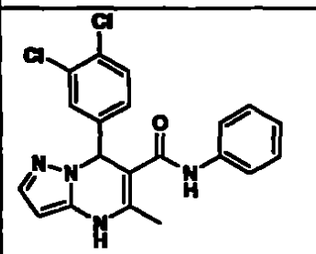
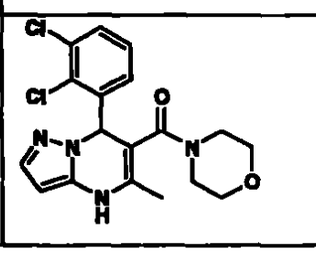
mL) was stirred at 70 °C overnight (17 h) The mixture was cooled to room temperature, transferred to a separatory funnel, diluted with water and ethyl acetate, washed with water (a small amount of methanol was added to breakup emulsions that formed) and brine, dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified by silica gel chromatography Elution with 50% ethyl acetate/hexanes followed by 100% ethyl acetate afforded 6 2 g (33% yield from compound 1) of the title compound The title compound could be resolved into the corresponding enantiomers A (Example 28) and B (Example 29) by preparative chiral HPLC (Chiracel OD column (50 X 500 mm), eluting with 30% isopropanol/hexanes containing 0 1 % triethylamine amine at 50 mL/min), UV detection at 254λ, enantiomer A Rt= 42 min, enantiomer B Rt= 54 min. Analytical HPLC (Chiracel OD column (4 6 X 250 mm) eluting with 30% isopropanol/hexanes containing 0 1 % triethylamine amine at 1 mL/min), UV detection at 254λ, enantiomer A Rt= 11 7 min, enantiomer B Rt= 17 6 min Data given for enantiomer A Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220λ, 4 min. gradient 0-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min Rt = 3.54min, (91% pure) MS (M+H 468) HMR (HCl salt of 8a, CD_3OD, 400 MHz) 7 94(1H, d, J=3 Hz), 7 56(8H, m), 7 38(1H, m) 6 05(1H, d, J=3 Hz), 4 23(1H,m), 3.57(7H, m), 2 01(3H s)

Step C Variation 2 A mixture of compound 5 (6 0 g, 15 mmol) 3-aminopyrazole 7 (1 24 g, 15 mmol) in n-propanol (50 mL) was refluxed overnight (19 h) The mixture was cooled to room temperature, transferred to a separatory funnel, diluted with ethyl acetate. An attempt to wash the solution with saturated ammonium chloride resulted in the formation of a precipitate. The precipitate was dissolved with water and methanol The resulting mixture was washed with water and brine, dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified by silica gel chromatography Elution with 70% ethyl acetate/hexanes followed by 100% ethyl acetate afforded 2.7 g (39% yield) of the title compound as a white solid. The title compound could be resolved into the corresponding enantiomers A and B as described in Step C variation 1

Examples 19-27

The compounds of Examples 19-27, shown in the table provided below, were prepared in a manner similar to that described in Example 18, Method 1

Example	Structure	Name	(M+H)
19		1-[[7-(3,4-Dichlorophenyl)-4 7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine	468
20		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-propylpyrazolo[1,5-a]pyrimidine-6-carboxamide	365
21		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-phenyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide	399
22		4-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6 yl]carbonyl]morpholine	393

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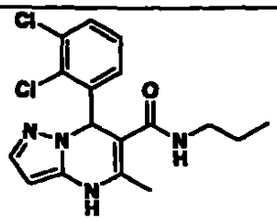
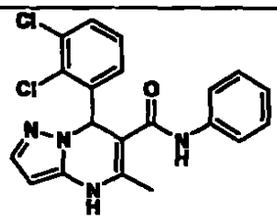
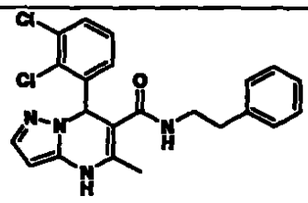
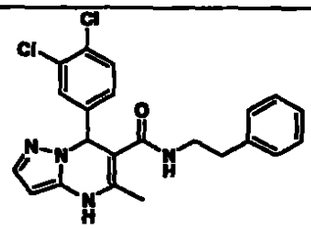
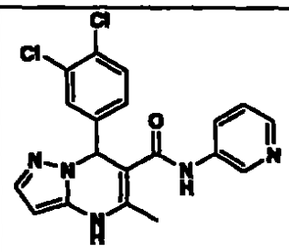
676

23		7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-N-propylpyrazolo[1,5-a]pyrimidine-6-carboxamide	365
24		7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-N phenylpyrazolo[1 5 a]pyrimidine-6-carboxamide	399
25		7-(2,3-Dichlorophenyl)-4,7 dihydro-5-methyl-N-(2-phenylethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	427
26		7-(3 4-Dichlorophenyl)-4 7 dihydro-5-methyl-N-(2-phenylethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	427
27		7 (3 4-Dichlorophenyl)-4,7-dihydro-5 methyl-N-3-pyridinylpyrazolo[1,5-a]pyrimidine-6-carboxamide	400

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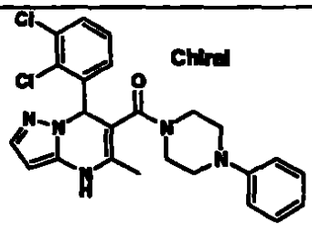
Examples 28-82

The compounds of Examples 28-82, shown in the table provided below, were prepared in a manner similar to that described in Example 18, Method 2

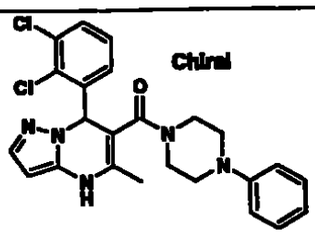
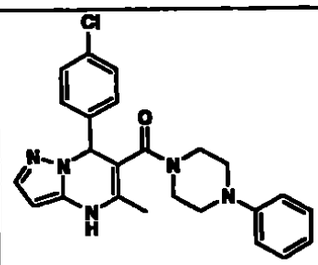
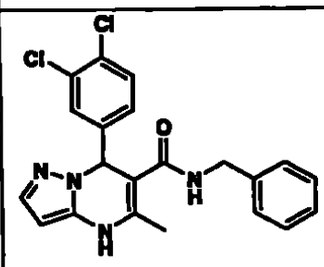
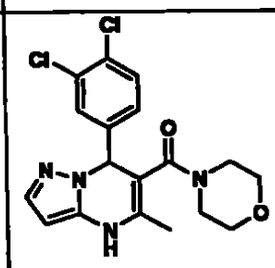
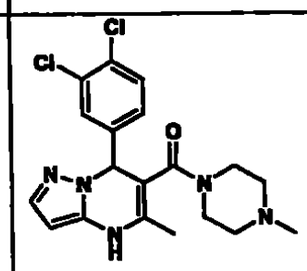
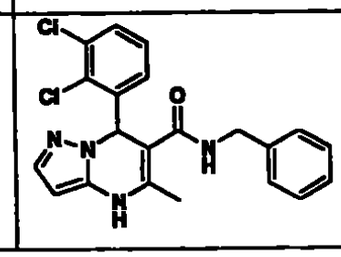
HPLC resolution of Example 47, Chiralcel OD column (50 X 500 mm), eluting with 30% isopropanol/hexanes containing 0.1 % triethylamine at 50 mL/min), UV detection at 254λ, provided enantiomers A (Example 50) and B (Example 51) Chiralcel OD column (4 6 X 250 mm) eluting with 30% isopropanol/hexanes containing 0 1 % triethylamine at 1 mL/min), UV detection at 254 λ, enantiomer A Rt = 9 8 min, >99% ee. Enantiomer B Rt = 14 2 min, >99% ee.

HPLC resolution of Example 70, Chiralpak AD column (50 X 500 mm), eluting with 15% ethanol/hexanes containing 0 1 % triethylamine at 50 mL/min), UV detection at 254 λ, provided enantiomers A (Example 72) and B (Example 71) Chiralpak AD column (4 6 X 250 mm) eluting with 15% ethanol/hexanes containing 0 1 % triethylamine at 1 mL/min), UV detection at 254 λ, enantiomer A Rt = 6 9 min, >99% ee. Enantiomer B Rt= 13.4 min, >99% ee.

HPLC resolution of Example 80 Chiralpak AD column (50 X 500 mm), eluting with 25% isopropanol/hexanes containing 0 1 % triethylamine at 50 mL/min) UV detection at 254 λ, provided enantiomers A (Example 81) and B (Example 82) Chiralpak AD column (4 6 X 250 mm) eluting with 30% isopropanol/hexanes containing 0 1 % triethylamine at 1 mL/min), UV detection at 254 λ, enantiomer A Rt = 5.3 min >99% ee. Enantiomer B Rt = 7 1 min, >99% ee.

Example	Structure	Name	(M+H)
28		1-[[7-(2,3-Dichlorophenyl)-4,7 dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenyl-piperazine enantiomer A	468

651 628

29		1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1 5-a]pyrimidin-6 yl]carbonyl]-4-phenyl-piperazine enantiomer B	468
30		1 [[7-(4-Chlorophenyl)-4,7 dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine	433
31		1-[[7 (3,4-Dichlorophenyl)-4,7-dihydro-5 methyl-N (phenylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	413
32		4-[[7 (3,4-Dichlorophenyl)-4,7 dihydro-5 methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]morpholine	393
33		1-[[7-(3 4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1 5-a]pyrimidin-6-yl]carbonyl]-4-methyl-piperazine	406
34		7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl N-(phenylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	413

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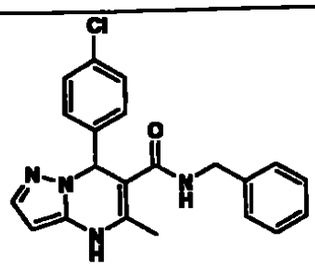
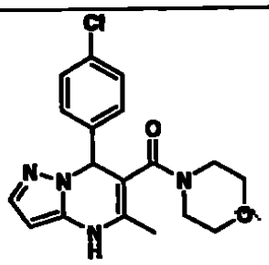
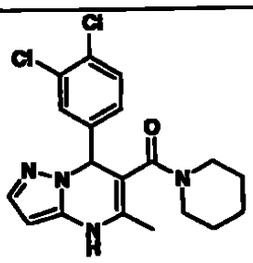
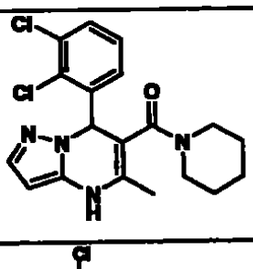
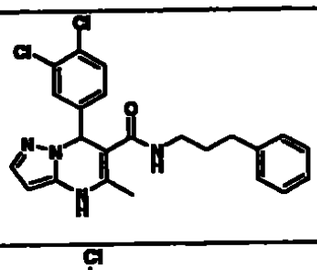
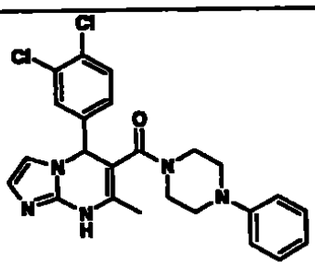
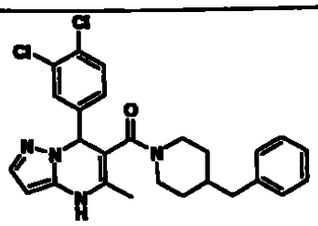
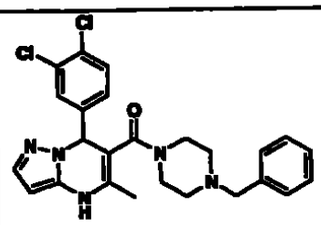
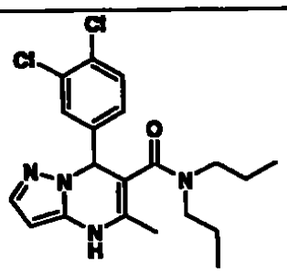
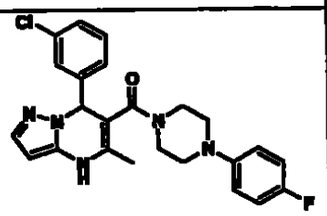
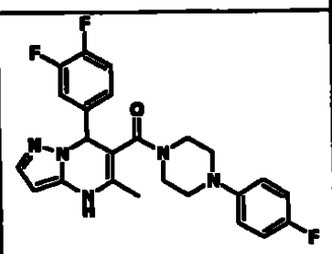
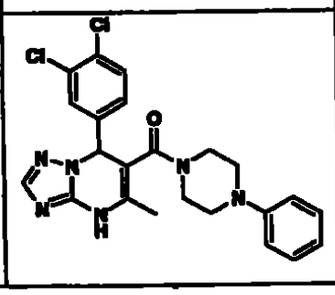
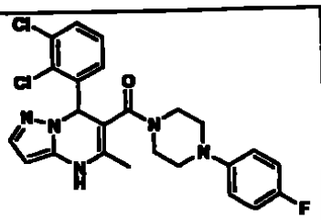
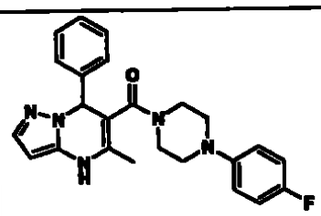
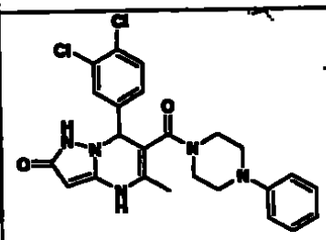
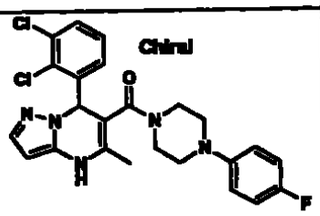
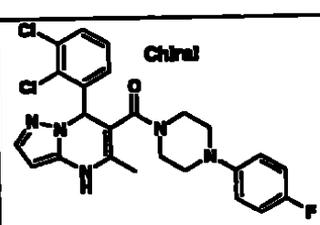
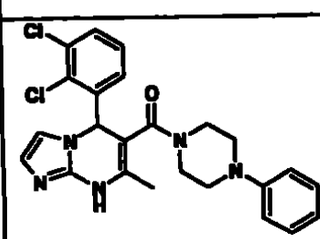
629

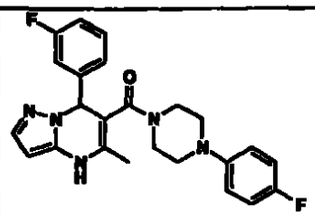
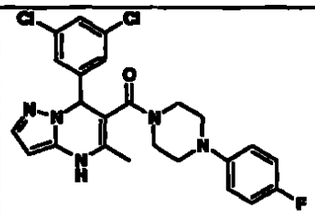
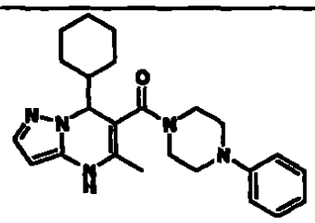
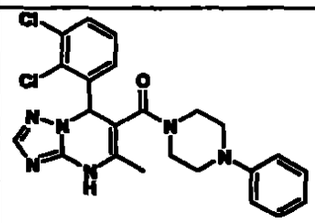
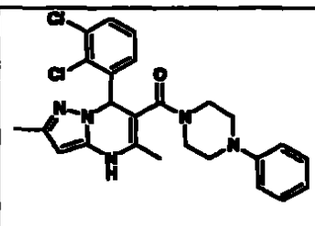
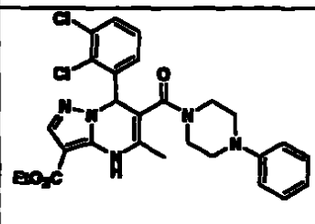
35		7-(4-Chlorophenyl)-4,7-dihydro-5-methyl-N-(phenylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	378
36		4-[[7-(4-Chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]morpholine	358
37		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1 5-a]pyrimidin-6 yl]carbonyl]piperidine	391
38		1-[[7-(2,3-Dichlorophenyl)-4 7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine	391
39		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(3-phenylpropyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	441
40		1-[[5-(3,4-Dichlorophenyl)-5,8-dihydro-7-methyl-imidazo[1,2-a]pyrimidin-6-yl]carbonyl]-4-phenyl-piperazine	468

653
630

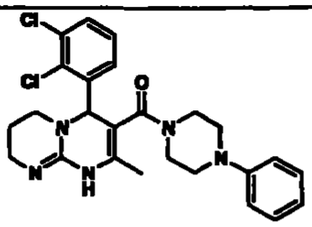
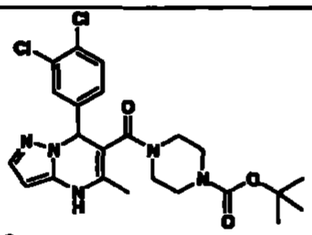
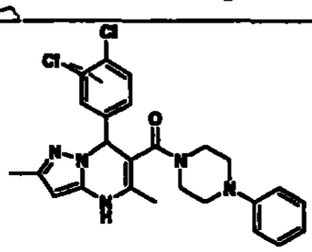
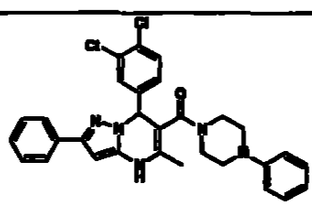
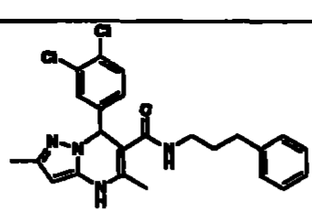
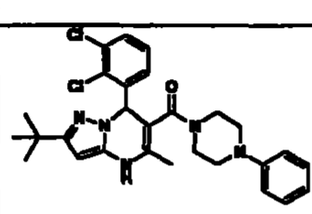
41		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(phenyl methyl)piperidine	481
42		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6 yl]carbonyl]-4-(phenyl-methyl)piperazine	482
43		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N N-dipropylpyrazolo[1,5-a]pyrimidine-6-carboxamide	407
44		1-[[7-(3-Chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	451
45		1-[[7-(3,4-Difluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	453
46		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine	469

47		1 [[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine	486
48		1-(4-Fluorophenyl)-4-[(4,7-dihydro-5-methyl-7-phenylpyrazolo[1,5-a]pyrimidin-6-yl)carbonyl]piperazine	417
49		1-[[7-(3,4-Dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine	484
50		1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine, enantiomer A	486
51		1-[[7-(2,3-Dichlorophenyl)-4 7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine, enantiomer B	486
52		1 [[5-(2,3-Dichlorophenyl)-5,8-dihydro-7-methyl-imidazo[1,2-a]pyrimidin-6-yl]carbonyl]-4-phenyl-piperazine	468

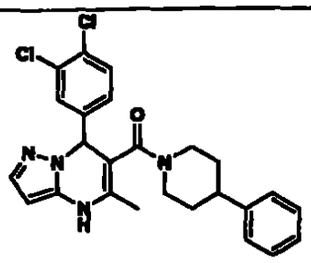
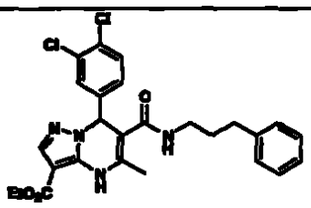
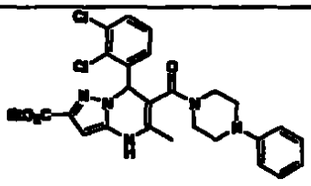
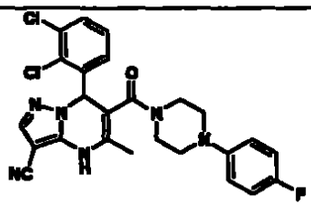
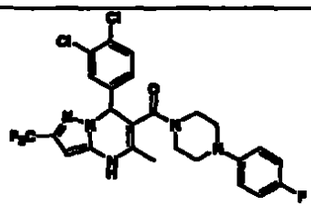
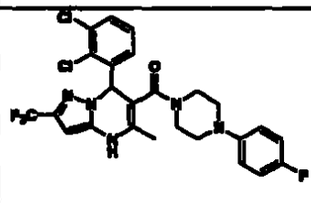
655
632

53		1-(4-Fluorophenyl)-4-[[7-(3-fluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-piperazine	435
54		1 [[7-(3,5-Dichlorophenyl)-4,7 dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine	486
55		1-[(7-Cyclohexyl-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl)carbonyl]-4-phenylpiperazine	405
56		1-[[7-(2,3-Dichlorophenyl)-4,7 dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)carbonyl]-4-phenyl-piperazine	469
57		1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenyl-piperazine	482
58		7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-6-[(4-phenyl-1-piperazinyl)-carbonyl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester	540

656 633

59		1-[[4-(2,3-Dichlorophenyl)-4,6,7,8-tetrahydro-2-methyl-1H-pyrimido[1,2-a]pyrimidin-3-yl]carbonyl]-4-phenyl-piperazine	484
60		4-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl pyrazolo[1 5-a]pyrimidin-6-yl]carbonyl]-1-pipera-zinecarboxylic acid 1 1-dimethylethyl ester	492
61		1-[[7 (3,4-Dichlorophenyl)-4,7-dihydro-2,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine	482
62		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-phenylpyrazolo[1,5 a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine	544
63		7-(3,4-Dichlorophenyl)-4,7-dihydro-2,5-dimethyl-N-(3-phenylpropyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	455
64		1-[[7-(2,3-Dichlorophenyl)-2-(1,1-dimethylethyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine	524

657 634

65		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1 5-a]pyrimidin-6-yl]carbonyl]-4-phenyl-piperidine	467
66		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-6-[[(3-phenylpropyl)amino]carbonyl] pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester	513
67		7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-6-[(4-phenyl-1 piperazinyl)-carbonyl]pyrazolo[1,5-a]pyrimidine-2-carboxylic acid ethyl ester	540
68		1-[[3-Cyano-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	511
69		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	554
70		1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-2 (trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	554

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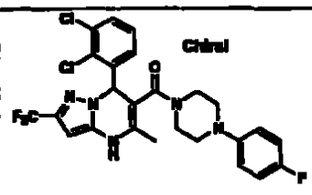
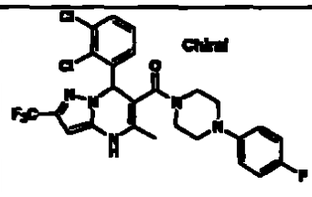
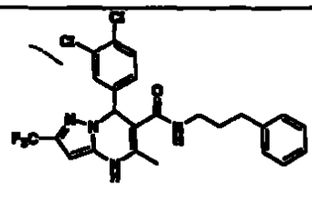
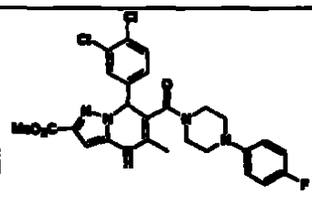
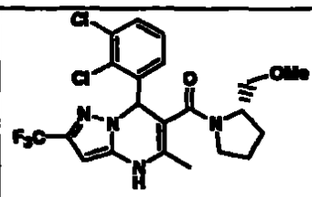
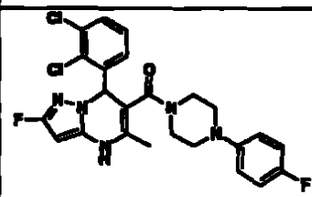
655

71		1-[[7-(2,3-Dichlorophenyl)-4,7dihydro-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer B	554
72		1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2 5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine, enantiomer B	554
73		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(3-phenylpropyl)-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	509
74		7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-pipera-zinyl]carbonyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyri-midine-2-carboxylic acid methyl ester	544
75		(2S)-1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine	489
76		1-[[7-(2,3-Dichlorophenyl)-2-fluoro-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	504

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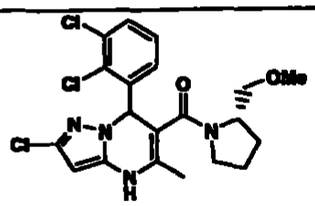
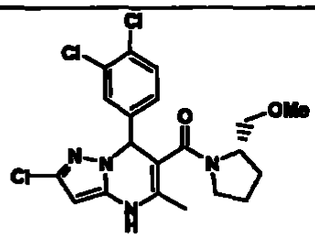
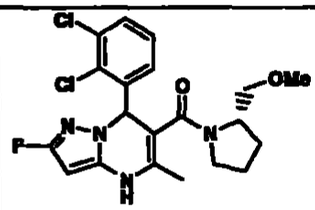
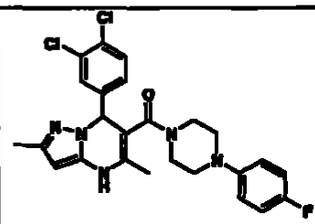
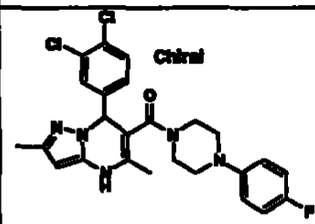
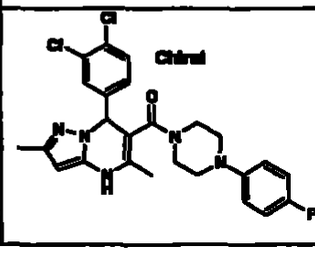
77		(2S)-1-[[2-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrro-lidine	455
78		(2S)-1-[[2-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrroli-dine	455
79		(2S)-1-[[7-(2,3-Dichloro-phenyl)-2-fluoro-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxy-methyl)pyrrolidine	439
80		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-2,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	500
81		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-2,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer A	500
82		1 [[7-(3,4-Dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine enantiomer B	500

637
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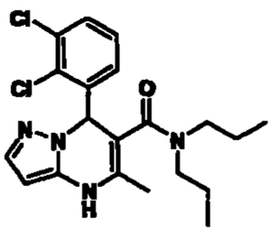
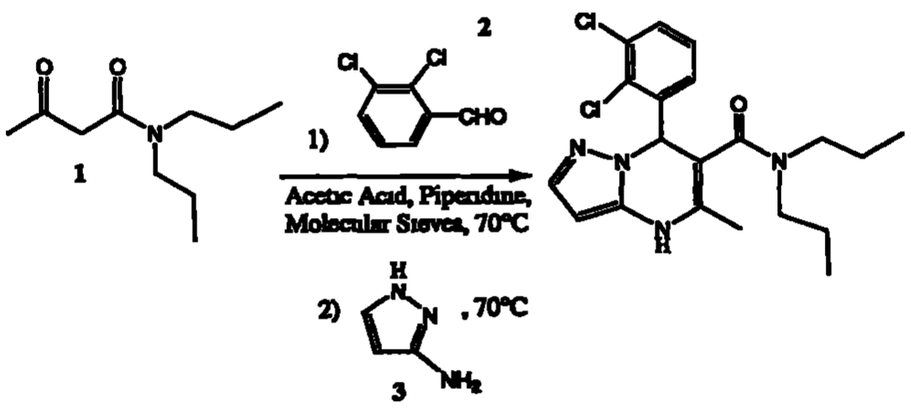
Example 83

7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-N,N-dipropylpyrazolo[1,5-a]pyrimidine-6-carboxamide



Method.



Compound 1 Compound 1 was prepared as described in Example 18, Method 2 Step A1 from t-butoxyacetoacetate and dipropylamine.

Title Compound A mixture of compound 1 (0.2 g, 1.1 mmol), 2,3-dichlorobenzaldehyde 2 (0.23 g, 1.3 mmol), piperidine (0.015 ml, 0.27 mmol), acetic acid (0.027 mL, 0.27 mmol) and 4A Molecular Sieves (spatula tip) in

661
638

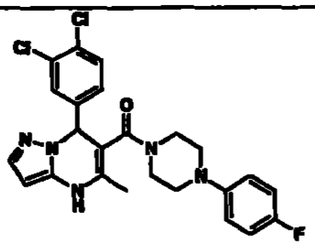
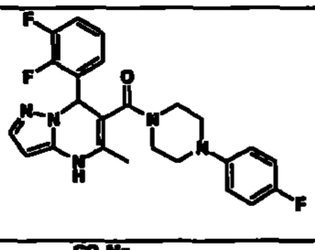
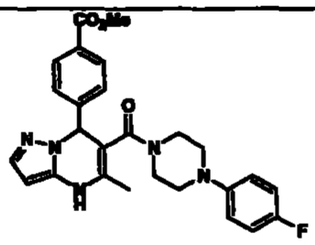
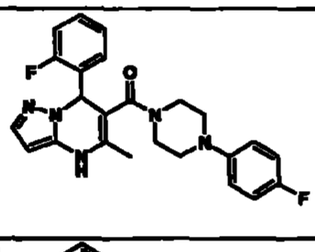
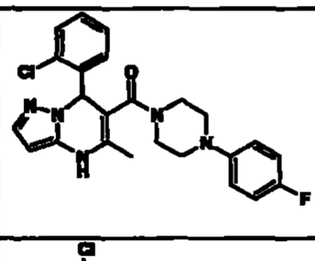
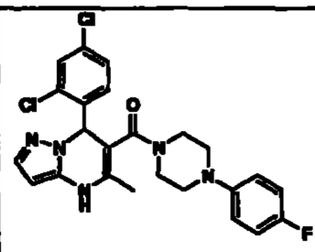
dimethylformamide (1 mL) was stirred at 70 °C overnight. The mixture was cooled to room temperature. 3-aminopyrazole 3 (0 13 g, 1 6 mmol) and sodium acetate (0 28 g, 3.5 mmol) were added and the mixture was stirred overnight at 70 °C The mixture was cooled to room temperature, transferred to a separatory funnel, diluted with water and ethyl acetate, washed with water (a small amount of methanol was added to breakup emulsions that formed) and brine, dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified by silica gel chromatography (50% ethyl acetate/hexanes followed by 100% ethyl acetate) to afford 0.10 g (23% yield from compound 1) of the title compound. Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 40-100% Solvent B/A (Solvent A. 10% MeOH/H20 with 0.1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min Rt = 2.94 min, (96% pure) MS (M+H 407)

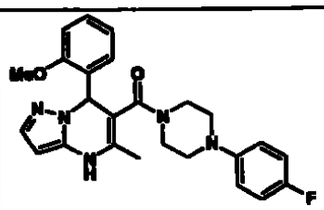
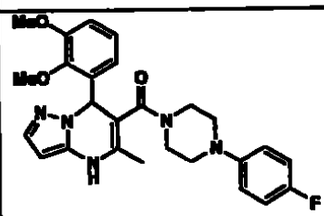
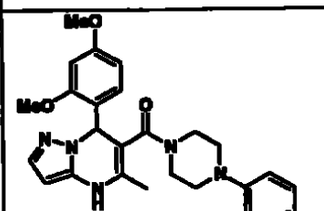
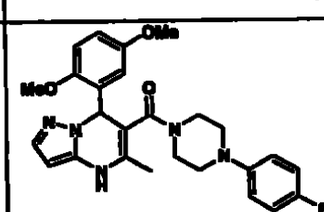
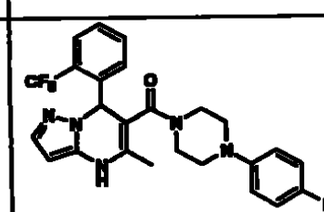
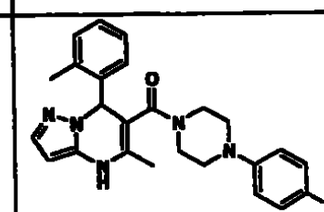
Examples 84-169

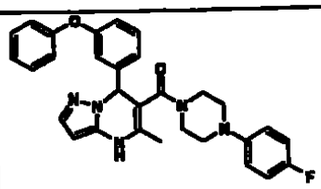
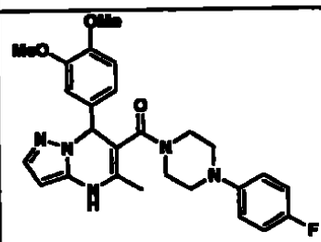
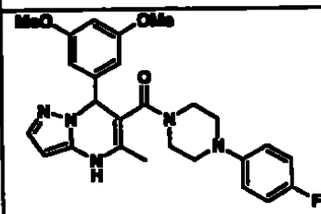
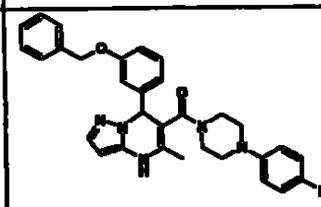
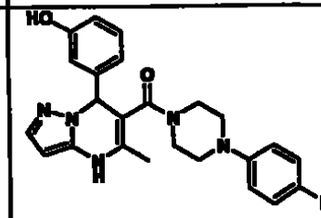
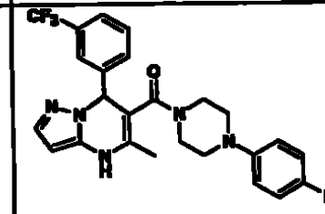
The compounds of Examples 84-169, shown in the table provided below, were prepared in a manner similar to that described in Example 83

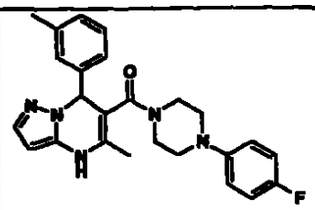
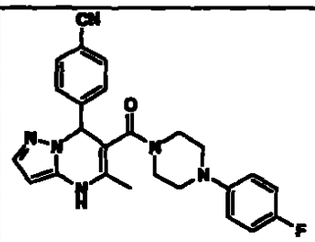
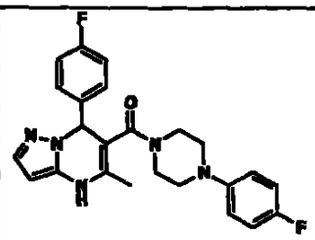
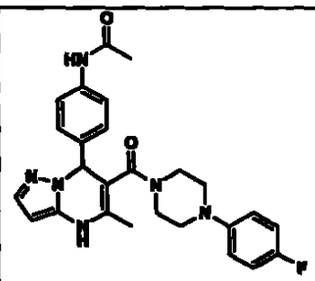
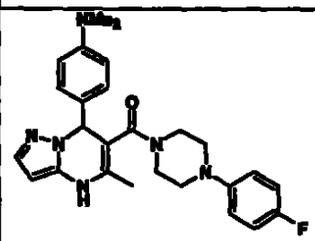
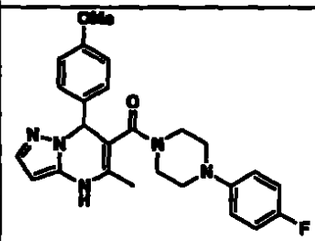
HPLC resolution of Example 84, Chiralpak AS column (50 X 500 mm), eluting with 30% isopropanol/hexanes containing 0 1 % triethylamine at 50 mL/min), UV detection at 254 λ, provided enantiomers A (Example 166) and B (Example 167) Chiralpak AS column (4 6 X 250 mm) eluting with 40% isopropanol/hexanes containing 0 1 % triethylamine at 1 mL/min), UV detection at 254 λ, enantiomer A Rt = 5.53 min, >99% ee. Enantiomer B Rt = 12.0 min, 98% ee.

HPLC resolution of Example 165, Chiralpak AD column (50 X 500 mm), eluting with 20% isopropanol/hexanes containing 0 1 % triethylamine at 50 mL/min), UV detection at 254 λ provided enantiomers A (Example 169) and B (Example 168). Chiralpak AD column (4 6 X 250 mm) eluting with 20% isopropanol/hexanes containing 0 1 % triethylamine at 1 mL/min), UV detection at 254 λ, enantiomer A Rt = 8 3 min, >99% ee. Enantiomer B Rt = 12.8 min, 98% ee.

Example	Structure	Name	(M+H)
84		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	486
85		1-[[7-(2,3-Difluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	453
86		4-[6-[[4-(4-Fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-7-yl]benzoic acid methyl ester	475
87		1-(4-Fluorophenyl)-4-[[7-(2-fluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-piperazine	435
88		1-[[7-(2-Chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	451
89		1-[[7-(2,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine	486

90		1-[[4,7 Dihydro-7-(2-methoxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4 fluorophenyl)piperazine	447
91		1 [[7-(2,3-Dimethoxyphenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine	477
92		1-[[7-(2,4-Dimethoxyphenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine	477
93		1 [[7 (2,5-Dimethoxyphenyl)-4 7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine	477
94		1-[[4,7-Dihydro-5-methyl-7-[2-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	485
95		1 [[4,7-Dihydro-5-methyl-7-(2-methylphenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	431

96		1-[[4,7-Dihydro-5-methyl-7-(3-phenoxyphenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	509
97		1-[[7-(3,4-Dimethoxyphenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine	477
98		1-[[7-(3,5-Dimethoxyphenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine	477
99		1-[[4,7-Dihydro-5-methyl-7-[3-(phenylmethoxy)phenyl]pyrazolo[1 5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine	523
100		1 [[4,7-Dihydro-7-(3-hydroxyphenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine	433
101		1-[[4,7-Dihydro-5-methyl-7-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine	485

102		1-[[4 7-Dihydro-5-methyl 7-(3-methylphenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	431
103		1-[[7-(4-Cyanophenyl)-4 7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	442
104		1-(4-Fluorophenyl)-4-[[7-(4-fluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-piperazine	435
105		N-[4-[6-[[4-(4-Fluorophenyl)-1 piperazinyl]carbonyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl]acetamide	474
106		1 [[7-[4-(Dimethyl-amino)phenyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyri-midin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	460
107		1-[[4,7-Dihydro-7-(4-methoxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	447

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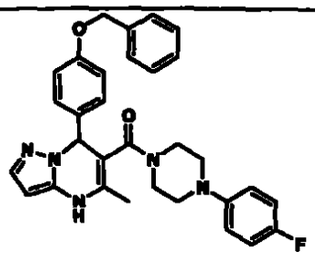
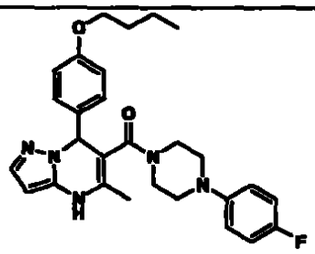
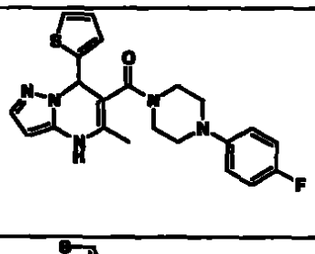
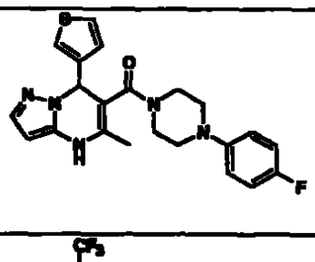
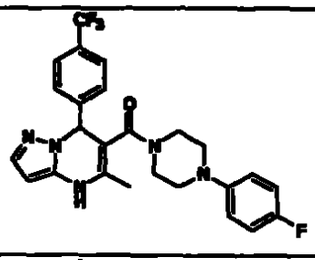
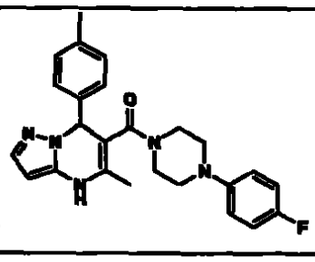
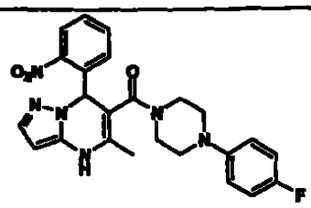
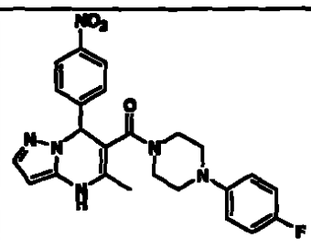
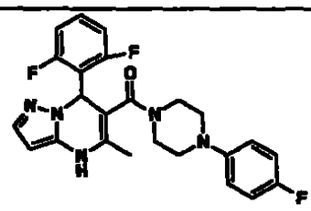
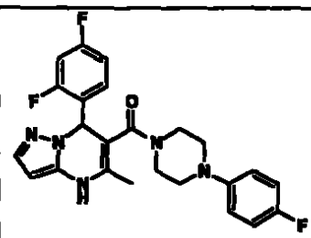
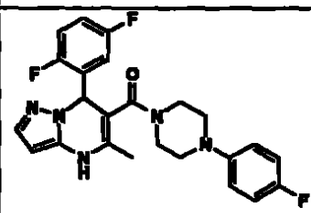
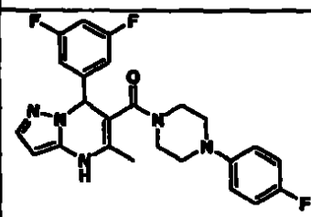
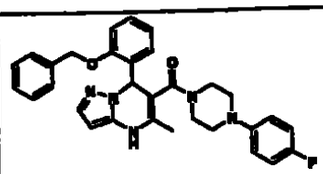
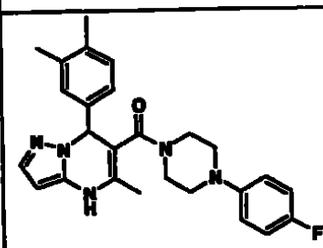
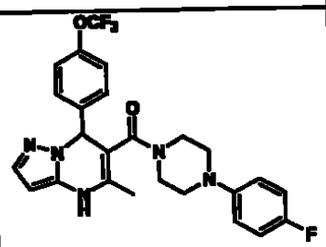
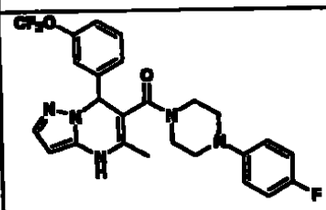
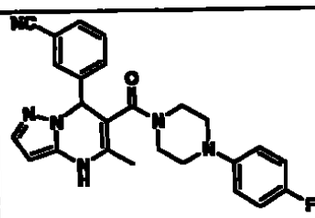
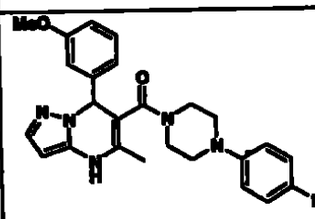
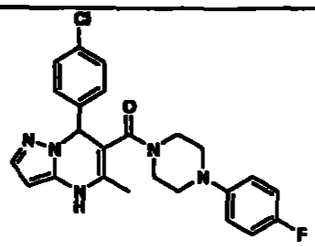
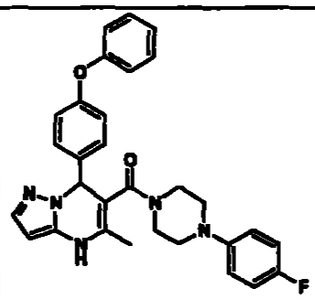
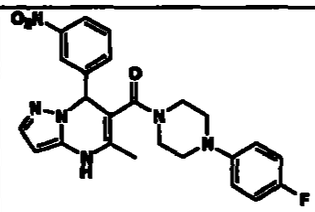
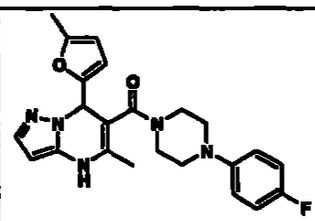
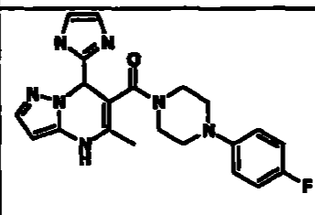
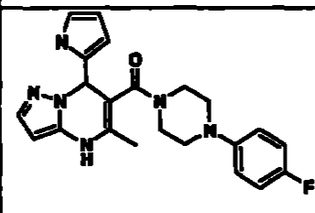
108		1-[[4,7-Dihydro-5-methyl-7-[4-(phenylmethoxy)phenyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	523
109		1 [[7-(4-Butoxyphenyl)-4 7 dihydro-5-methylpyrazolo[1 5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	489
110		1-[[4,7 Dihydro-5-methyl-7-(2-thienyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	423
111		1-[[4,7 Dihydro-5-methyl-7-(3-thienyl)pyrazolo[1 5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	423
112		1-[[4,7-Dihydro-5-methyl-7-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	485
113		1-[[4,7-Dihydro-5-methyl-7-(4-methylphenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	431

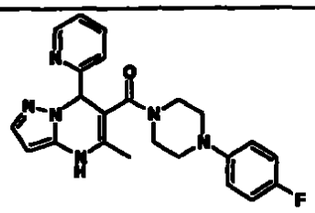
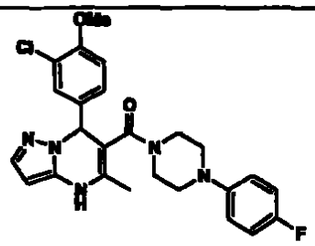
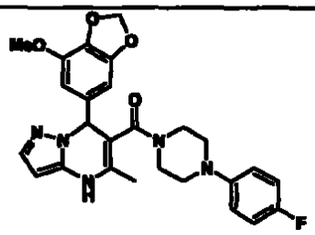
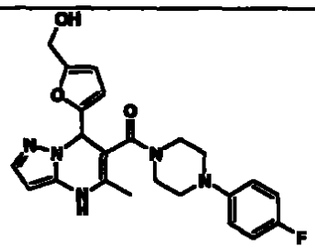
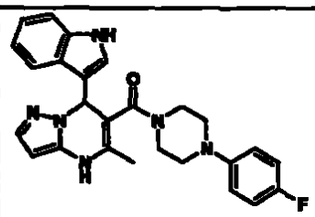
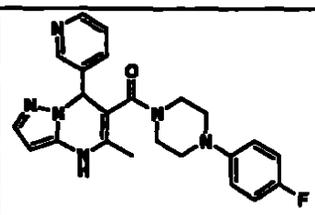
114		1-[[4,7 Dihydro-5-methyl-7-(2-nitrophenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	462
115		1-[[4,7-Dihydro-5-methyl-7-(4-nitrophenyl)pyrazolo[1 5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	462
116		1-[[7-(2,6-Difluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	453
117		1-[[7-(2,4-Difluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	453
118		1-[[7-(2,5-Difluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	453
119		1-[[7-(3,5-Difluorophenyl)-4,7 dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	453

668
645

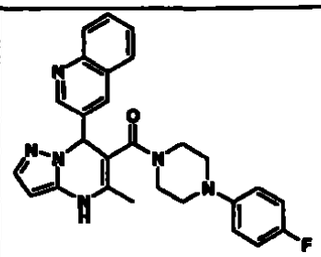
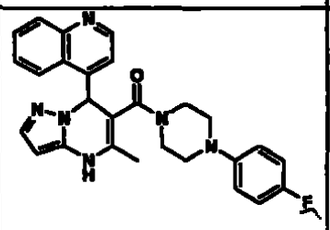
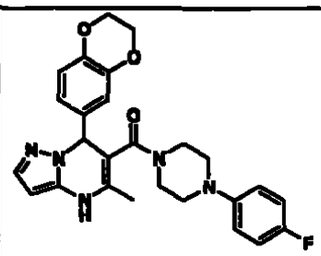
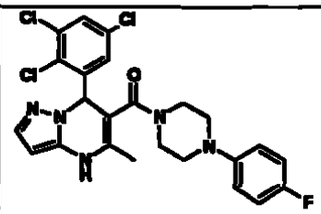
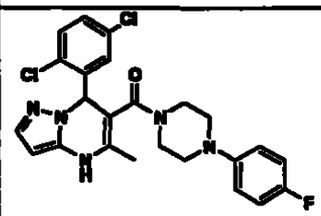
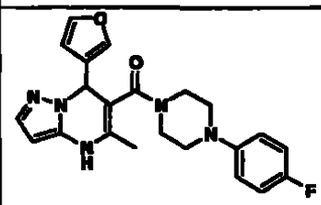
120		1-[[4,7-Dihydro-5-methyl-7-[2-(phenylmethoxy)phenyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	523
121		1-[[7-(3,4-Dimethylphenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	445
122		1-[[4,7-Dihydro-5-methyl-7-[4-(trifluoromethoxy)phenyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	501
123		1-[[4,7-Dihydro-5-methyl-7-[3-(trifluoromethoxy)phenyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	501
124		1-[[7-(3-Cyanophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	442
125		1-[[4,7-Dihydro-7-(3-methoxyphenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	447

669
646

126		1-[[7-(4-Chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	451
127		1-[[4 7 Dihydro-5-methyl-7-(4-phenoxyphenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	509
128		1 [[4,7-Dihydro-5-methyl-7-(3-nitrophenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	462
129		1-[[4,7 Dihydro-5-methyl-7-(5-methyl-2-furanyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	421
130		1-[[4,7-Dihydro-7-(1H-imidazol-2-yl)-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	407
131		1-[[4,7-Dihydro-5-methyl-7-(1H-pyrrol-2-yl)pyrazolo[1 5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	406

132		1-[[4,7-Dihydro-5-methyl-7-(2-pyridinyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	418
133		1-[[7-(3-Chloro-4-methoxy-phenyl)-4,7-dihydro-5-methylpyrazolo[1 5-a]pyri-midin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	481
134		1-[[4,7 Dihydro-7-(4-methoxy-1,3-benzodioxol-6-yl)-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	491
135		1-[[4 7-Dihydro-7-[5-(hydroxymethyl)-2-furanyl]-5 methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	437
136		1-[[4,7-Dihydro-7-(1H-indol-3-yl)-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	456
137		1-[[4,7-Dihydro-5-methyl-7-(3-pyridinyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	418

671 649

138		1-[[4 7-Dihydro-5-methyl-7-(3-quinolinyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	468
139		1 [[4 7 Dihydro-5-methyl-7-(4-quinolinyl)pyrazolo[1 5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	468
140		1-[[7-(2,3-Dihydro-1,4-benzodioxin-6-yl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	475
141		1-[[4,7 Dihydro-5-methyl-7-(2,3,5-trichloro-phenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	520
142		1 [[7-(2,5-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	486
143		1-(4-Fluorophenyl)-4-[[7-(3-furanyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl] piperazine	407

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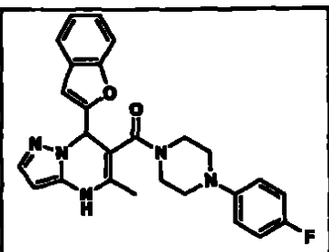
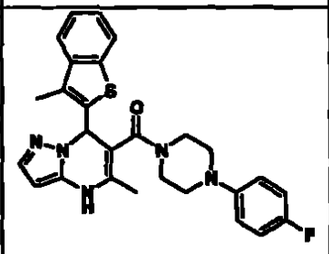
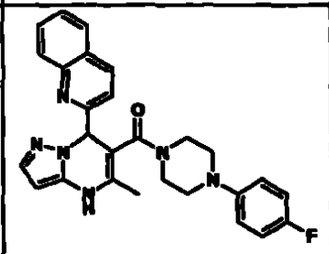
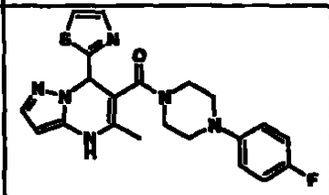
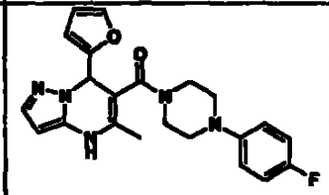
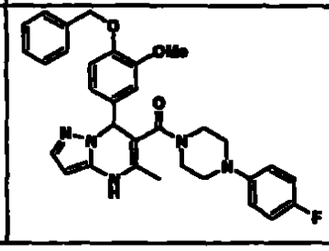
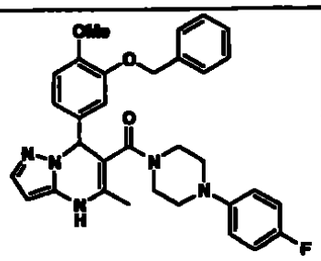
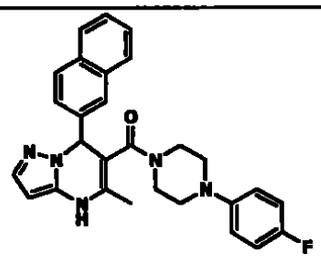
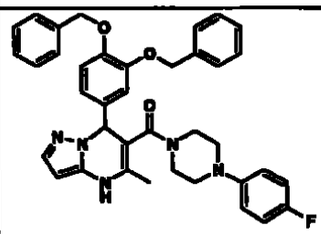
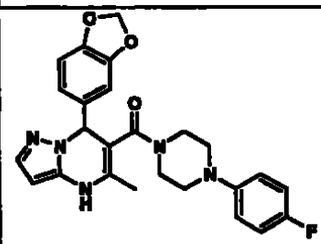
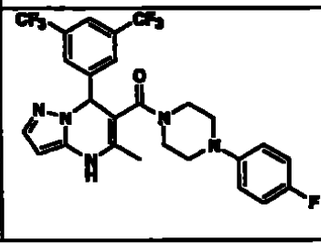
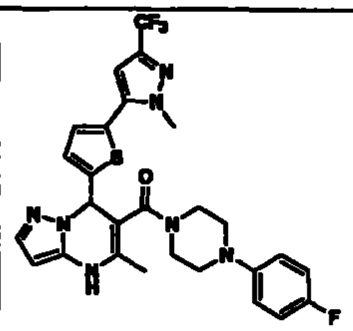
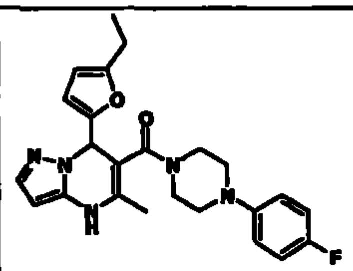
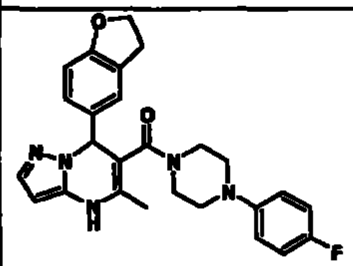
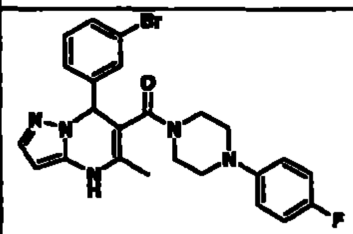
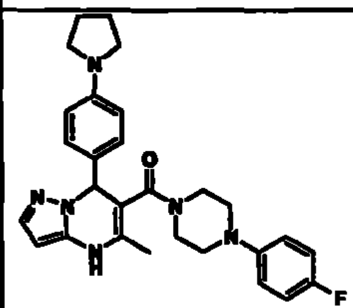
649

144		1-[[7-(2-Benzofuranyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	457
145		1-[[4,7-Dihydro-5-methyl-7-(3-methylbenzo[b]thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	487
146		1-[[4,7-Dihydro-5-methyl-7-(2-quinolinyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	468
147		1 [[4,7-Dihydro-5-methyl-7-(2-thiazolyl)pyrazolo[1 5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	424
148		1-(4-Fluorophenyl)-4-[[7-(2-furanyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-piperazine	407
149		1-[[4 7-Dihydro-7-[3-methoxy-4-(phenylmethoxy)phenyl]-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	553

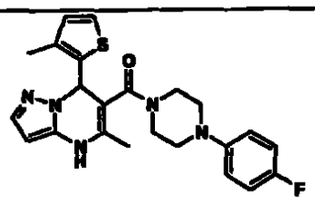
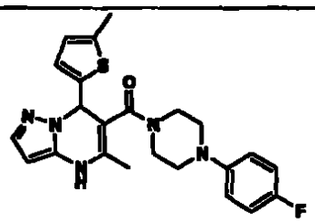
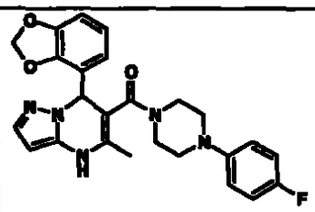
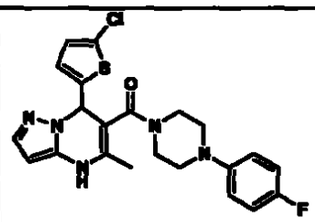
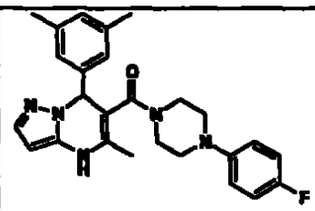
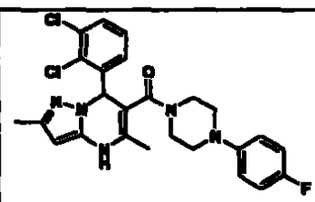
623 850

150		1-[[4,7-Dihydro-7-[4-methoxy-3-(phenylmethoxy)phenyl]-5-methylpyrazolo[1 5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	553
151		1-[[4 7-Dihydro-5-methyl-7-(2-naphthalenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	467
152		1-[[7 [3,4-Bis(phenyl-methoxy)phenyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	629
153		1-[[7-(1,3-Benzodioxol-5-yl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine	461
154		1-[[7-[3,5-Bis(trifluoro-methyl)phenyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyri-midin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	553

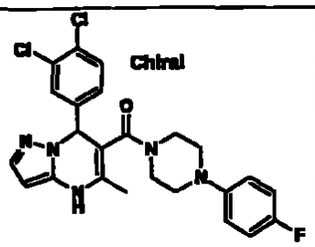
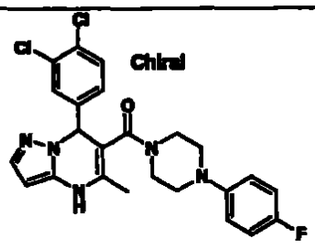
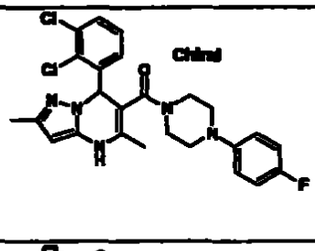
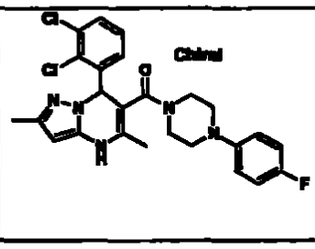
674
857

155		1-[[4,7-Dihydro-5-methyl-7-[5-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]-2-thienyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	571
156		1 [[7-(5-Ethyl-2-furanyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	435
157		1-[[7-(2,3-Dihydro-5-benzofuranyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimdin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	459
158		1-[[7-(3-Bromophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	496
159		1-[[4,7-Dihydro-5-methyl-7-[4-(1-pyrrolidinyl)-phenyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	486

675
652

160		1-[[4,7-Dihydro-5-methyl-7-(3-methyl 2-thienyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	437
161		1-[[4,7-Dihydro-5-methyl-7-(5-methyl-2-thienyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	437
162		1 [[7-(1,3-Benzodioxol-4-yl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	461
163		1-[[7-(5-Chloro-2-thienyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	457
164		1-[[7-(3,5-Dimethylphenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine	445
165		1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2 5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	500

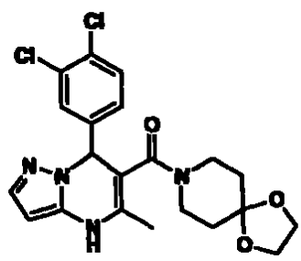
676
653

166		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine, enantiomer A	486
167		1-[[7-(3 4-Dichlorophenyl)-4 7 dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine enantiomer B	486
168		1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine, enantiomer B	500
169		1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine, enantiomer A	500

Example 170

8-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,4-dioxa-8-azaspiro[4 5]decane

5



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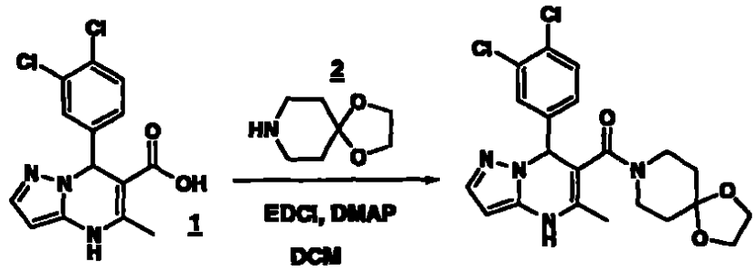
654

Method.



Compound 1 Compound 1 was prepared as described in Example 16

Title Compound. Compound 2 (0 068 g, 0 47 mmol) was added to a suspension of compound 1 (0 10 g, 0 32 mmol), EDCI (0 09 g, 0 47 mmol), DMAP(0 004g, 0.03 mmol) in dichloromethane (1 mL) When LC/MS indicated the reaction was complete the mixture was loaded directly onto a Worldwide Monitoring CLEAN-UP CARTRIDGE (silica gel, CUSIL12M6) which had been equilibrated with 100% hexanes. Elution with 100% hexanes (40 mL), followed by 50% Ethyl acetate/hexanes (40 mL) and 100% ethyl acetate (70 mL) The purest fractions (TLC analysis) were combined to give 0.043 g (30% yield) of the title compound as a white solid. Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 40-100% Solvent B/A (Solvent A. 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min. Rt = 2.12 min, (97% pure) MS (M+H. 449). HMR (DMSO-d_6, 400 MHz, 100 ^{0}C) 9 02(1H, bs), 7.49(1H, d, J= 8Hz), 7 26(1H, d, J=2 Hz), 7 14(1H, d, J=2 Hz), 6 95(1H, d, J=8 Hz), 6.08(1H, s), 5.55(1H, d, J=2 Hz), 3 84(4H, m) 3.55(2H,m), 3 20(2H, m), 1 86(3H, s), 1.37(2H, m), 1 26(2H, m)

Examples 171-377

The compounds of Examples 171-377, shown in the table provided below, were prepared in a manner similar to that described in Example 170

HPLC resolution of Example 194, Chiralpak AD column (50 X 500 mm), eluting with 30% isopropanol/hexanes containing 0 1 % triethylamine at 50 mL/min), UV detection at 254 λ, provided enantiomers A (Example 250)and B (Example 251). Chiralpak AD column (4 6 X 250 mm) eluting with 30% isopropanol/hexanes containing 0 1 % triethylamine at 1 mL/min), UV detection at 254 λ, enantiomer A Rt = 5 32 min, 99% ee. Enantiomer B Rt = 8.59 min, 98% ee.

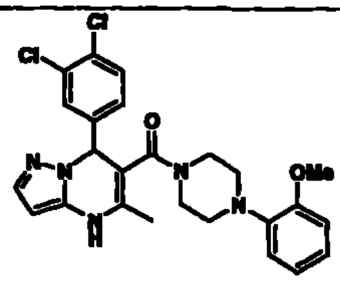
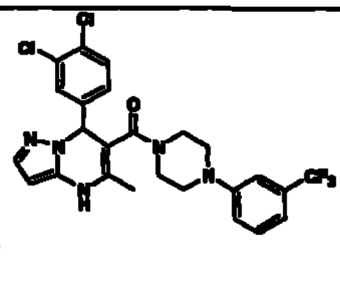
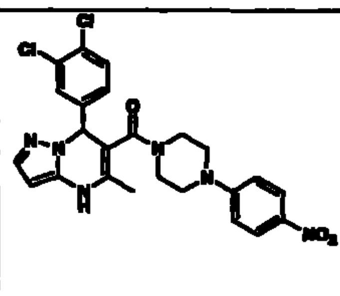
HPLC resolution of Example 221, Chiralpak AS column (50 X 500 mm), eluting with 50% isopropanol/hexanes containing 0 1 % triethylamine at 42 mL/min), UV detection at 254 λ provided enantiomers A (Example 328) and B (Example 329). Chiralpak AS column (4 6 X 250 mm) eluting with 30% isopropanol/hexanes containing 0 1 % triethylamine amine at 1 mL/min), UV detection at 254 λ, enantiomer A Rt = 5 12 min, >99% ee. Enantiomer B Rt = 8 70 min, >99% ee.

HPLC resolution of Example 288, Chiralpak AD column (50 X 500 mm), eluting with 30% isopropanol/hexanes containing 0 1 % triethylamine at 50 mL/min), UV detection at 254 λ provided enantiomers A (Example 376) and B (Example 377) Chiralpak AD column (4 6 X 250 mm) eluting with 30% isopropanol/hexanes containing 0 1 % triethylamine at 1 mL/min), UV detection at 254 λ, enantiomer A Rt = 3 8 min, >99% ee. Enantiomer B Rt = 5 6 min, >99% ee.

HPLC resolution of Example 333, Chiralpak AD column (50 X 500 mm), eluting with 40% isopropanol/hexanes containing 0 1 % triethylamine at 50 mL/min), UV detection at 254 λ, provided enantiomers A (Example 364) and B (Example 365). Chiralpak AD column (4.6 X 250 mm) eluting with 40% isopropanol/hexanes containing 0 1 % triethylamine at 1 mL/min), UV detection at 254 λ, enantiomer A Rt = 4.92 min, >99% ee. Enantiomer B Rt = 8 0 min, >97% ee.

The compound of Example 360 was separated into pure diastereo-isomers by column chromatography (silica gel eluted with 75% ethyl acetate, hexane) The faster eluting isomer is diastereomer 1, the slower eluting isomer is diasteromer 2. When separated by TLC (20% acetone, dichloromethane), diasteriomer 1 has an R_f of 0 26 and diastereromer 2 has an R_f of 0 17 Diastereomer 2 was further separated into pure chiral form via preparative chiral HPLC (Chiralpak AD 5 cm x 50 cm column eluted with 13% ethanol in hexane with 0 1% TEA at 50 mL/min with UV detection at 254 nM) The faster eluting isomer is enantiomer A (HPLC retention time 8 1 min,

4.6x250mm Chiralpak AD column eluted with 10% ethanol, hexane with 0 1% triethylamine at 2 mL/min with UV detection at 254 nm) and the slower eluting isomer is enantiomer B (HPLC retention time 10 6 min, 4 6x250mm Chiralpak AD column eluted with 10% ethanol, hexane with 0 1% triethylamine at 2 mL/min with UV detection at 254nm) Diastereomer 1 can also be further separated into chiral pure form by similar methodology as that descibed for diastereomer 2 above to form enantiomers C and D

Example	Structure	Name	(M+H)
171		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(2-methoxy-phenyl)piperazine	498
172		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]-pyrimidin-6-yl]carbonyl]-4-[3-(trifluoromethyl)-phenyl]piperazine	536
173		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-nitrophenyl)piperazine	513

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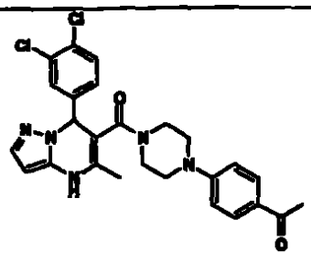
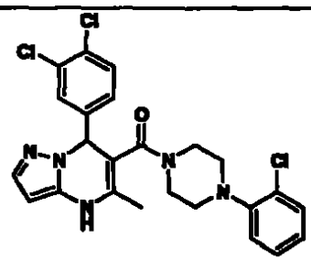
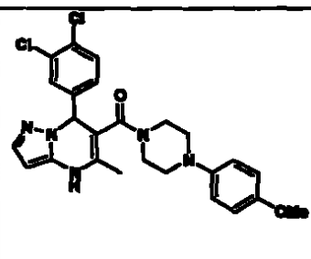
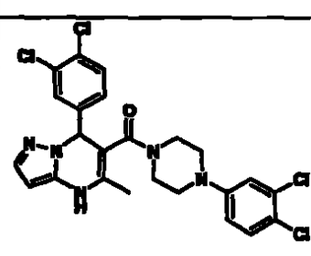
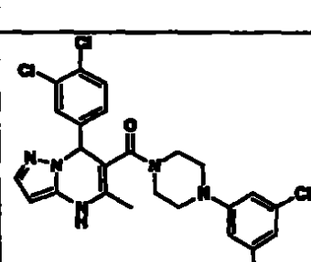
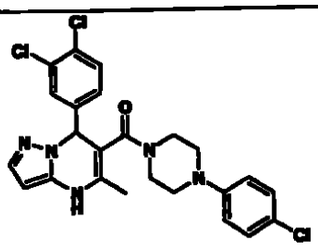
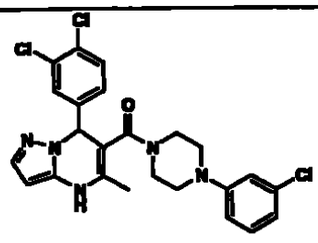
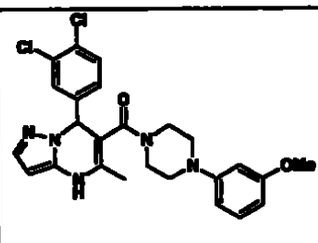
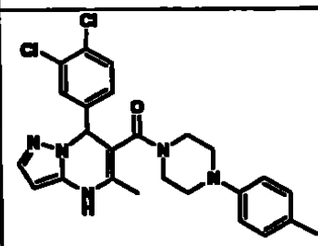
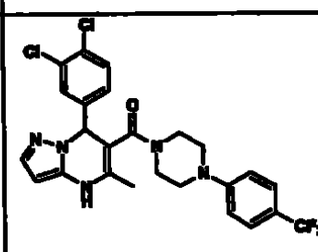
174		1-(4-Acetylphenyl)-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine	510
175		1-(2-Chlorophenyl)-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine	502
176		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]-carbonyl]-4-(4-methoxy-phenyl)piperazine	498
177		1-(3,4-Dichlorophenyl)-4-[[7-(3,4-dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]-carbonyl]piperazine	537
178		1-(3,5-Dichlorophenyl)-4-[[7-(3,4-dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]-carbonyl]piperazine	537

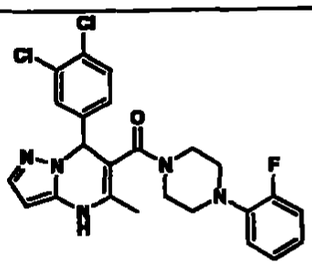
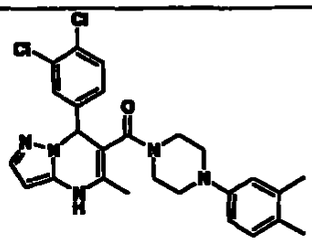
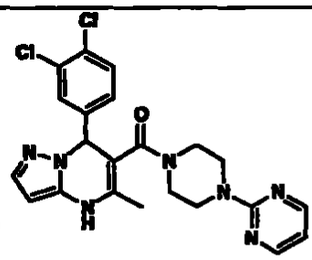
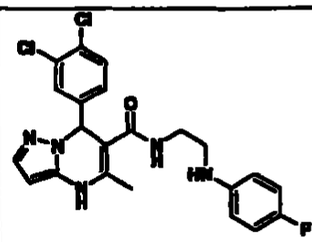
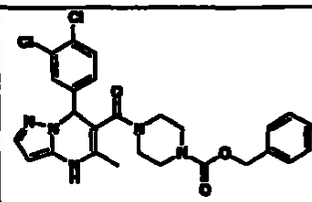
681

658

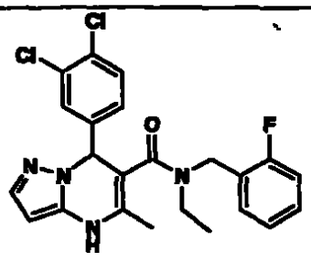
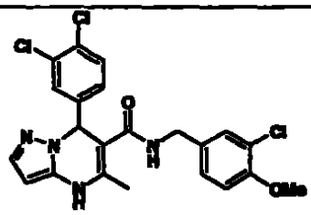
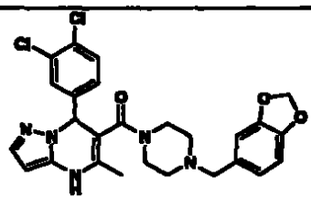
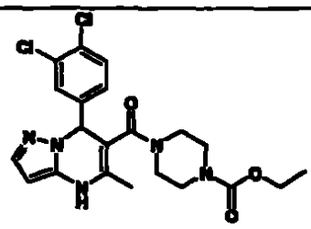
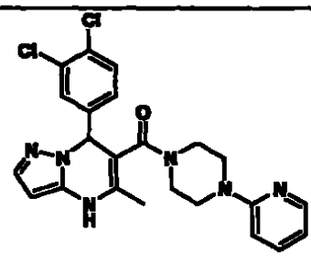
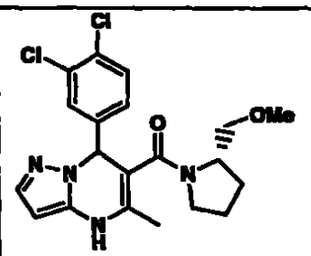
179		1-(4-Chlorophenyl)-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine	502
180		1-(3-Chlorophenyl)-4-[[7-(3,4-dichlorophenyl)-4 7-dihydro-5-methylpyra-zolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine	502
181		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-(3-methoxy-phenyl)piperazine	498
182		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-(4-methyl-phenyl)piperazine	482
183		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5a]-pyrimidin-6-yl]car-bonyl]-4-[4-(trifluoromethyl)-phenyl]piperazine	536

682

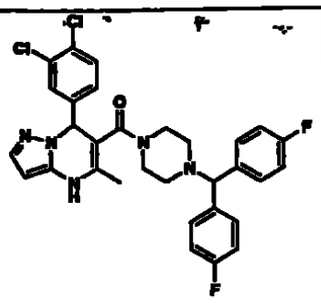
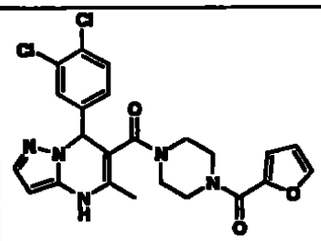
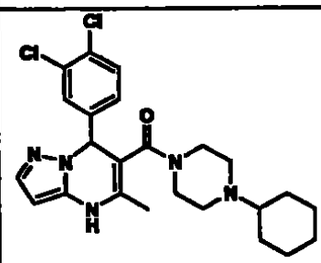
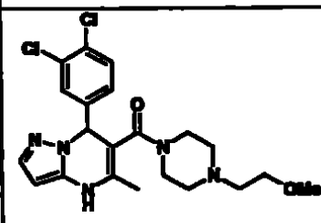
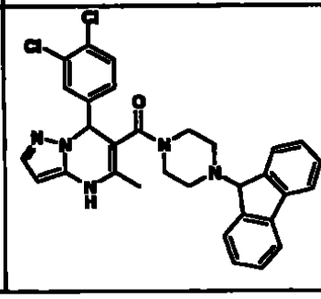
859

184		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(2-fluoro-phenyl)piperazine	486
185		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(3,4-dimethyl-phenyl)piperazine	496
186		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(2-pyrimidinyl)piperazine	470
187		7-(3,4-Dichlorophenyl)-N-[2-[(4-fluoro-phenyl)amino]ethyl]-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyri-midine-6-carboxamide	460
188		4-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1-piperazinecarboxylic acid phenylmethyl ester	526

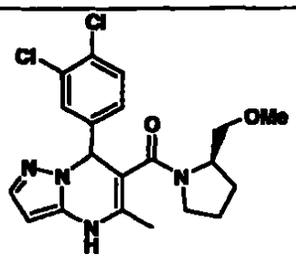
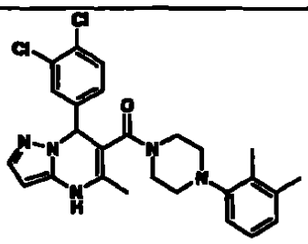
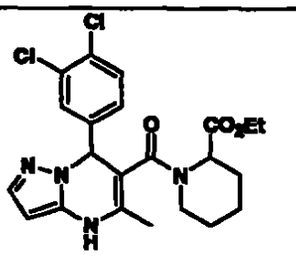
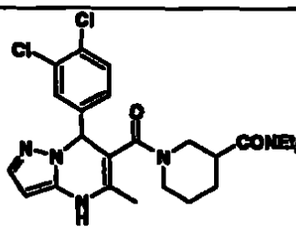
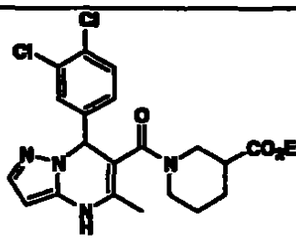
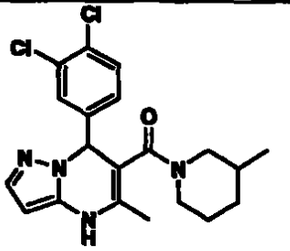
683
660

189		7-(3,4-Dichlorophenyl)-N-ethyl-N-[(2-fluorophenyl)methyl]-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide	459
190		N-[(3-Chloro-4-methoxyphenyl)methyl]-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide	477
191		1-(1,3-Benzodioxol-5-ylmethyl)-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine	526
192		4-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1-piperazinecarboxylic acid ethyl ester	464
193		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(2-pyridinyl)piperazine	469
194		(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine	421

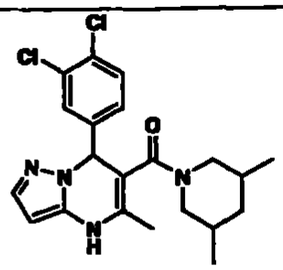
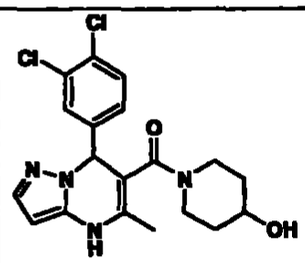
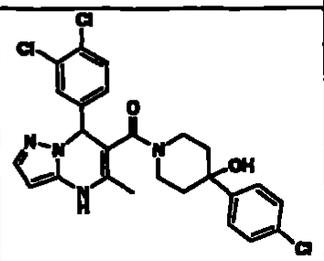
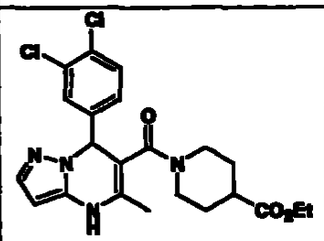
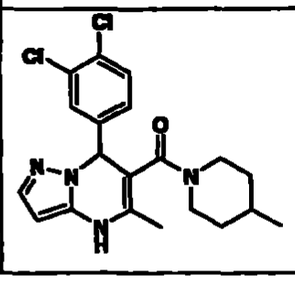
684
661

195		1-[Bis(4-fluorophenyl)-methyl]-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine	594
196		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-(2-furanyl-carbonyl)piperazine	486
197		1-Cyclohexyl-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine	474
198		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(2-methoxyethyl)piperazine	450
199		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(9H-fluoren-9-yl)piperazine	556

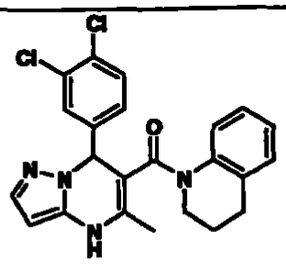
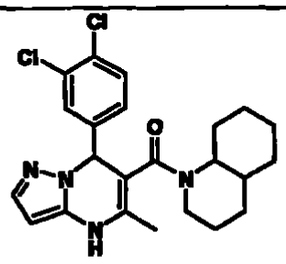
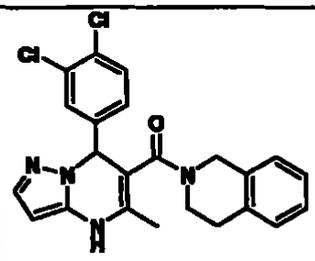
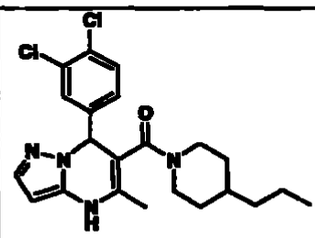
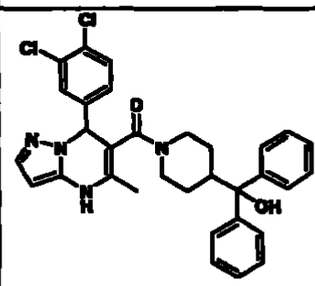
685
667

200		(2R)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine	421
201		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(2,3-dimethylphenyl)piperazine	496
202		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-piperidinecarboxylic acid ethyl ester	463
203		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-N,N-diethyl-3-piperidinecarboxamide	490
204		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-piperidinecarboxylic acid ethyl ester	463
205		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-methylpiperidine	405

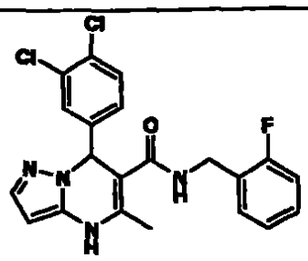
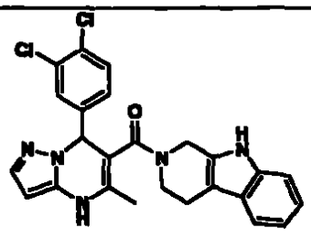
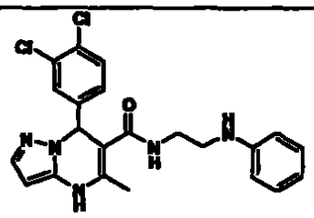
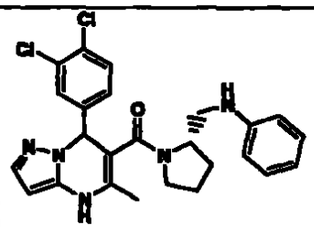
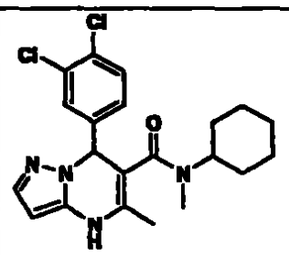
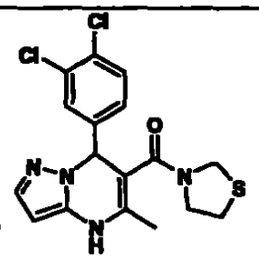
686 663

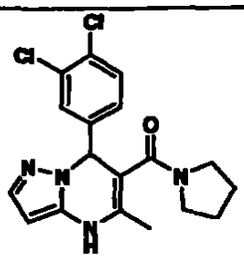
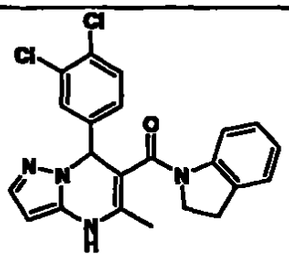
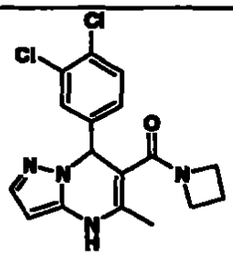
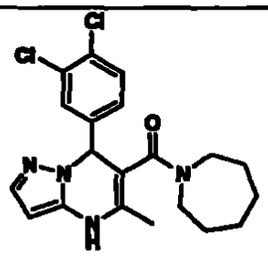
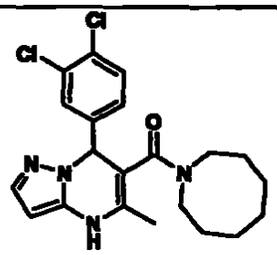
206		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3,5-dimethylpiperidine	419
207		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-hydroxypiperidine	407
208		4-(4-Chlorophenyl)-1-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-hydroxypiperidine	517
209		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-piperidinecarboxylic acid ethyl ester	463
210		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-methylpiperidine	405

687
667

211		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,4-tetrahydroquinoline	439
212		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]-pyrimidin-6-yl]carbonyl]-decahydroquinoline	445
213		2-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,4-tetrahydroisoquinoline	439
214		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-propylpiperidine	433
215		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(hydroxydiphenylmethyl) pipendine	573

688
665

216		7-(3,4-Dichlorophenyl)-N-[(2-fluoro-phenyl)methyl]-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide	431
217		2-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole	478
218		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-[2-(phenylamino)-ethyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	442
219		(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-[(phenyl-amino)methyl]pyrrolidine	482
220		N-Cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydro-N,5-dimethyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide	419
221		3-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]thiazole	395

222		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]pyrrolidine	377
223		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3,4-dihydro-1H-indole	425
224		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]azetidine	363
225		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]hexahydro-1H-azepine	405
226		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]octahydroazocine	419

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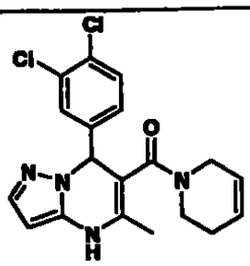
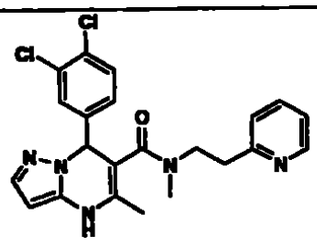
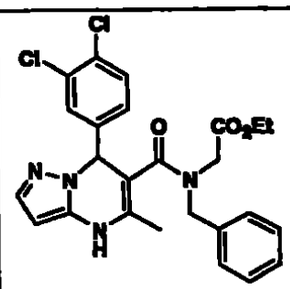
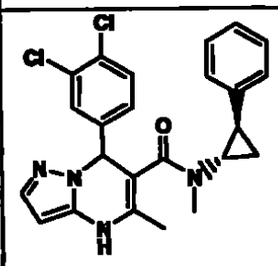
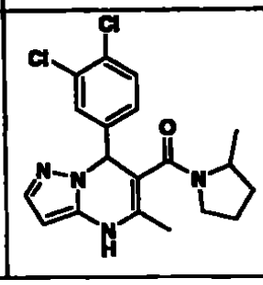
667

227		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,6-tetrahydropyridine	389
228		7-(3,4-Dichlorophenyl)-4,7dihydro-N,5-dimethyl-N-[2-(2-pyridinyl)-ethyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	442
229		N-[[7-(3,4-Dichlorophenyl)-4,7dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-N-(phenylmethyl)glycine ethyl ester	499
230		trans-7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(2-phenylcyclopropyl)pyrazolo[1,5-a]pyrimidine-6-carboxamde	439
231		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-methylpyrrolidine	391

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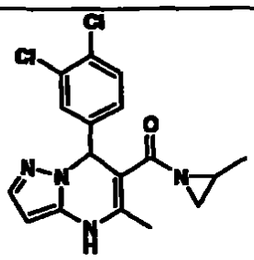
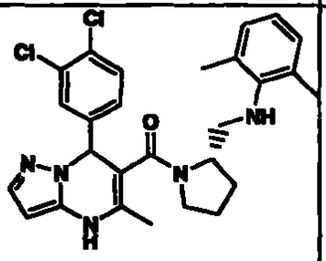
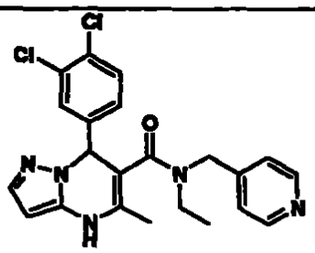
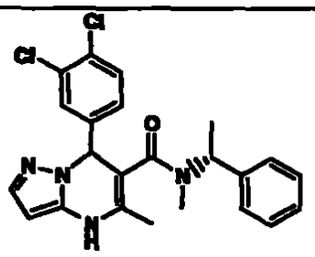
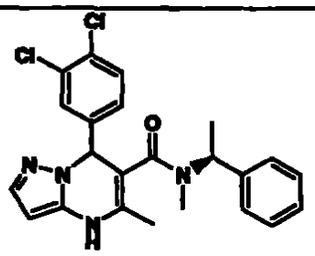
668

232		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-methylaziridine	363
233		(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-[[(2,6-dimethylphenyl)amino]methyl]pyrrolidine	510
234		7-(3,4-Dichlorophenyl)-N-ethyl-4,7-dihydro-5-methyl-N-(4-pyridinylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	442
235		7-(3,4-Dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-[(1R)-1-phenylethyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	441
236		7-(3,4-Dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-[(1S)-1-phenylethyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide	441

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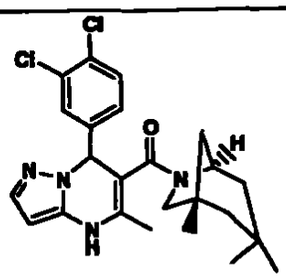
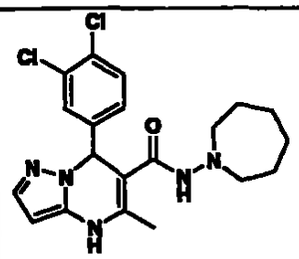
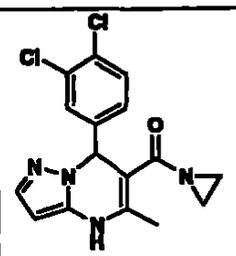
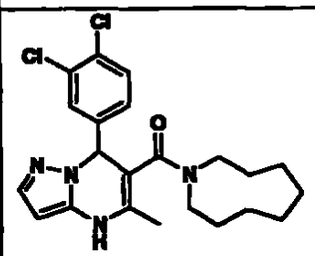
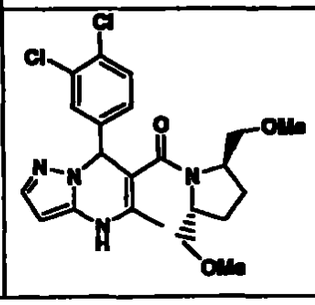
669

237		6-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,3,3-trimethyl-6-azabicyclo[3.2.1]octane	459
238		7-(3,4-Dichlorophenyl)-N-(hexahydro-1H-azepin-1-yl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	420
239		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]azindine	349
240		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]octahydro-1H-azonine	433
241		(2R-trans)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,5-bis(methoxymethyl)-pyrrolidine	465

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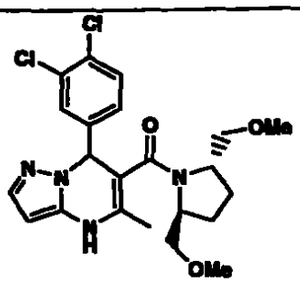
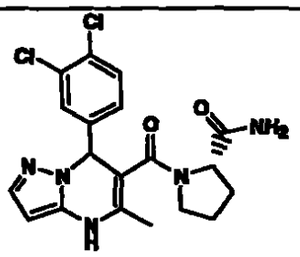
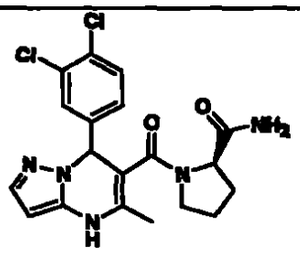
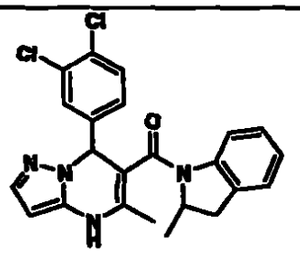
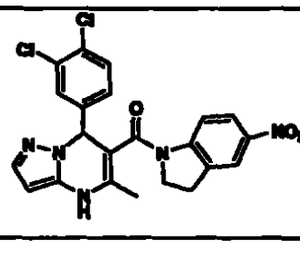
242		(2S-trans)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,5-bis-(methoxymethyl)pyrrolidine	465
243		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-L-prolinamide	420
244		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-D-prolinamide	420
245		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,3-dihydro-2-methyl-1H-indole	439
246		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,3-dihydro-5-nitro-1H-indole	470

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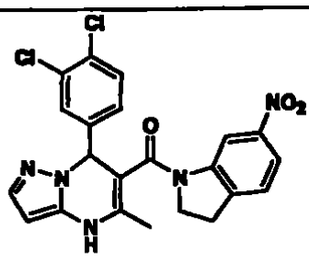
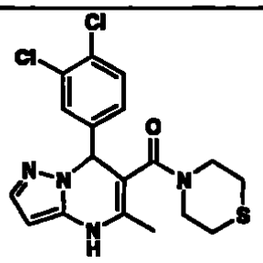
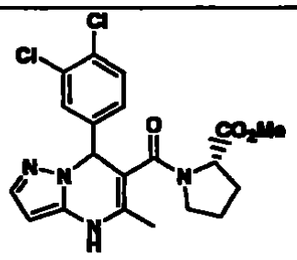
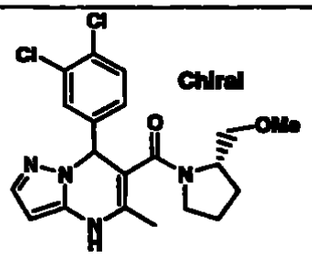
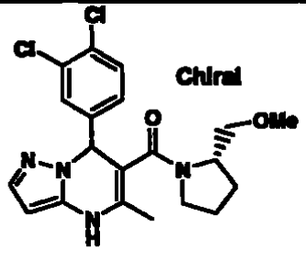
247		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,3-dihydro-6-nitro-1H-indole	470
248		4-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-thiomorpholine	409
249		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-L-proline methyl ester	435
250		(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrro-lidine, enantiomer A	421
251		(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine, enantiomer B	421

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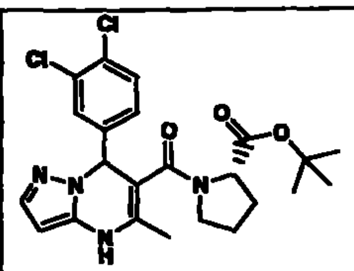
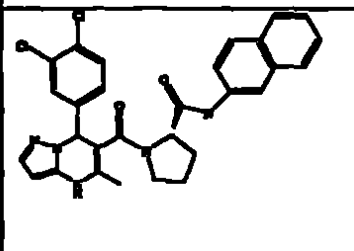
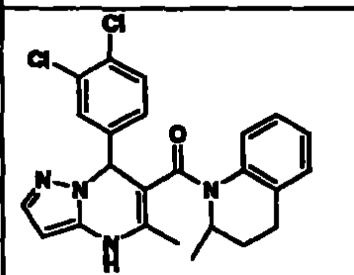
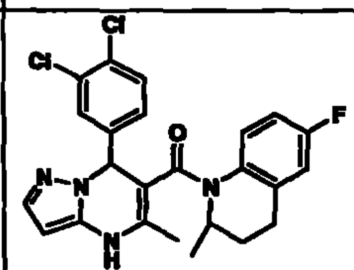
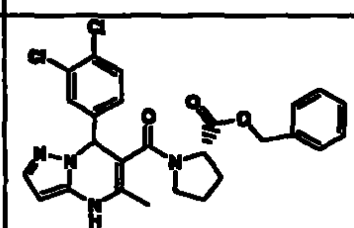
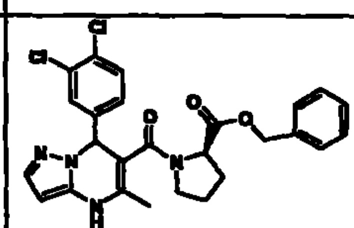
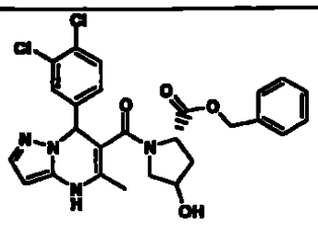
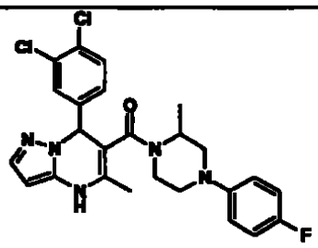
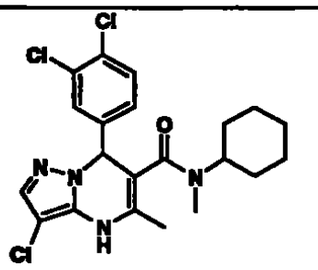
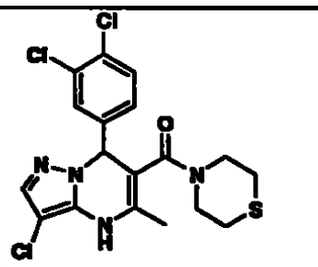
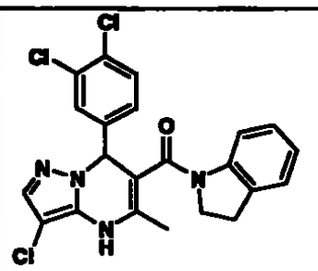
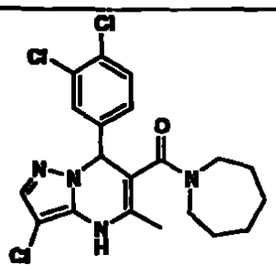
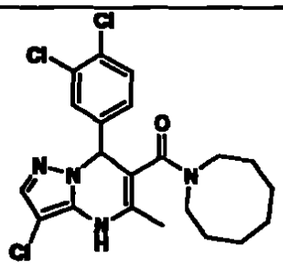
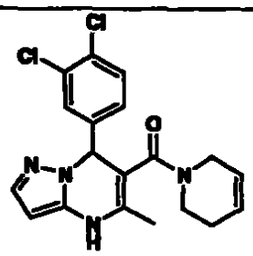
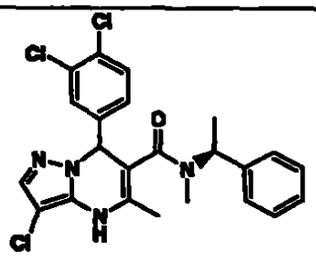
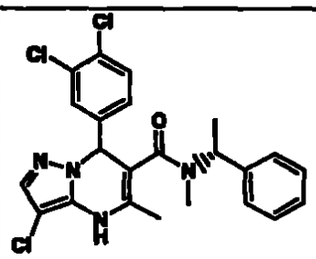
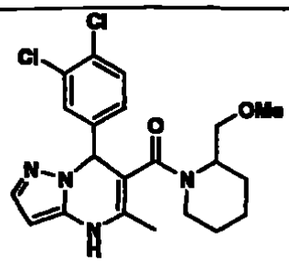
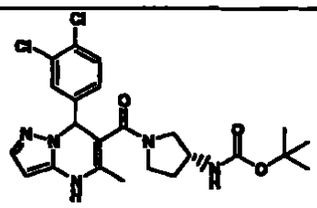
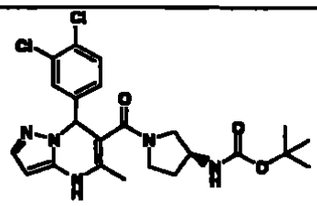
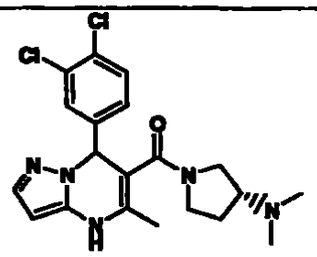
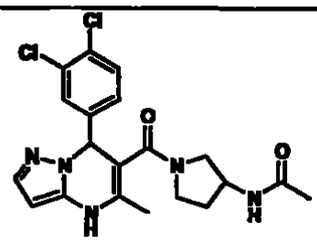
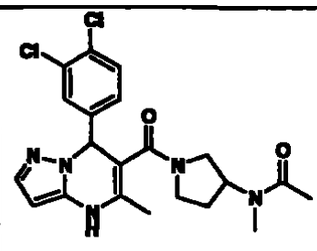
252		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-L-proline 1,1-dimethylethyl ester	477
253		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-N-(2-naphthalenyl)-L-prolinamide	560
254		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,4-tetrahydro-2-methylquinoline	453
255		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-6-fluoro-1,2,3,4-tetrahydro-2-methylquinoline	471
256		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-L-proline phenylmethyl ester	511
257		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-D-proline phenylmethyl ester	511

696
673

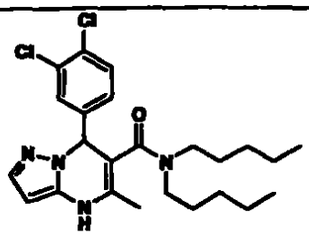
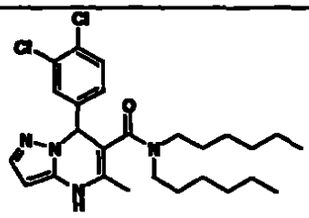
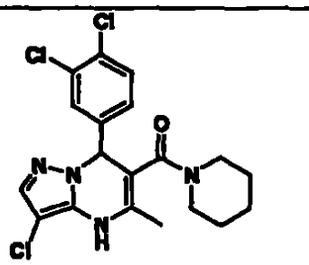
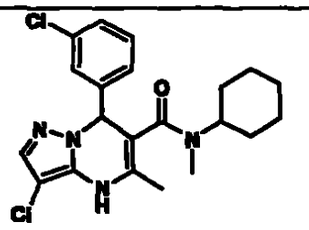
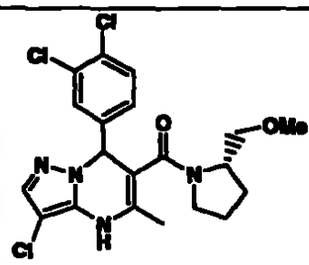
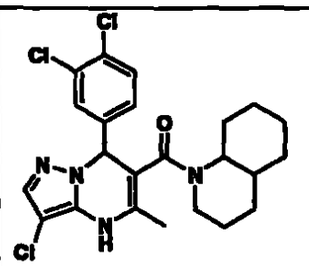
258		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-hydroxy-L-proline phenylmethyl ester	527
259		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)-2-methylpiperazine	500
260		3-Chloro-N-cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydro-N,5-dimethyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide	453
261		4-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-thiomorpholine	443
262		1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,3-dihydro-1H-indole	459

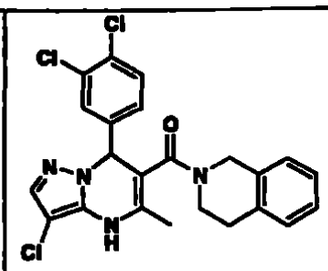
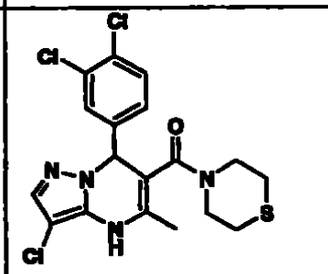
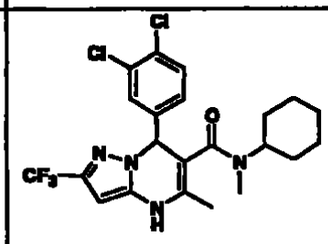
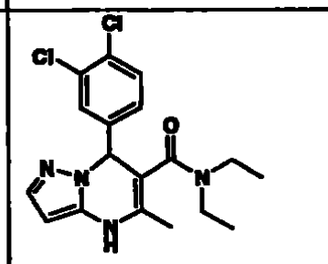
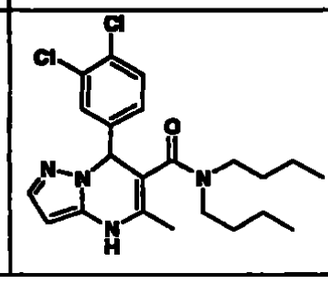
697 674

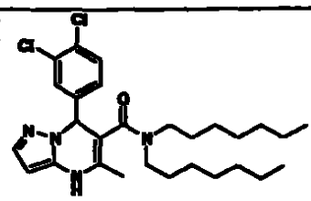
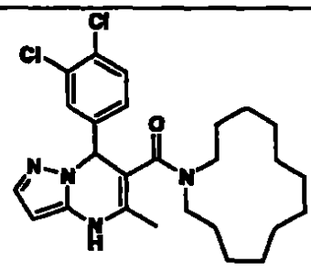
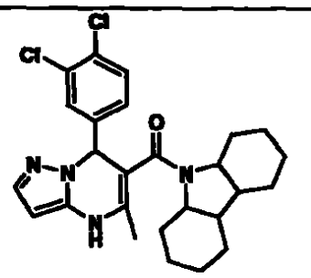
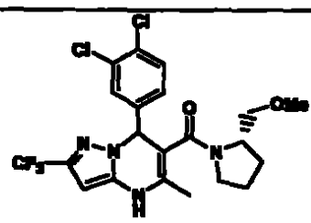
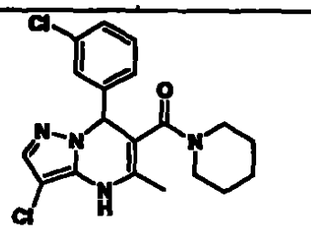
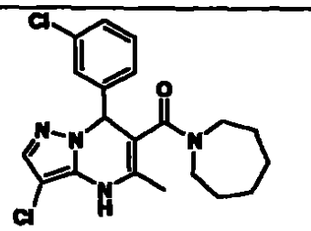
263		1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]hexahydro-1H-azepine	439
264		1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-octahydroazocine	453
265		1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,6-tetrahydropyridine	423
266		3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-[(1S)-1-phenylethyl]-pyrazolo[1,5-a]pyrimidine-6-carboxamide	475
267		3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-[(1R)-1-phenylethyl]-pyrazolo[1,5-a]pyrimidine-6-carboxamide	475

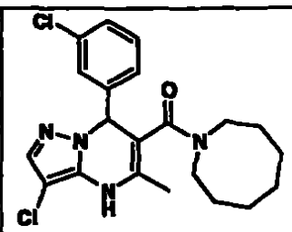
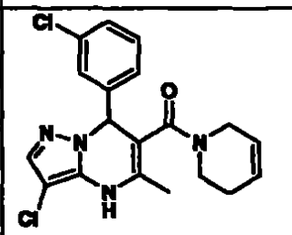
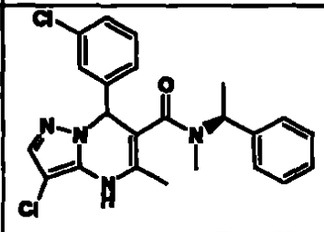
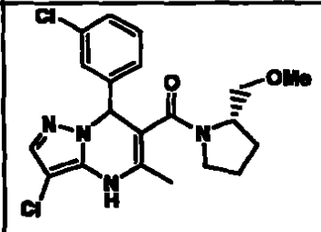
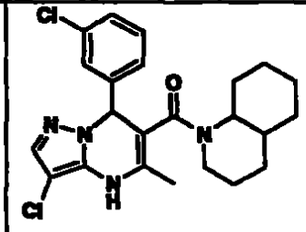
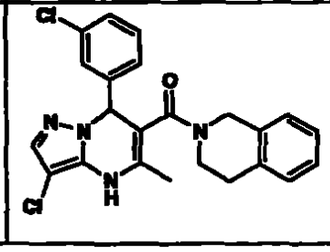
268		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]-carbonyl]-2-(methoxy-methyl)piperidine	435
269		[(3R)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-pyrrolidinyl]carbamic acid 1,1-dimethylethyl ester	492
270		[(3S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-pyrrolidinyl]carbamic acid 1,1-dimethylethyl ester	492
271		(3R)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-(di-methylamino)pyrrolidine	420
272		N-[1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-pyrrolidinyl]acetamide	434
273		N-[1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-pyrrolidinyl]-N-methylacetamide	448

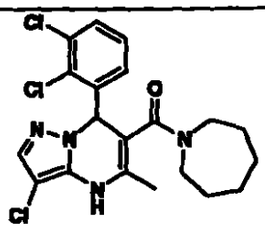
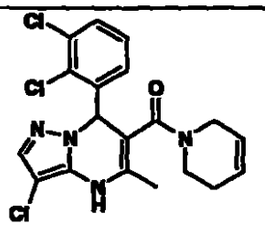
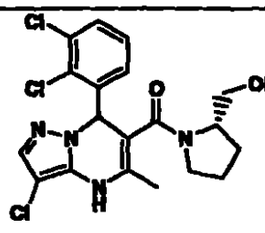
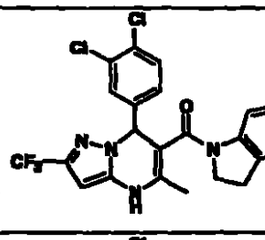
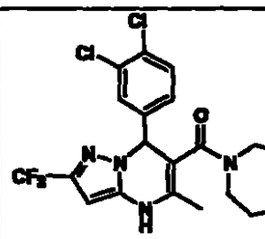
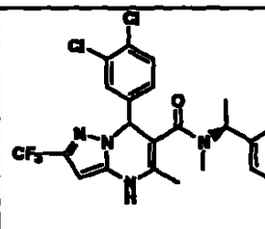
699
676

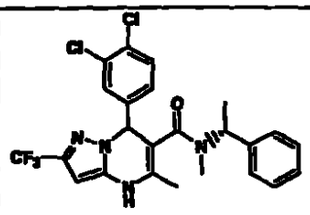
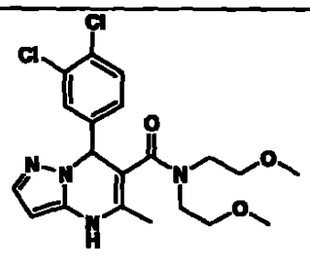
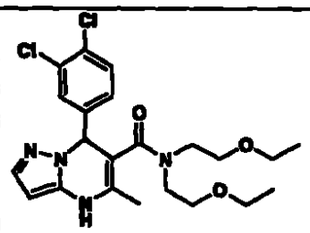
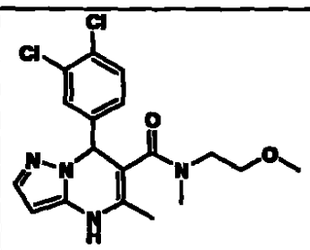
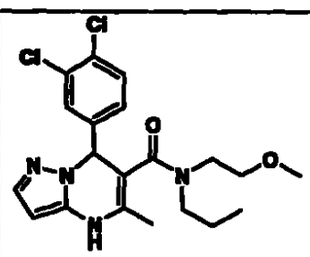
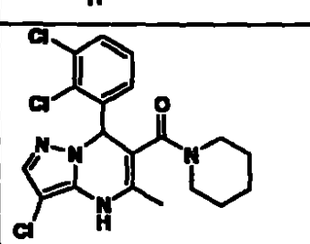
274		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N,N-dipentyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide	463
275		7-(3,4-Dichlorophenyl)-N,N-dihexyl-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	491
276		1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine	425
277		3-Chloro-7-(3-chlorophenyl)-N-cyclohexyl-4,7-dihydro-N,5-dimethyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide	419
278		(2S)-1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine	455
279		1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-decahydroquinoline	479

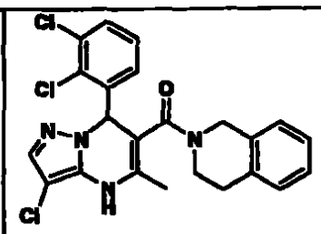
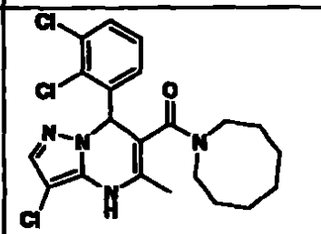
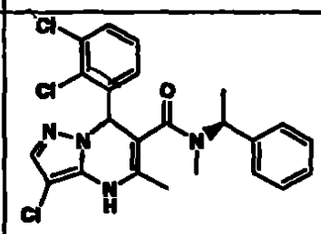
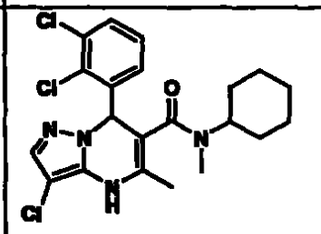
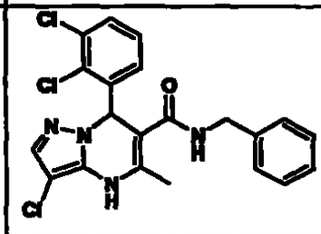
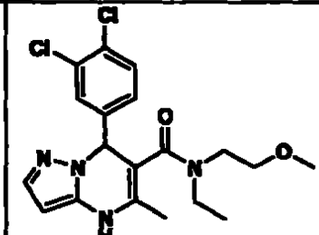
280		2-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,4-tetrahydroisoquinoline	473
281		4-[[3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-thiomorpholine	409
282		N-Cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydro-N,5-dimethyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	487
283		7-(3,4-Dichlorophenyl)-N,N-diethyl-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	379
284		N,N-Dibutyl-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide	435

285		7-(3,4-Dichlorophenyl)-N,N-diheptyl-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide	519
286		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-azacyclotridecane	489
287		9-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-dodecahydro-1H-fluorene	485
288		(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoromethyl)pyrazolo-[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine	489
289		1-[[3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine	391
290		1-[[3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]hexahydro-1H-azepine	405

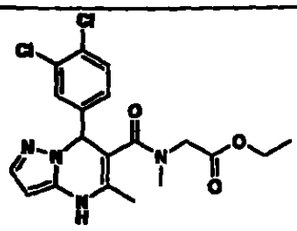
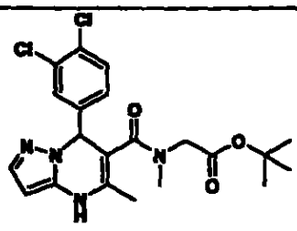
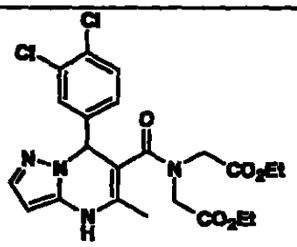
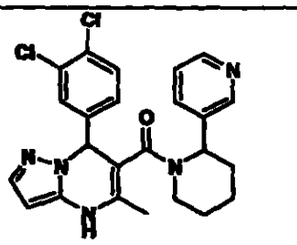
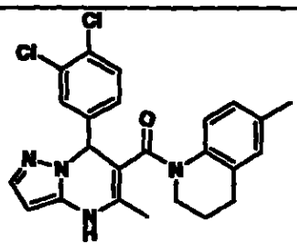
291		1-[[3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-octahydroazocine	419
292		1-[[3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,6-tetrahydropyridine	389
293		3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-N,5-dimethyl-N-[(1S)-1-phenyl-ethyl]pyrazolo[1,5-a]pyrimidine-6-carboxa-mide	441
294		(2S)-1-[[3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrro-lidine	421
295		1-[[3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-decahydroquinoline	445
296		2-[[3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,4-tetrahydroisoquinoline	439

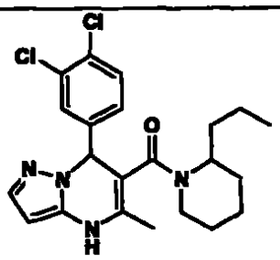
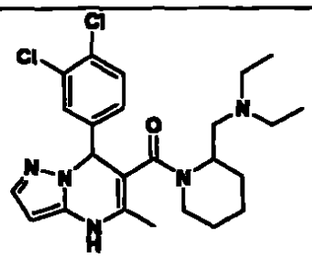
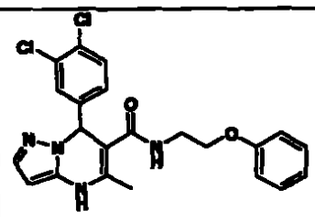
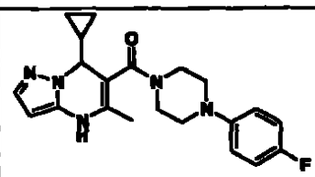
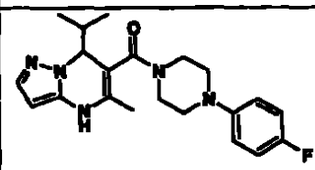
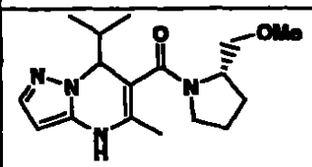
297		1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]hexahydro-1H-azepine	439
298		1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,6-tetrahydropyridine	423
299		(2S)-1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine	455
300		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,3-dihydro-1H-indole	493
301		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]hexahydro-1H-azepine	473
302		7-(3,4-Dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-[(1S)-1-phenylethyl]-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	509

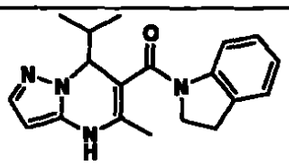
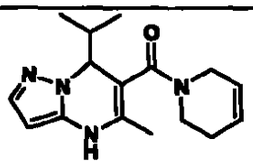
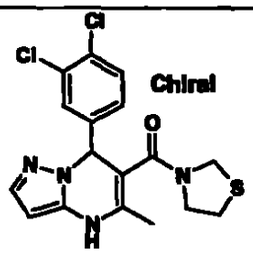
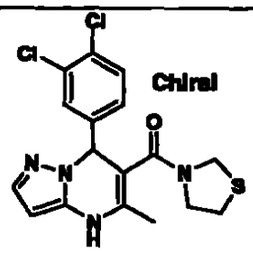
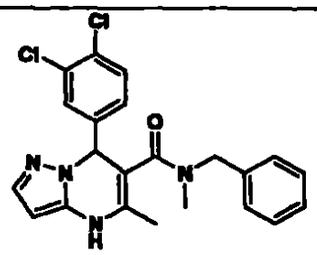
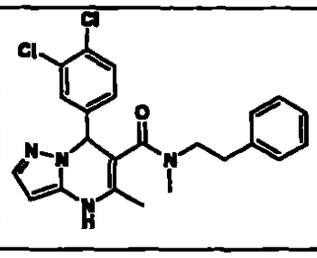
303		7-(3,4-Dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-[(1R)-1-phenylethyl]-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	509
304		7-(3,4-Dichlorophenyl)-4,7-dihydro-N,N-bis(2-methoxyethyl)-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	439
305		7-(3,4-Dichlorophenyl)-N,N-bis(2-ethoxyethyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	467
306		7-(3,4-Dichlorophenyl)-4,7-dihydro-N-(2-methoxyethyl)-N,5-dimethylpyrazolo[1,5-a]pyrimidine-6-carboxamide	395
307		7-(3,4-Dichlorophenyl)-4,7-dihydro-N-(2-methoxyethyl)-5-methyl-N-propylpyrazolo[1,5-a]pyrimidine-6-carboxamide	423
308		1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine	425

309		2-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,4-tetrahydroisoquinoline	473
310		1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-octahydroazocine	453
311		3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-[(1S)-1-phenylethyl]-pyrazolo[1,5-a]pyrimidine-6-carboxamide	475
312		3-Chloro-N-cyclohexyl-7-(2,3-dichlorophenyl)-4,7-dihydro-N,5-dimethyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide	453
313		3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-N-(phenylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	447
314		7-(3,4-Dichlorophenyl)-N-ethyl-4,7-dihydro-N-(2-methoxyethyl)-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	409

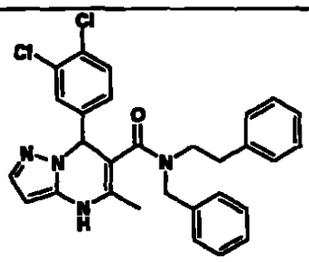
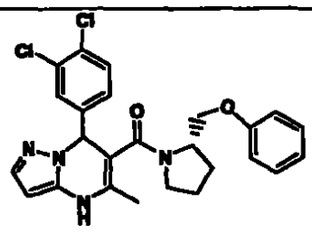
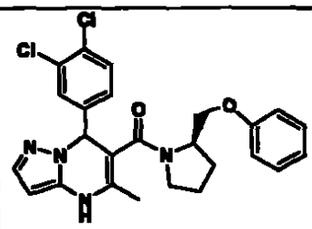
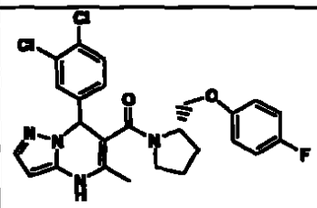
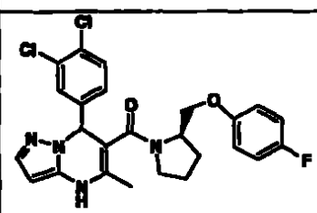
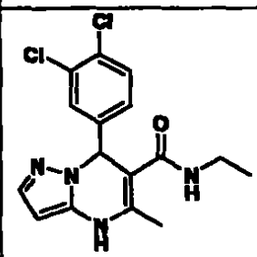
706

315		N-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-N-methylglycine ethyl ester	423
316		N-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-N-methylglycine 1,1-dimethylethyl ester	451
317		N-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-N-(2-ethoxy-2-oxoethyl)glycine ethyl ester	495
318		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(3-pyridinyl)pipendine	468
319		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,4-tetrahydro-6-methylquinoline	453

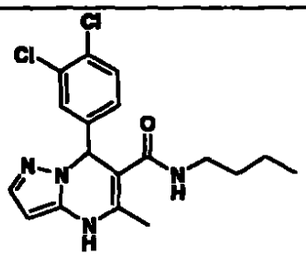
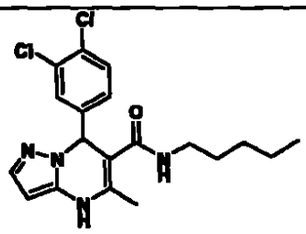
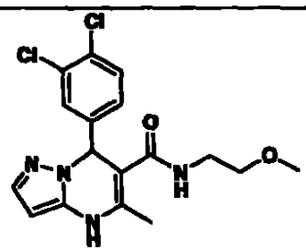
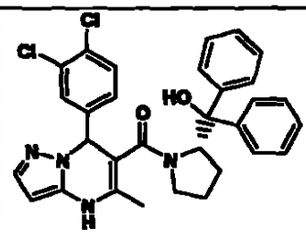
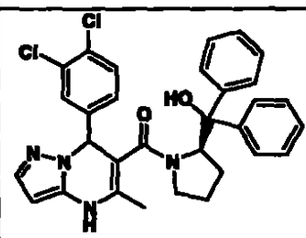
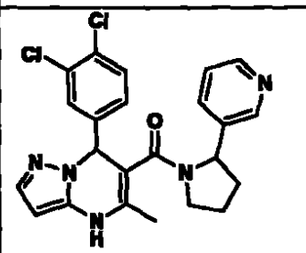
320		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-propylpiperidine	433
321		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-[(diethylamino)methyl]piperidine	476
322		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(2-phenoxyethyl)-pyrazolo[1,5-a]pyrimidine-6-carboxamide	443
323		1-[(7-Cyclopropyl-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl)carbonyl]-4-(4-fluorophenyl)piperazine	381
324		1-[[4,7-Dihydro-5-methyl-7-(1-methyl-ethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	383
325		(2S)-1-[[4,7-Dihydro-5-methyl-7-(1-methyl-ethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxy-methyl)pyrrolidine	318

326		1-[[4,7-Dihydro-5-methyl-7-(1-methyl-ethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,3-dihydro-1H-indole	322
327		1-[[4,7-Dihydro-5-methyl-7-(1-methylethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,6-tetrahydropyridine	286
328		3-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]thiazolidine, enantiomer A	395
329		3-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]thiazolidine, enantiomer B	395
330		7-(3,4-Dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-(phenylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	427
331		7-(3,4-Dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-(2-phenylethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	441

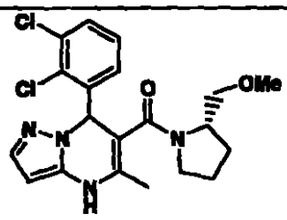
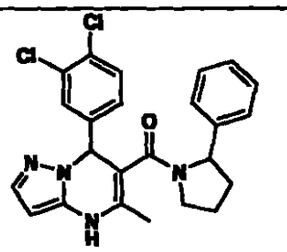
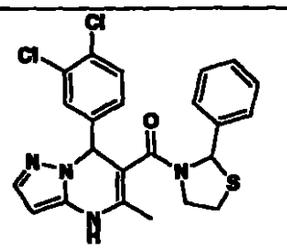
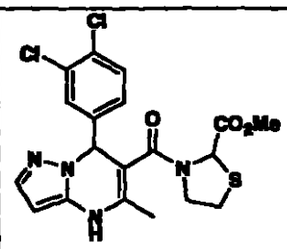
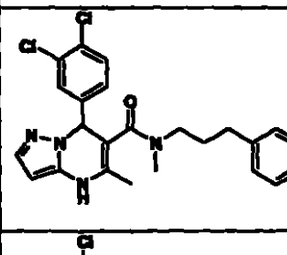
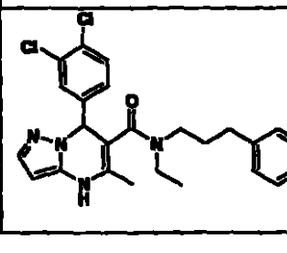
709

332		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(2-phenylethyl)-N-(phenylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	517
333		(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(phenoxymethyl)pyrrolidine	483
334		(2R)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(phenoxymethyl)pyrrolidine	483
335		(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-[(4-fluorophenoxy)methyl]-pyrrolidine	501
336		(2R)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-[(4-fluorophenoxy)methyl]-pyrrolidine	501
337		7-(3,4-Dichlorophenyl)-N-ethyl-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	351

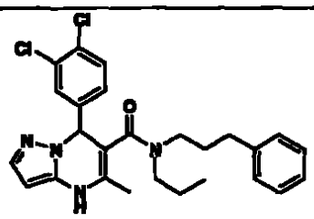
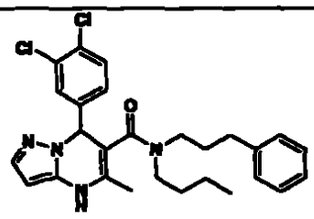
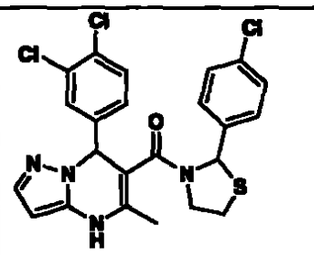
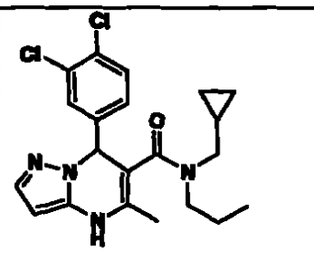
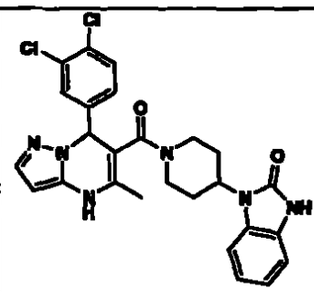
710
687

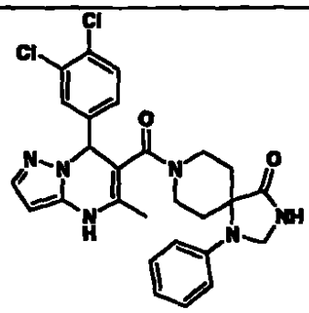
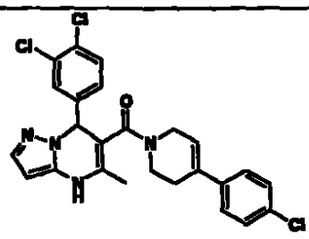
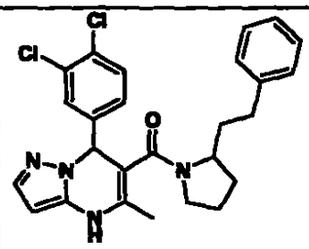
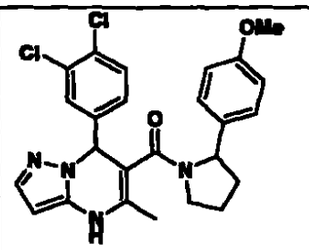
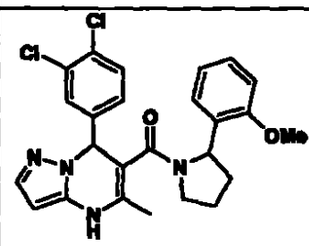
338		N-Butyl-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide	379
339		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-pentylpyrazolo[1,5-a]pyrimidine-6-carboxamide	393
340		7-(3,4-Dichlorophenyl)-4,7-dihydro-N-(2-methoxyethyl)-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide	381
341		(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(hydroxydiphenylmethyl) pyrrolidine	559
342		(2R)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(hydroxydiphenylmethyl) pyrrolidine	559
343		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(3-pyridinyl)pyrrolidine	454

711
688

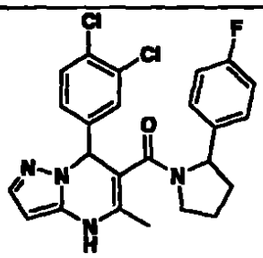
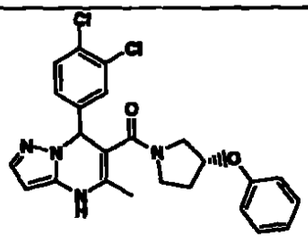
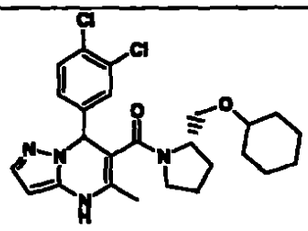
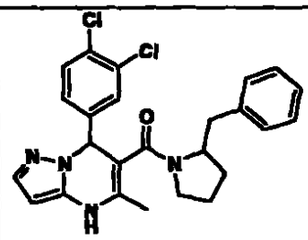
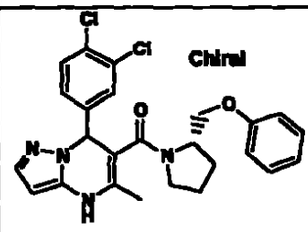
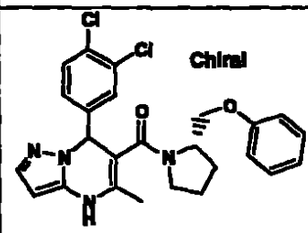
344		(2S)-1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine	421
345		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-phenylpyrrolidine	453
346		3-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-phenylthiazolidine	471
347		3-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-thiazolidinecarboxylic acid methyl ester	453
348		7-(3,4-Dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-(3-phenylpropyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	455
349		7-(3,4-Dichlorophenyl)-N-ethyl-4,7-dihydro-5-methyl-N-(3-phenylpropyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	469

712
684

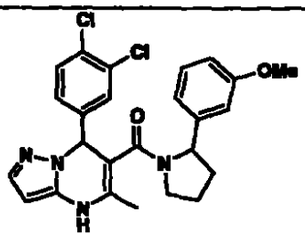
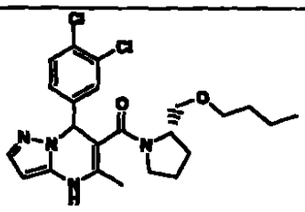
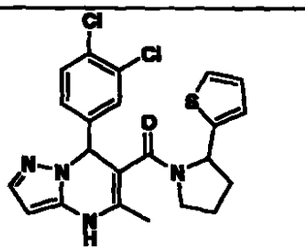
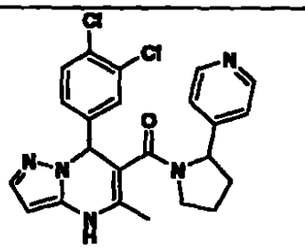
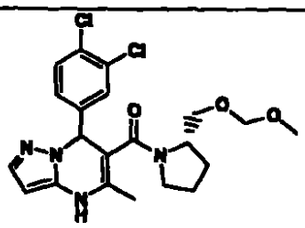
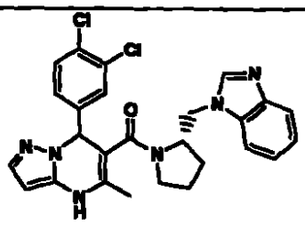
350		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(3-phenylpropyl)-N-propylpyrazolo[1,5-a]pyrimidine-6-carboxamide	483
351		N-Butyl-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-N-(3-phenylpropyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	497
352		2-(4-Chlorophenyl)-3-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]thiazolidine	505
353		N-(Cyclopropylmethyl)-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-N-propylpyrazolo[1,5-a]pyrimidine-6-carboxamide	419
354		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)piperidine	523

355		8-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1-phenyl-1,3,8-triazaspiro[4 5]decan-4-one	537
356		4-(4-Chlorophenyl)-1-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,6-tetrahydropyridine	499
357		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(2-phenylethyl)pyrrolidine	481
358		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(4-methoxyphenyl)pyrrolidine	483
359		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(2-methoxyphenyl)pyrrolidine	483

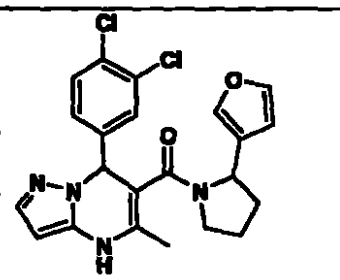
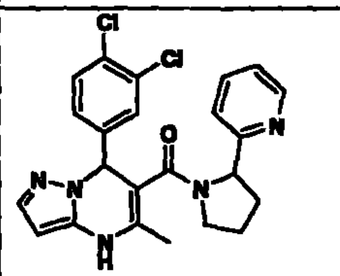
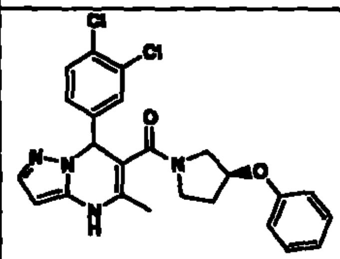
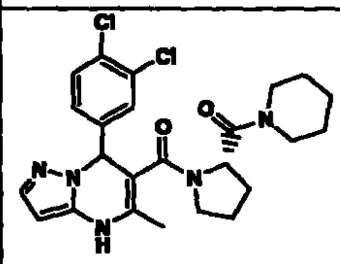
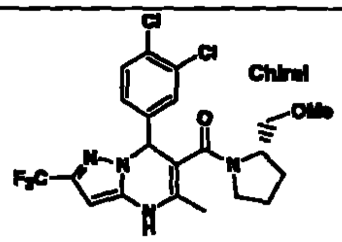
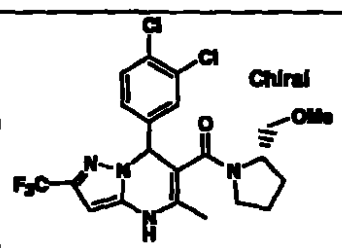
714
694

360		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(4-fluoro-phenyl)pyrrolidine	471
361		(3R)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl[-3-phenoxypyrrolidine	469
362		(2S)-2-[(Cyclohexyl-oxy)methyl]-1-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]pyrrolidine	489
363		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(phenyl-methyl)pyrrolidine	467
364	 Chiral	(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(phenoxymethyl)pyrro-lidine, diastereomer A	483
365	 Chiral	(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(phenoxymethyl)pyrro-lidine, diastereomer B	483

715
692

366		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-2-(3-methoxy-phenyl)pyrrolidine	483
367		(2S)-2-(Butoxymethyl)-1-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]pyrrolidine	463
368		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(2-thienyl)pyrrolidine	459
369		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(4-pyridinyl)pyrrolidine	454
370		(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-[(methoxymethoxy)-methyl]pyrrolidine	451
371		(2S)-2-(1H-Benzimidazol-1-ylmethyl)-1-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]pyrrolidine	507

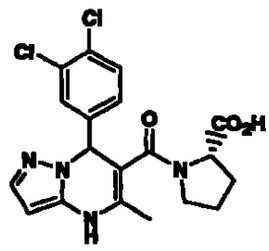
716
693

372		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(3-furanyl)pyrrolidine	443
373		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(2-pyridinyl)pyrrolidine	454
374		(3S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-phenoxypyrrolidine	469
375		(3S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-phenoxypyrrolidine	488
376		(2S)-1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methyl-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine, enantiomer A	489
377		(2S)-1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methyl-2-(trifluoro-methyl)pyrazolo[1,5-a]-pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine, enantiomer B	489

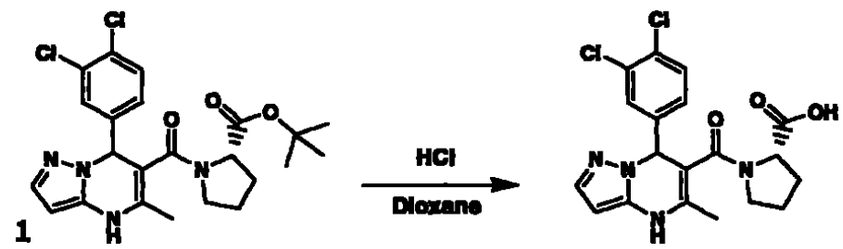
717
694

Example 378

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-L-proline



Method



1

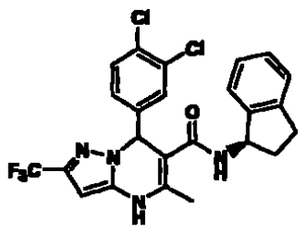
Compound 1 Compound 1 (the compound of Example 252) was prepared in a manner similar to that described in Example 170

Title Compound Hydrochloric acid (5 mL, 4M in Dioxane) was added to compound 1 (0 05 g, 0 1 mmol) The resulting mixture was stirred at room temperature. After 3 h the mixture was concentrated in vacuo LC/MS analysis of the residue indicated that starting material remained. Additional Hydrochloric acid (5 mL, 4M in Dioxane) was added. The resulting mixture was stirred at room temperature for 7 h. TLC analysis indicated that compound 1 was consumed. The mixture was concentrated in vacuo The residue was purified by preparative reverse phase HPLC to give the title compound as a mixture of diastereomers LC/MS indicated that the compound was still impure (50% pure) Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic,

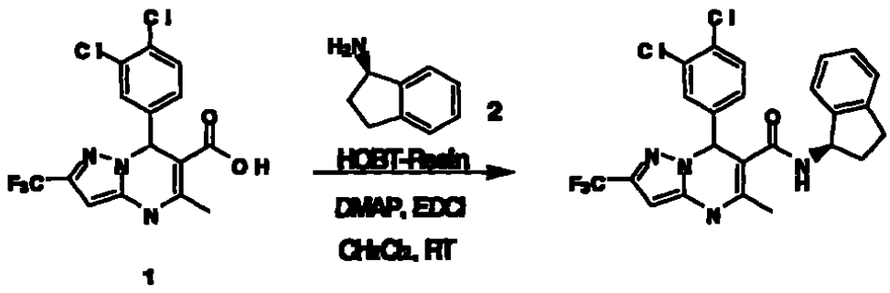
UV detection at 220 λ, 4 min. gradient, 0-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min Diastereomer A Rt = 3 34, Diastereomer B Rt = 3.49 min MS (M+H 421) The product was triturated with dichlormethane to give 0 014 g (32 % yield) of the title compound (85% pure by HPLC) Reverse Phase LC/MS YMC S5 4 6 x 50 mm combiscreen, UV detection at 220 λ, 4 min. gradient, 0-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0 2% H_3PO_4, Solvent B 90% MeOH/H_2O with 0 2% H_3PO_4), 4 mL/min Diastereomer A Rt = 2.82, Diastereomer B Rt = 2 97 min

Example 379

7-(3,4-Dichlorophenyl)-4,7-dihydro-N-[(1R)-2,3-dihydro-1H-inden-1-yl]-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide



Method



Compound 1 Compound 1 was prepared as described in Example 17

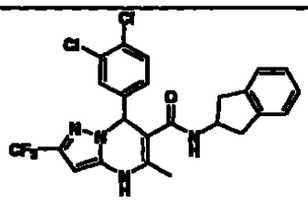
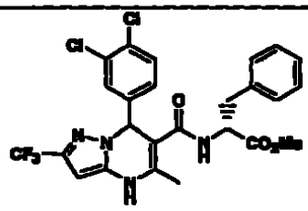
Title Compound To a suspension of polystyrene-supported HOBt resin (NovaBiochem, >1 2 mmol/g, 50 mg, 1 0 eq) in anhydrous CH_2Cl_2 (1 0 mL) was added Compound 1 (47 mg, 2 0 eq), EDCI (23 mg, 2.0 eq), and DMAP (0 7 mg, 0 1

719
696

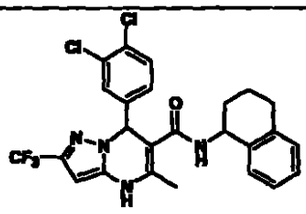
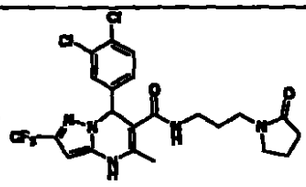
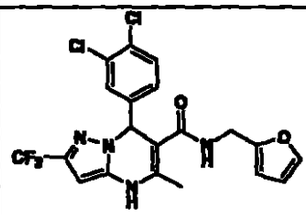
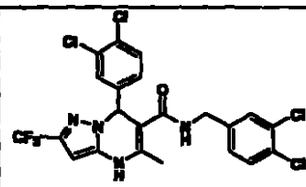
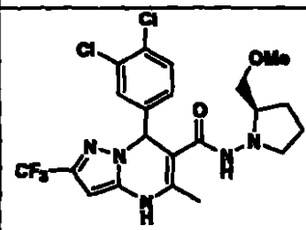
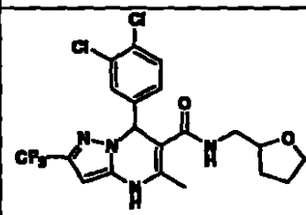
eq) The suspension was shaken vigorously using a VORTEX-GENIE2 for 1 hr Solvent was then drained and the resin was washed sequentially with DMF (3x2 mL), THF (3x2 mL), and CH_2Cl_2 (3x2 mL) with vigorous shaking The resin was resuspended in CH_2Cl_2 (1 mL) and to which was added (R)-(-)-Aminoindan 2 (0 006 mL, 0 8 eq) The mixture was shaken for 2 hr Solvent was drained and the resin was washed with CH_2Cl_2 (3x1 mL) with vigorous shaking All the washing solutions were combined and the solvent was removed under reduced pressure The residue was purified through a silica gel cartridge eluting with 100 % EtOAc to give the title compound as a white solid. Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min gradient 0-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0 2% H_3PO_4, Solvent B 90% MeOH/H_2O with 0 2% H_3PO_4), 4 mL/min Rt = 2.96 min, (diastereomers, 96% pure) MS (M+H) 507

Examples 380-391

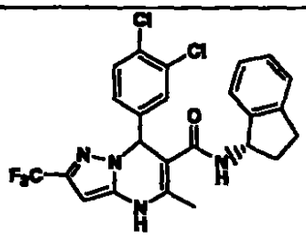
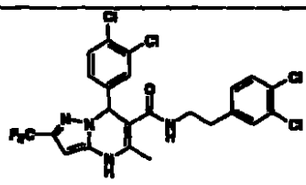
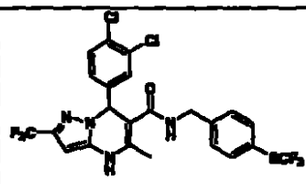
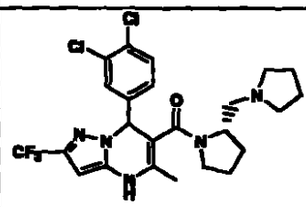
The compounds of Examples 380-391, shown in the table provided below, were prepared in a manner similar to that described in Example 379

Example	Structure	Name	(M+H)
380		7-(3,4-Dichlorophenyl)-N-(2,3-dihydro-1H-inden-2-yl)-4,7-dihydro-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	507
381		N-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-D-phenylalanine methyl ester	553

720
697

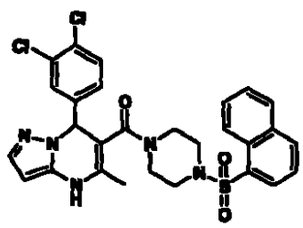
382		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(1,2,3,4-tetrahydro-1-naphthalenyl)-2-(trifluoro-methyl)pyrazolo[1,5-a]pynmidine-6-carboxamide	521
383		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-[3-(2-oxo-1-pyrrolidinyl)propyl]-2-(trifluoromethyl)pyrazolo[1,5-a]pynmidine-6-carboxamide	516
384		7-(3,4-Dichlorophenyl)-N-(2-furanylmethyl)-4,7-dihydro-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	471
385		7-(3,4-Dichlorophenyl)-N-[(3,4-dichlorophenyl)methyl[-4,7-dihydro-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	550
386		7-(3,4-Dichlorophenyl)-4,7-dihydro-N-[(2R)-2-(methoxymethyl)-1-pyrrolidinyl]-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pynmidine-6-carboxamide	504
387		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-[(tetrahydro-2-furanyl)-methyl]-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidine-6-carbo-xamide	475

721
698

388		7-(3,4-Dichlorophenyl)-4,7-dihydro-N-[(1S)-2,3-dihydro-1H-inden-1-yl]-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	507
389		7-(3,4-Dichlorophenyl)-N-[2-(3,4-dichlorophenyl)ethyl]-4,7-dihydro-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	564
390		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoromethyl)-N-[[4-[(trifluoromethyl)thio]-phenyl]methyl]pyrazolo-[1,5-a]pyrimidine-6-carboxamide	581
391		(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7dihydro-5-methyl-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(1-pyrrolidinylmethyl)-pyrrolidine	666

Example 392

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(1-naphthalenylsulfonyl)piperazine



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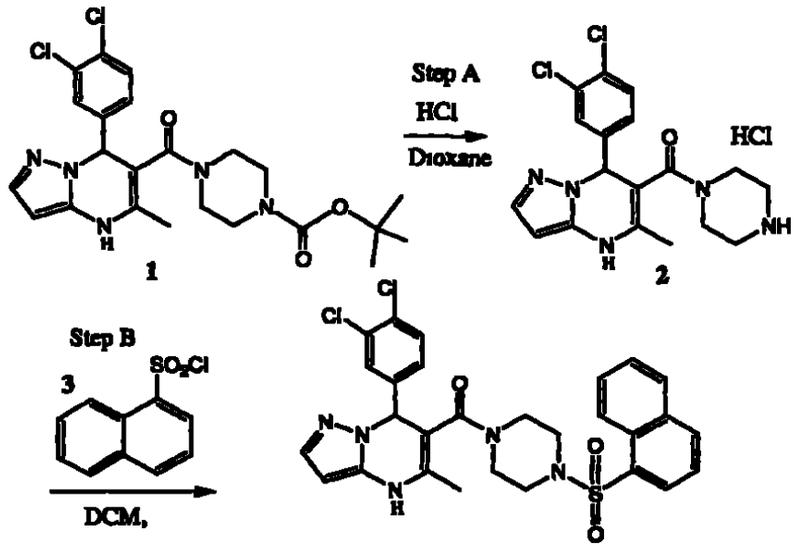
Method



1 2

Compound 1 Compound 1 (the compound of Example 60) was prepared in a manner similar to that described in Example 18, Method 2.

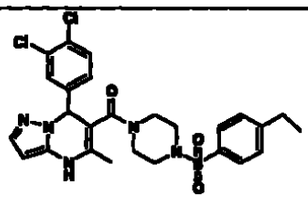
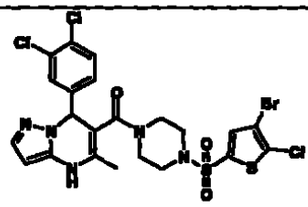
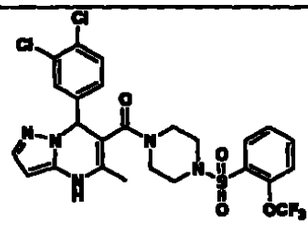
Step A HCl (4M in dioxane) was added to solid compound 1 (0.53 g, 1 1 mmol) A gummy precipitate forms immediately Dichloromethane was added, the gummy precipitate remained. The solvent was decanted and the residue was triturated with ethyl acetate (3X), concentrated to give 0 63 g (130 % contains residual dioxane) of the hydrochloride salt compound 2 as a light yellow powder Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min gradient 40-100% Solvent B/A (Solvent A. 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min Rt = 0 57 min, (92% pure) MS (M+H) 392 Compound 2 was used without purification

Step B Compound 2 (0 077 g, 0 18 mmol) and compound 3 (0 049 g, 0 22 mmol) were suspended in dichloromethane (1 mL) Triethylamine (0 05 mL, 0 36 mmol) was added A clear solution results. TLC after 30 min indicated consumption of starting material The mixture was loaded directly onto a Worldwide Monitoring CLEAN-UP

CARTRIDGE (silica, CUSIL12M6) which had been equilibrated with 100% hexanes Elution with 100% hexanes (40 mL), followed by 50% Ethyl acetate/hexanes (40 mL) and 100% ethyl acetate (40 mL) The purest fractions (TLC analysis) were combined to give 0 068 g (65% yield) of the title compound as a white solid. Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 40-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0 1% TFA Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min. Rt = 3.46 min, (90% pure) MS (M+H. 582) HMR ($CDCl_3$ 400 MHz) 8 60(1H, d, J=8), 8 05(2H, m) 7 95(1H, m), 7 62(4H, m), 7 35(1H, d, J=2 Hz), 7 17(1H, d, J=8 Hz), 7 06(1H d, J=2 Hz), 6.81(1H, d, J=6 Hz), 6 17(1H, m), 5 54(1H, d, J=2 Hz), 3.23(8H,m), 1 86(3H, s)

Examples 393-396

The compounds of Examples 393-396, shown in the table provided below, were prepared in a manner similar to that described in Example 392

Example	Structure	Name	(M+H)
393		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-[(4-ethylphenyl)sulfonyl]-piperazine	560
394		1-[(4-Bromo-5-chloro-2-thienyl)sulfonyl]-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimi-din-6-yl]carbonyl]-piperazine	651
395		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-[[2-(trifluoro-methoxy)phenyl]sul-fonyl]piperazine	616

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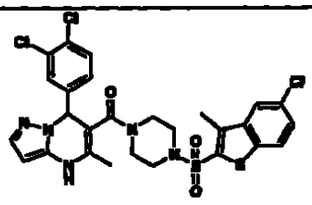
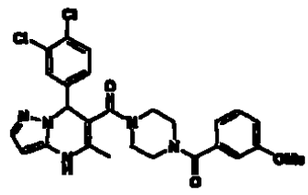
701

396		1-[(5-Chloro-3-methyl-benzo[b]thiophen-2-yl)sulfonyl]-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyra-zolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine	637

Example 397

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-[(3-methoxyphenyl)carbonyl]piperazine



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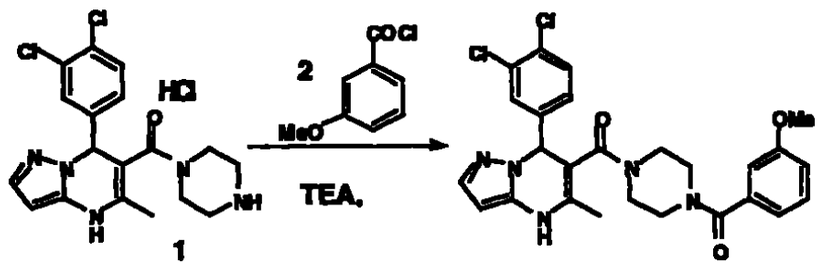


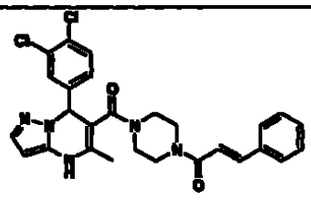
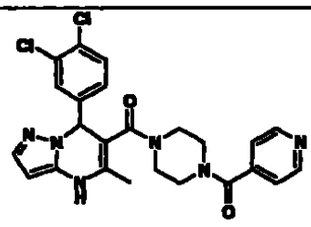
Compound 1 Compound 1 was prepared as described in Step A of Example 392

Title Compound Compound 1 (0.062 g, 0 15 mmol) and compound 2 (0.025 mL, 0 17 mmol) were suspended in dichloromethane (1 mL) Triethylamine (0.040, 0 29 mmol) was added A clear solution results. TLC after 30 min indicated consumption of starting material. The mixture was loaded directly onto a Worldwide Monitoring CLEAN-UP CARTRIDGE (CUSIL12M6) which had been equilibrated with 100%

hexanes. Elution with 100% hexanes (40 mL), followed by 50% Ethyl acetate/hexanes (100 mL) and 100% ethyl acetate (100 mL) The purest fractions (TLC analysis) were combined to give 0.022 g (29% yield) of the title compound as a white solid. Reverse Phase LC/MS. YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min gradient 40-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min Rt = 2 69 min, (90% pure) MS (M+H 526)

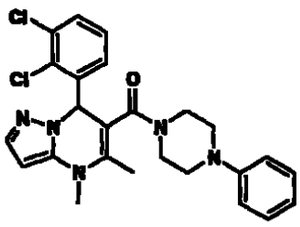
Examples 398 and 399

The compounds of Examples 398 and 399, shown in the table provided below, were prepared in a manner similar to that described in Example 397

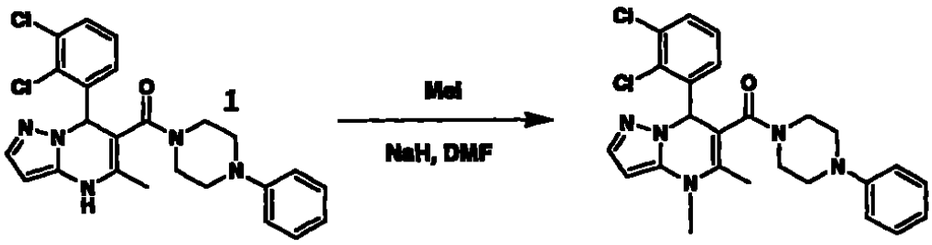
Example	Structure	Name	(M+H)
398		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(1-oxo-3-phenyl-2-propenyl)-piperazine	522
399		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-pyridinylcarbonyl)piperazine	497

Example 400

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine



Method



Compound 1 Compound 1 was prepared as described in Example 18.

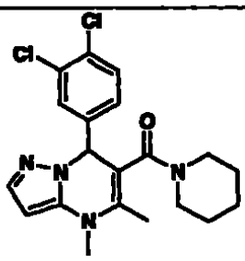
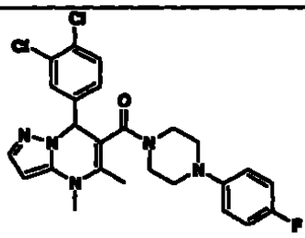
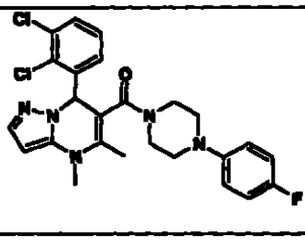
Title Compound Compound 1 (0 08g, 0 17 mmol) was dissolved in dimethylformamide (1 0 mL). NaH (0 005g, 0 22 mmol, 60% in oil) was added and the mixture was stirred for 5 min. Iodomethane (0.012 mL, 0 18 mmol) was added When TLC (5% methanol/dichloromethane) analysis indicated consumption of starting material the reaction was quenched with water, diluted with ethyl acetate, transferred to a separatory funnel, washed with saturated water and brine, dried over anhydrous sodium sulfate and concentrated The residue was purified by silica gel chromatography eluting with 100% dichloromethane followed by 3% methanol/dichloromethane to provide 0 06g (75%) of the title compound as a amber oil Reverse Phase LC/MS YMC S5 ODS 4.6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 40-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min Rt = 2.99 min, (96% pure) MS (M+H 482)

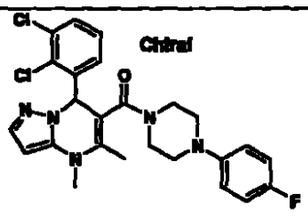
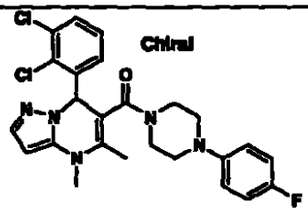
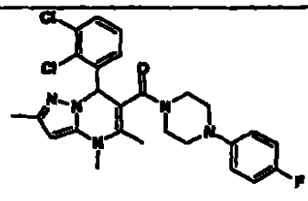
727
704

Examples 401-406

The compounds of Examples 401-406, shown in the table provided below, were prepared in a manner similar to that described in Example 400

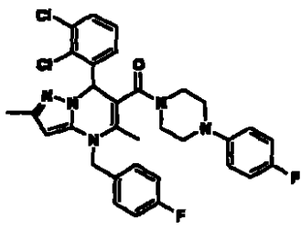
HPLC resolution of Example 403, Chiralpak AD column (50 X 500 mm), eluting with 35% isopropanol/hexanes containing 0 1 % triethylamine at 50 mL/min), UV detection at 254 λ provided enantiomers A (Example 405) and B (Example 404) Chiralpak AD column (4 6 X 250 mm) eluting with 30% isopropanol/hexanes containing 0 1 % triethylamine at 1 mL/min), UV detection at 254 λ, enantiomer A Rt = 14 4 min, >99% ee Enantiomer B Rt = 28 7 min, >99% ee.

Example	Structure	Name	(M+H)
401		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine	405
402		1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	500
403		1-[[7-(2,3-Dichloro-phenyl)-4,7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	500

404	 Chiral	1-[[7-(2,3-Dichloro-phenyl)-4,7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer B	500
405	 Chiral	1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer A	500
406		1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2,4,5-trimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	514

Example 407

1-[[7-(2,3-Dichlorophenyl)-4-[(4-fluorophenyl)methyl]-4,7dihydro-2,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine



Method

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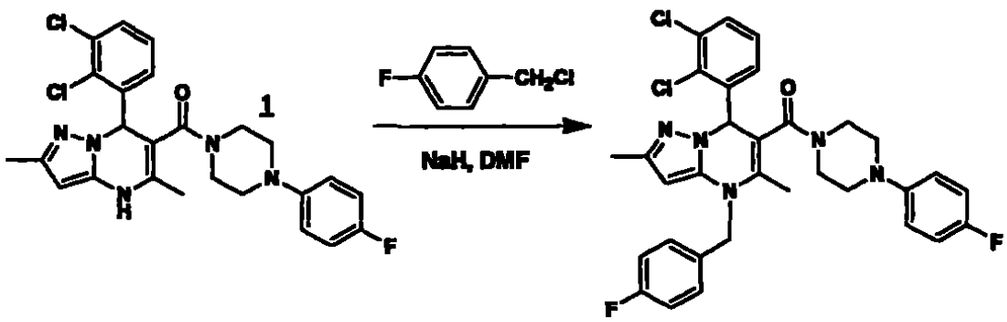
706



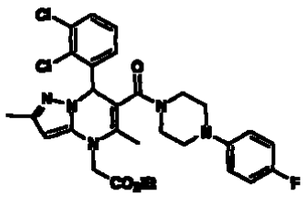
Compound 1 Compound 1 was prepared in a manner similar to that described in Example 18, Method 2.

Title Compound Compound 1 (0 10g, 0 21 mmol) was dissolved in dimethylformamide (1 0 mL). NaH (0 007g, 0.27 mmol, 60% in oil) was added and the mixture was stirred for 5 min. 4-Fluorobenzyl chloride (0 028 mL, 0.23 mmol) was added When TLC (5% methanol/ dichloromethane) analysis indicated consumption of starting material the reaction was quenched with water, diluted with ethyl acetate, transferred to a separatory funnel, washed with saturated water and brine, dried over anhydrous sodium sulfate and concentrated The residue was purified by silica gel chromatography eluting with 100% dichloromethane followed by 3% methanol/dichloromethane to provide 0 09g (69%) of the title compound as a amber oil Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 40-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA) 4 mL/min Rt = 3 20 min, (93% pure) MS (M+H 608)

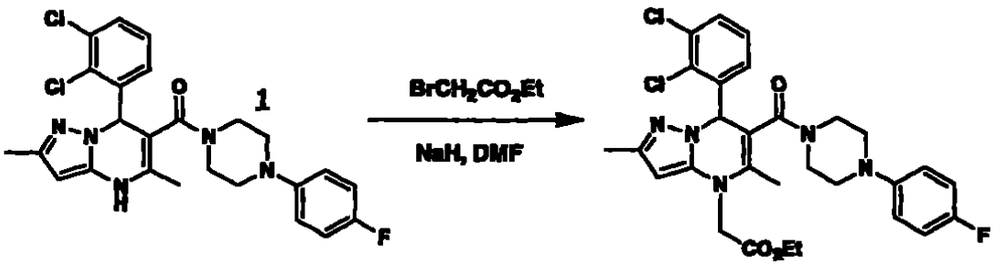
Example 408

7-(2,3-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-2,5-dimethylpyrazolo[1,5-a]pyrimidine-4(7H)-acetic acid ethyl ester

730
707



Method



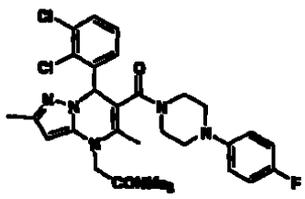
Compound 1 Compound 1 was prepared in a manner similar to that described in Example 18, Method 2.

Title Compound Compound 1 (0 10g, 0.21 mmol) was dissolved in dimethylformamide (1 0 mL) NaH (0 006g, 0.24 mmol, 60% in oil) was added and the mixture was stirred for 5 min Ethyl bromoacetate (0.029 mL, 0.26 mmol) was added. When TLC (5% methanol/dichloromethane) analysis indicated consumption of starting material the reaction was quenched with water, diluted with ethyl acetate, transferred to a separatory funnel, washed with saturated water and brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography eluting with 100% dichloromethane followed by 3% methanol/dichloromethane to provide 0 086g (74%) of the title compound as a yellow glass. Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min gradient 40-100% Solvent B/A (Solvent A. 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min. Rt = 3.22 min, (97% pure) MS (M+H 586)

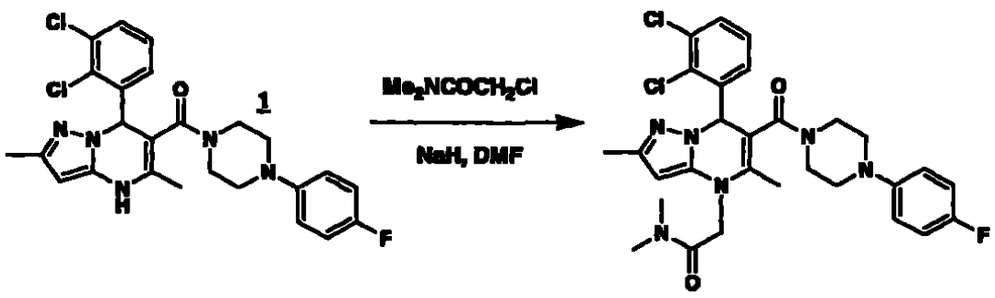
231
208

Example 409

7-(2,3-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-N,N,2,5-tetramethylpyrazolo[1,5-a]pyrimidine-4(7H)-acetamide



Method.



Compound 1 Compound 1 was prepared in a manner similar to that described in Example 18, Method 2.

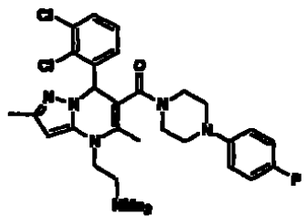
Title Compound. Compound 1 (0.08g, 0.16 mmol) was dissolved in dimethylformamide (0.8 mL). NaH (0.005g, 0.19 mmol, 60% in oil) was added and the mixture was stirred for 5 min. 2-chloro-N,N-dimethylacetamide (0.021 mL, 0.21 mmol) was added. When TLC (5% methanol/dichloromethane) analysis indicated consumption of starting material the reaction was quenched with water, diluted with ethyl acetate, transferred to a separatory funnel, washed with water and saturated brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography eluting with 100% dichloromethane followed by 3% methanol/dichloromethane to provide 0.058g (62%) of the title compound as a yellow

732
709

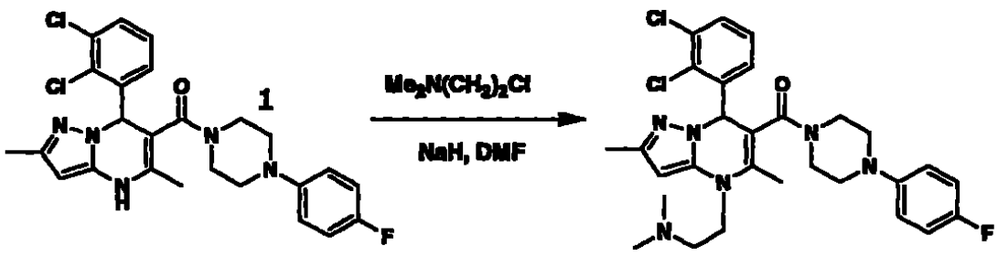
oil. Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min gradient 40-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0.1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min. Rt = 2.63 min, (93% pure) MS (M+H 585).

Example 410

1-[[7-(2,3-Dichlorophenyl)-4-[2-(dimethylamino)ethyl]-4,7-dihydro-2,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine



Method



Compound 1 Compound 1 was prepared in a manner similar to that described in Example 18, Method 2.

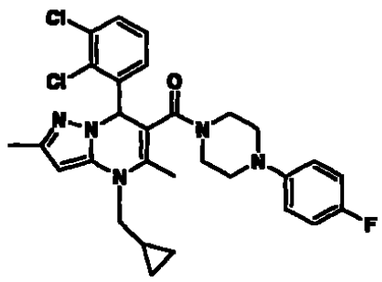
Title Compound Compound 1 (0 11g, 0 21 mmol) was dissolved in dimethylformamide (1 0 mL) Sodium hydride (0 054g, 0 47 mmol, 60% in oil) was added and the mixture was stirred for 5 min. 1-Chloro-2-dimethylaminoethane hydrochloride (0 040 g, 0.27 mmol) was added After 25 min the reaction was quenched with water diluted with ethyl acetate, transferred to a separatory funnel,

733
740

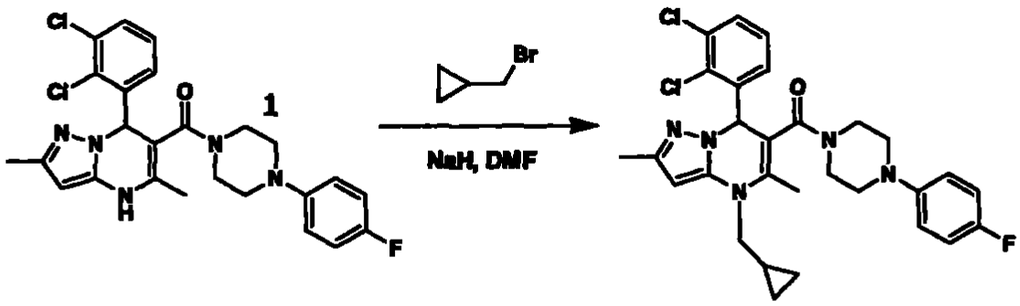
washed with saturated water and brine, dried over anhydrous sodium sulfate and concentrated LC/MS analysis of the residue indicated mostly unreacted starting material. The residue was redissolved in dimethylformamide (1 0 mL), Sodium hydride (0 10 g, 4 2 mmol) was added and the mixture was stirred for 5 min. 1-Chloro-2-dimethylaminoethane hydrochloride (0 15 g, 1 05 mmol) was added. When TLC (5% methanol/dichloromethane) analysis indicated consumption of starting material the reaction was quenched with water, diluted with ethyl acetate, transferred to a separatory funnel, washed with saturated water and brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography eluting with 100% dichloromethane followed by 3% methanol/dichloromethane to provide 0 030g (25%) of the title compound as a yellow glass Reverse Phase LC/MS YMC S5 ODS 4.6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 40-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min Rt = 1 72 min, (92% pure) MS (M+H 571)

Example 411

1-[[4-(Cyclopropylmethyl)-7-(2,3-dichlorophenyl)-4,7-dihydro-2,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine



Method.

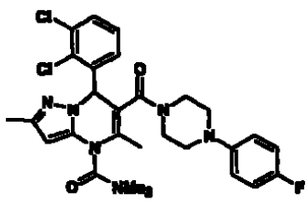


Compound 1 Compound 1 was prepared in a manner similar to that described in Example 18, Method 2.

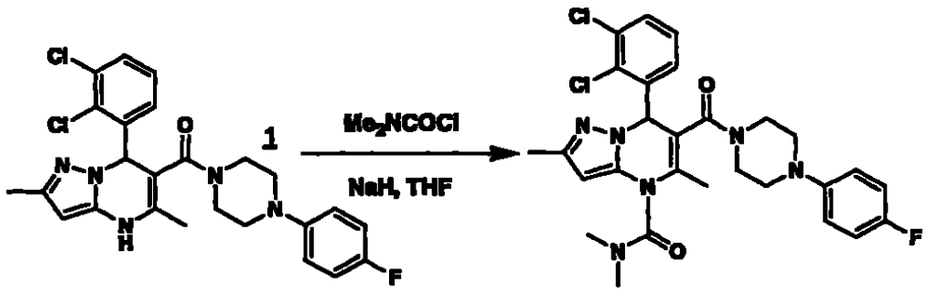
Title Compound Compound 1 (0 11g, 0 21 mmol) was dissolved in dimethylformamide (1 0 mL) Sodium hydride (0.006g, 0 25 mmol, 60% in oil) was added and the mixture was stirred for 5 min. (Bromomethyl)cylcopropane(0.0251 mL, 0 27 mmol) was added. When TLC (5% methanol/dichloromethane) analysis indicated consumption of starting material the reaction was quenched with water, diluted with ethyl acetate, transferred to a separatory funnel, washed with saturated water and brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography eluting with 100% dichloromethane followed by 3% methanol/dichloromethane to provide 0 104g (89%) of the title compound as a yellow glass Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 40-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min Rt = 2 99 min, (95% pure) MS (M+H. 554)

Example 412

7-(2,3-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-N,N,2,5-tetramethylpyrazolo[1,5-a]pyrimidine-4(7H)-carboxamide



Method.



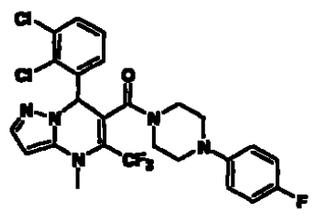
Compound 1 Compound 1 was prepared in a manner similar to that described in Example 18, Method 2.

Title Compound Compound 1 (0 22 g, 0.44 mmol) was dissolved in tetrahydrofuran (3 0 mL) Sodium hydride (0 106g, 4.44 mmol, 60% in oil) was added and the mixture was stirred for 5 min. N,N-Dimethylcarbamoyl chloride (0 12 mL, 1 33 mmol) was added. The mixture was stirred overnight TLC (5% methanol/dichloromethane) analysis indicated consumption of starting material the reaction was quenched with water, diluted with ethyl acetate, transferred to a separatory funnel, washed with saturated water and brine, dried over anhydrous sodium sulfate and concentrated The residue was purified by silica gel chromatography eluting with 100% dichloromethane followed by 3% methanol/dichloromethane to provide 0 22 g (87% yield) of the title compound. *LC/MS* indicated that the compound was impure. The title compound was further purified by silica gel chromatoagraphy eluting with 10% ethyl acetate/hexanes, followed by 50% ethyl acetate/hexanes and 100% ethyl acetate to afford 0 118 g (47%

yield) of the title compound as a white glass Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 40-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min Rt = 2 45 min, (95% pure) MS (M+H 571)

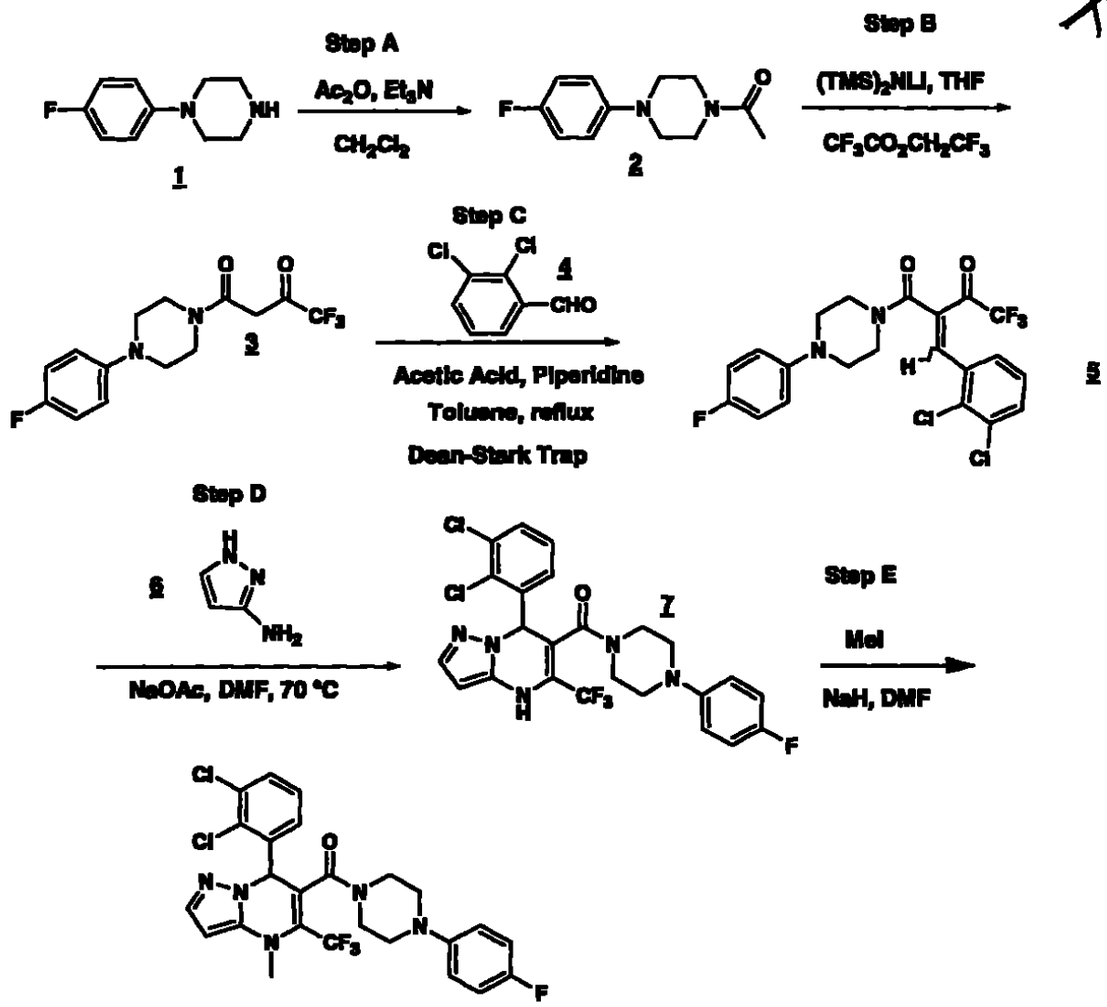
Example 413

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-4-methyl-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine



Method.

737
744



Step A Acetic anhydride (0 77 mL, 8 14 mmol) was dropwise added to a solution of 4-(4-fluorophenyl)piperazine 1 (1 17 g, 6.49 mmol) in dichloromethane (10 mL) TLC after 30 min. indicated reaction was complete. The mixture was transferred to a separatory funnel, washed with water and brine, dried over anhydrous sodium sulfate and concentrated to give 1 28 g (89% yield) of compound 2 as a clear solid. Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 0-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0.1% TFA), 4 mL/min. Rt = 1.58 min, (92% pure) MS (M+H 223) HMR ($CDCl_3$, 400 MHz) 6 96(2H, m), 6 89(2H, m), 3 77(2H, m),

3 62(2H, m), 3 07(4H, m), 2 14(3H, s) Compound 2 was used without further purification in the next step

Step B Lithium hexamethyldisilylazide (6 1 mL, 6 1 mmol, 1M in tetrahydrofuran) was dropwise added to a –78 °C solution of compound 2 (1 22 g, 5 5 mmol) in tetrahydrofuran (25 mL) After 40 min 2,2,2-trifluoroethyl trifluoroacetate (0 9 mL, 6 6 mmol) was added to the yellow solution. The reaction turned from yellow to clear After an additional 10 min the cooling bath was removed and the mixture was allowed to warm to room temperature After 30 min more the reaction was quenched with saturated ammonium chloride, diluted with ethyl acetate, transferred to a separatory funnel, washed with saturated ammonium chloride, water and brine, dried over anhydrous sodium sulfate and concentrated onto enough silica gel such that a free flowing powder was obtained The resulting powder was loaded onto a chromatography column prepacked with silica gel and 30% ethylacetate/hexanes Elution with 30% ethyl acetate/hexanes gave 0 998 g (57% yield) of compound 3 as a yellow solid. Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column UV detection at 220 λ, 4 min gradient 40-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0.1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min Rt = 2 87 min, (90% pure) MS (M+H 319) HMR ($CDCl_3$, 400 MHz) (note compound exists in the enol form) 7.00(2H, m), 6.90(2H, m), 5 80(1H, s), 3 79(4H, m), 3 13(4H, m)

Step C. Compound 3 and compound 4 were condensed as described in Example 18, Method 2 Step B, to provide compound 5 Compound 5 was used in the next step without further purification.

Step D Compound 5 and compound 6 were condensed as described in Example 18, Method 2 Step C1, to afford compound 7 Reverse Phase LC/MS of crude 6 YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 0-100% Solvent B/A (Solvent A. 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min Rt = 4 12 min, (58% pure) MS (M+H 540) Compound 7 was purified by silica gel chromatography eluting with 20-50% ethyl

acetate/hexanes followed by recrystallization from ethyl acetate/hexanes to give 0 084 g (6% yield) of compound 7 as a white solid Reverse Phase LC YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 0-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0.2% H_3PO_4, Solvent B 90% MeOH/H_2O with 0.2% H_3PO_4), 4 mL/min Rt = 4 15 min, (92% pure)

Step E Compound 7 (0 08g, 0 14 mmol) was dissolved in dimethylformamide (1 0 mL) NaH (0 005g, 0 19 mmol, 60% in oil) was added and the mixture was stirred for 305 min. Iodomethane (0 010 mL, 0 16 mmol) was added. The mixture was stirred for 2h and then quenched with saturated ammonium chloride, diluted with ethyl acetate, transferred to a separatory funnel, washed with saturated water and brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by preparative reverse phase HPLC.YMC S5 ODS 20 x 100 mm Ballistic column, UV detection at 220 λ, 10 min. gradient 30-100% Solvent B/A (Solvent A. 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 20 mL/min Rt = 10 6 min, to provide 0.037g (45%) of the title compound. Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 0-100% Solvent B/A (Solvent A. 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min. Rt = 3 83 min MS (M+H 568) Reverse Phase LC YMC S5 ODS 4.6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 0-100% Solvent B/A (Solvent A. 10% MeOH/H20 with 0 2% H_3PO_4, Solvent B 90% MeOH/H_2O with 0 2% H_3PO_4), 4 mL/min Rt = 4.37 min , 89% pure.

Examples 414-421

The compounds of Examples 414-421 shown in the table provided below, were prepared in a manner similar to that described in Example 413

HPLC resolution of Example 416, Chiralpak AD column (50 X 500 mm), eluting with 50% isopropanol/hexanes containing 0 1 % triethylamine at 50 mL/min), UV detection at 254 λ, provided enantiomers A (Example 418) and B (Example 417) Chiralpak AD column (4 6 X 250 mm) eluting with 50% isopropanol/hexanes

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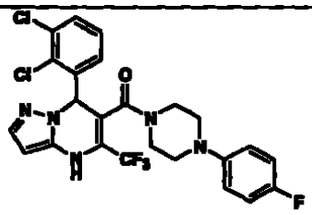
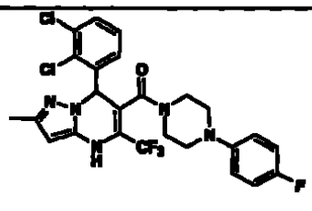
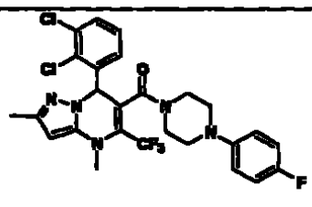
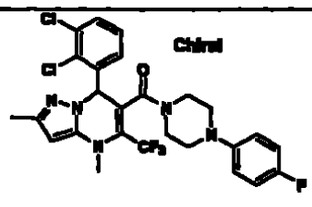
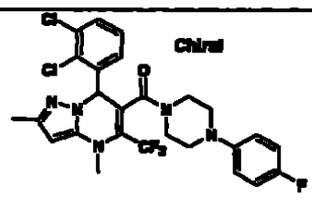
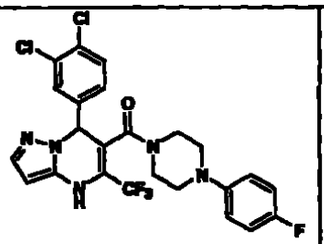
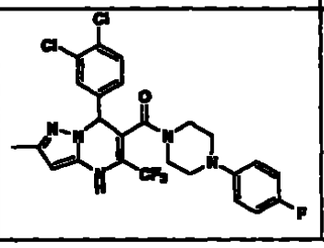
244

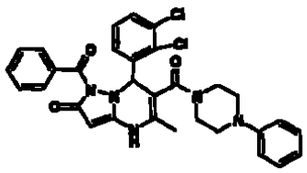
containing 0 1 % triethylamine at 1 mL/min), UV detection at 254 λ, enantiomer A Rt = 14.4 min, 89% ee. Enantiomer B Rt = 28 7 min, 87% ee

Example	Structure	Name	(M+H)
414		1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	554
415		1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2-methyl-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	554
416		1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2,4-dimethyl-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	568
417		1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2,4-dimethyl-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer B	568
418		1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2,4-dimethyl-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer A	568

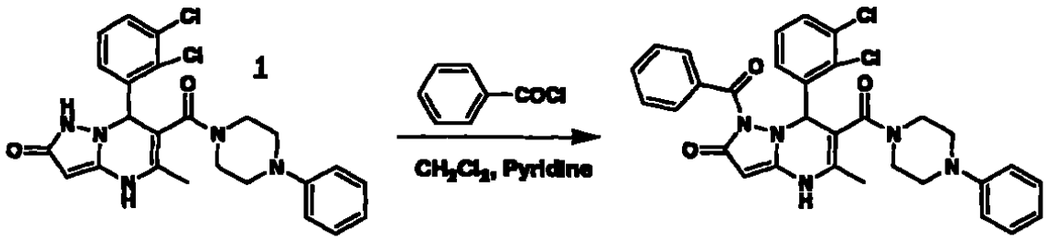
419		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	540
420		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-2-methyl-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	554

Example 421

1-[[1-Benzoyl-7-(2,3-dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine



Method.

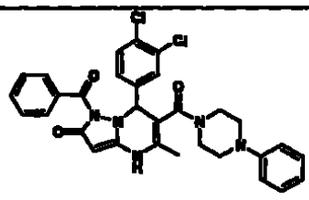
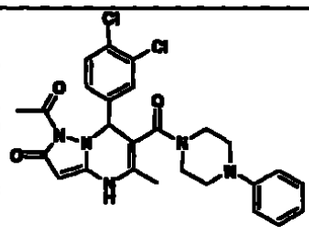
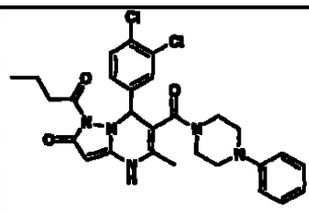


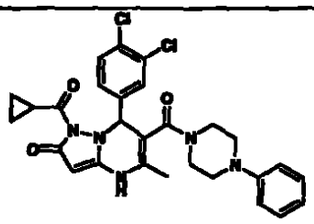
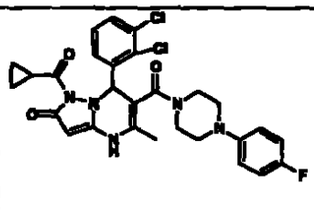
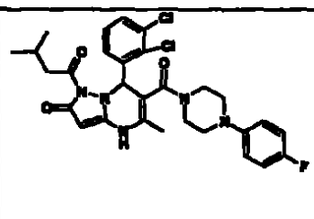
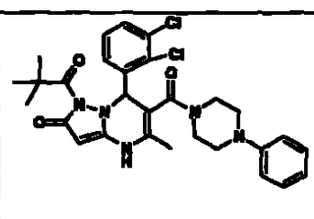
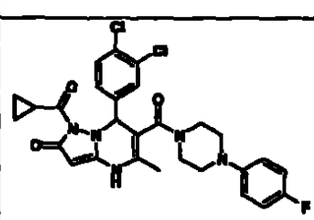
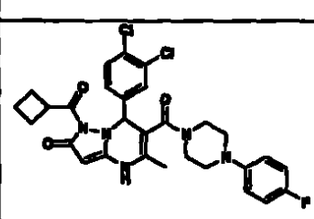
Compound 1 Compound 1 was prepared in manner similar to that described in Example 18, Method 2.

Title Compound Benzoyl chloride (0 007 mL, 0 06 mmol) and pyridine (0 008 mL, 0 10 mmol) were added to a 0 °C solution of compound 1 (0 08g, 0 17 mmol) in dichloromethane (5 mL) After 1h, TLC indicated the reaction was complete. The reaction was quenched with methanol and concentrated The residue was purified by silica gel chromatography eluting with 80% ethyl acetate/hexanes to afford 0 024 g (81%) of the title compound as a white solid. Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 0-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0.1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min Rt = 4.05 min, (86% pure) (M+H 588). HMR ($CDCl_3$, 400 MHz) 8.08(1H, s), 8.06(1H, s), 7 51(1H, m), 7 37(2H, t, J=8 Hz) 7 28(1H, m) 7 18(2H, m), 7 08(1H, m), 6.9-6 7(3H, m), 6 45 (1H, bs), 5 60(1H, bs), 4 15-2.8 (6H, m), 2.20(1H, bs), 1 88(3H, s), 1 45(1H, bs)

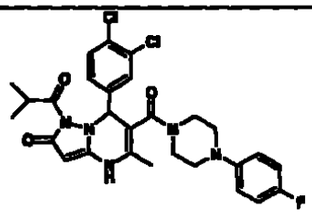
Examples 422-431

The compounds of Examples 422-431, shown in the table provided below were prepared in a manner similar to that described in Example 421

Example	Structure	Name	(M+H)
422		1-[[1-Benzoyl-7-(3,4-dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenyl-piperazine	588
423		1-[[1-Acetyl-7-(3,4-dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenyl-piperazine	526
424		1-[[7-(3,4-Dichloro-phenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxo-1-(1-oxobutyl)-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine	554

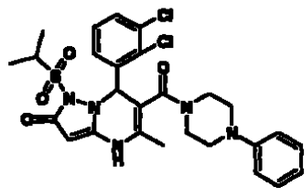
425		1-[[1-(Cyclopropyl-carbonyl)-7-(3,4-dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-phenyl-piperazine	552
426		1-[[1-(Cyclopropyl-carbonyl)-7-(2,3-dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-(4-fluoro-phenyl)piperazine	570
427		1-[[7-(2,3-Dichloro-phenyl)-1,2,4,7-tetra-hydro-5-methyl-1-(3-methyl-1-oxobutyl)-2-oxopyra-zolo[1,5-a]pyri-midin-6-yl]carbonyl]-4-(4-fluorophenyl)-piperazine	586
428		1-[[7-(2,3-Dichloro-phenyl)-(2,2-dimethyl-1-oxopropyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-phenyl-piperazine	568
429		1-[[1-(Cyclopropyl-carbonyl)-7-(3,4-dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-(4-fluoro-phenyl)piperazine	570
430		1-[[1-(Cyclobutyl-carbonyl)-7-(3,4-dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-(4-fluoro-phenyl)piperazine	584

744
727

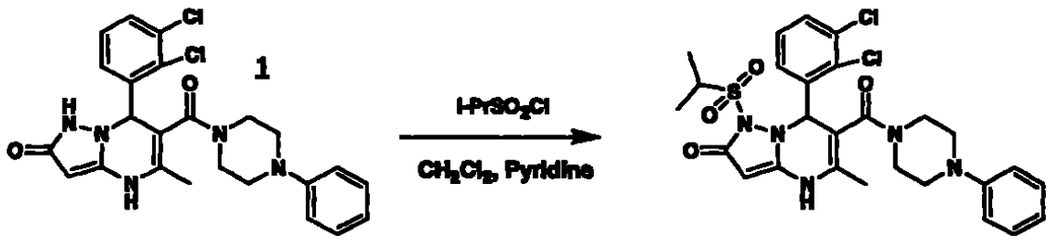
431		1-[[7-(3,4-Dichloro-phenyl)-1,2,4,7-tetrahydro-5-methyl-1-(2-methyl-1-oxopropyl)-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine	572

Example 432

1-[[7-(2,3-Dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-1-[(1-methylethyl)sulfonyl]-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine



Method.



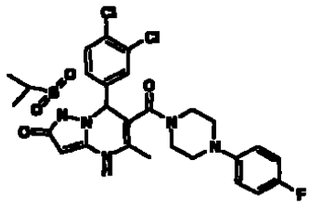
Compound 1 Compound 1 was prepared in a manner similar to that described in Example 18, Method 2.

Title Compound Isopropylsulfonyl chloride (0 11 mL, 0 97 mmol) and pyridine (0 12 mL, 1 46 mmol) were added to a 0 ^{0}C solution of compound 1 (0 234 g, 0.487 mmol) in dichloromethane (10 mL) The resulting mixture was allowed to warm to

room temperature. After 5h, TLC indicated the reaction was complete The reaction was quenched with methanol and concentrated The residue was purified by silica gel chromatography eluting with 5% methanol/ethyl acetate to afford 0 095 g (33%) of the title compound as a pale yellow solid. Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 0-100% Solvent B/A (Solvent A. 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min Rt = 3 57 min, (92% pure) (M+H 590)

Example 433

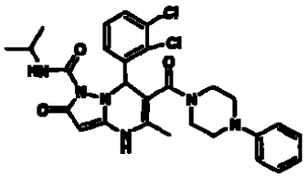
1-[[7-(3,4-Dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-1-[(1-methylethyl)sulfonyl]-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine



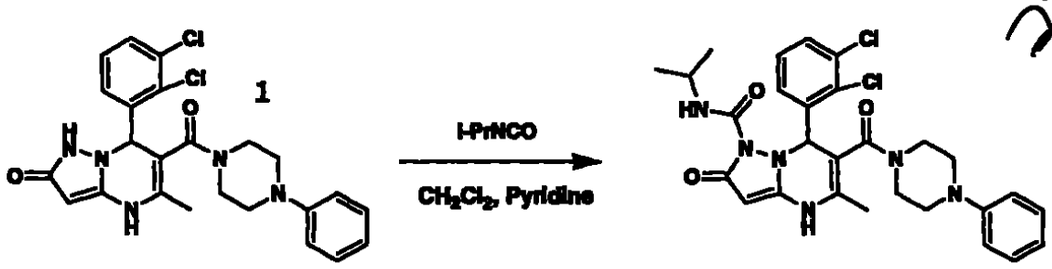
The title compound was prepared in a manner similar to that described in Example 432. (M+H) 608

Example 434

7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(1-methylethyl)-2-oxo-6-[(4-phenyl-1-piperazinyl)carbonyl]pyrazolo[1,5-a]pyrimidine-1(2H)-carboxamide



Method.

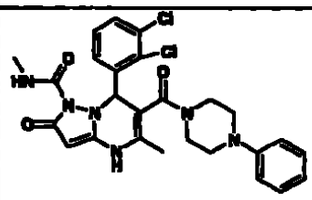


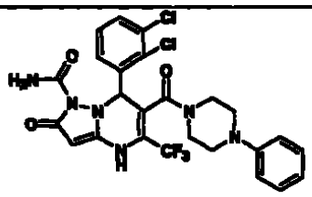
Compound 1 Compound 1 was prepared in a manner similar to that described in Example 18, Method 2

Title Compound Isopropyl isocyanate (0 034 mL, 0 35 mmol) and pyridine (0.057 mL, 0.706 mmol) were added to a 0 °C solution of compound 1 (0 170 g, 0.350 mmol) in dichloromethane (50 mL) The resulting mixture was allowed to warm to room temperature. After 5h, TLC indicated the reaction was complete The reaction was quenched with methanol and concentrated The residue was purified by silica gel chromatography eluting with 75% ethyl acetate/hexanes to afford 0 027 g (13%) of the title compound as a white solid. Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min gradient 0-100% Solvent B/A (Solvent A. 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min. Rt = 3 68 min, (95% pure) (M+H 569)

Examples 435 and 436

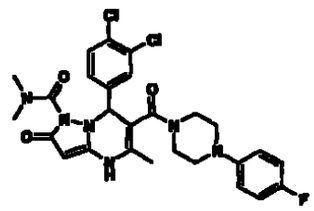
The compounds of Examples 435 and 436, shown in the table provided below, were prepared in a manner similar to that described in Example 434.

Example	Structure	Name	(M+H)
435		7-(2,3-Dichlorophenyl)-4,7-dihydro-N,5-dimethyl-2-oxo-6-[(4-phenyl-1-piperazinyl)-carbonyl]pyrazolo[1,5-a]pyrimidine-1(2H)-carboxamide	541

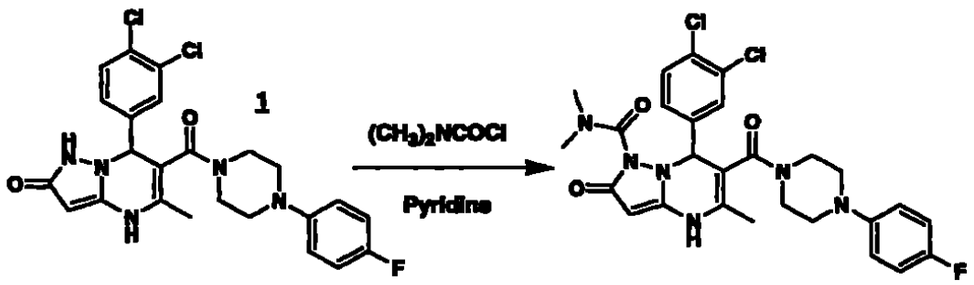
436		7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-2-oxo-6-[(4-phenyl-1-piperazinyl)carbonyl]-pyrazolo[1,5-a]pyrimidine-1(2H)-carboxamide	527

Example 437

7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-N,N,5-trimethyl-2-oxopyrazolo[1,5-a]pyrimidine-1(2H)-carboxamide



Method.



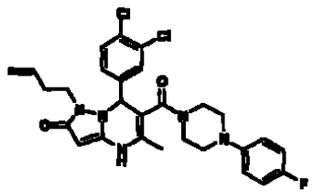
Compound 1 Compound 1 was prepared in a manner similar to that described in Example 18, Method 2

Title Compound Dimethylcarbamoyl chloride (0.10 mL, 1.1 mmol) was added to a 0 °C solution of compound 1 (0.52 g, 1.0 mmol) in pyridine (5 mL). The resulting mixture was stirred at 0 °C for 30 min, the cooling bath was removed, and the mixture was concentrated. The residue was dissolved in ethyl acetate and washed with water and brine, dried over anhydrous sodium sulfate and concentrated. The residue

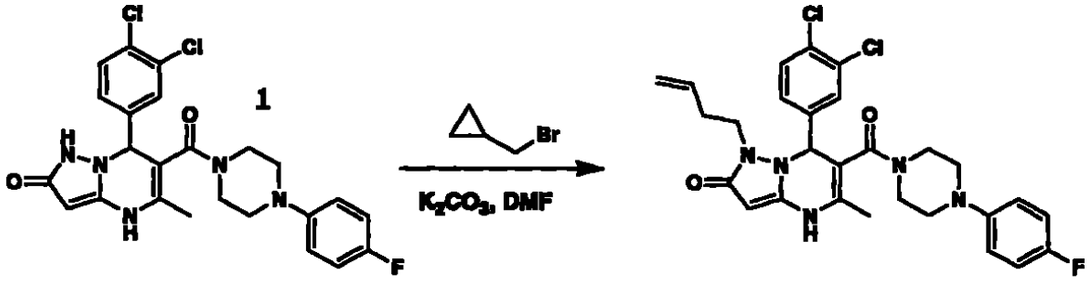
was purified by silica gel chromatography eluting with 5% methanol/ethyl acetate to afford 0 038 g (6%) of the title compound as a white solid Reverse phase *LC/MS* YMC S5 TurboPack Pro 4.6 x 33 column, UV detection at 220 λ, 2 min gradient 0 – 100 % Solvent B/A (Solvent A 10 % MeOH/H_2O with 0 1 % TFA, Solvent B 90 % MeOH/H_2O with 0 1 % TFA), 4 mL/min Rt = 1 97 min, 92 % pure) MS (M+H 573)

Example 438

1-[[1-(3-Butenyl)-7-(3,4-dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine



Method.



Compound 1 Compound 1 was prepared in a manner similar to that described in Example 18, Method 2

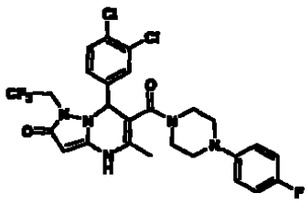
Title Compound (Bromomethyl)cyclopropane (0 246 mL, 1 82 mmol) was added to a mixture of compound 1 (0 831 g, 1 66 mmol) and potassium carbonate (g, mmol)

726 749

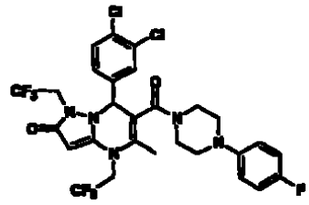
m dimethylformamide (10 mL) The resulting mixture was allowed to stir at room temperature for 4h. The reaction was diluted with ethyl acetate, transferred to a separatory funnel, washed with water and brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography eluting with 5% methanol/ethyl acetate to afford 0.030 g (3%) of the title compound Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min gradient 0-100% Solvent B/A (Solvent A. 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min Rt = 2 99 min, (87% pure) (M+H. 556)

Examples 439 and 440

1-[[7 (3,4-Dichlorophenyl) 1,2,4,7-tetrahydro-5-methyl-2-oxo-1-(2,2,2-trifluoroethyl)pyrazolo-[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	1-[[7-(3,4-Dichlorophenyl)-1,2,4 7 tetrahydro-5-methyl-2-oxo-1,4-bis(2,2,2 trifluoroethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine

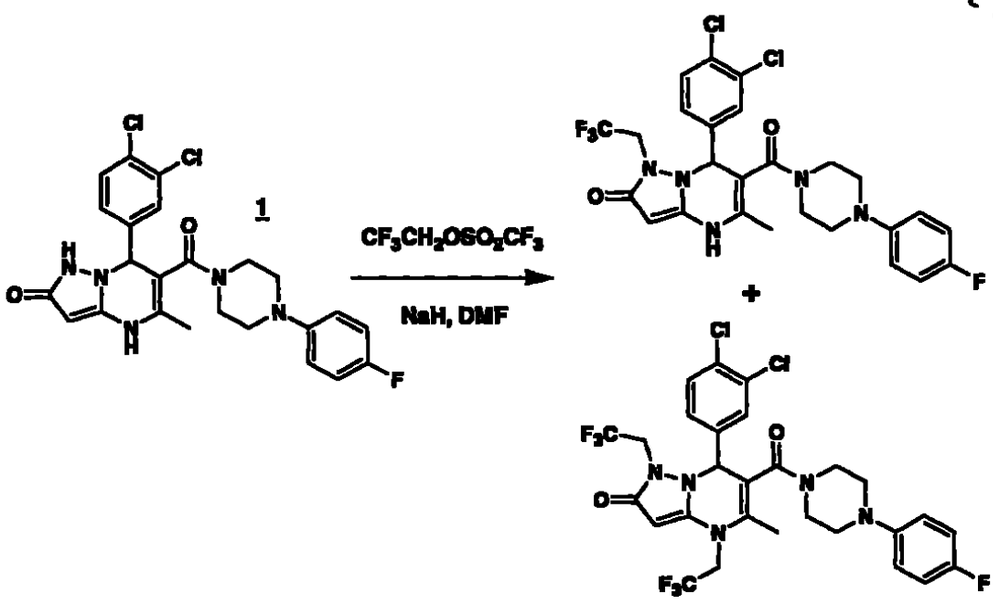


Example 439



Example 440

Method



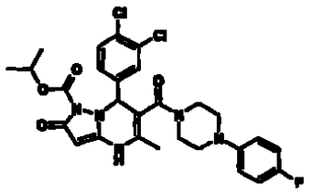
Compound 1 Compound 1 was prepared in a manner similar to that described in Example 18, Method 2.

Title Compounds. 2,2,2-trifluoroethyl trifluormethanesulfonate (0.49 g, 2 1 mmol) was added to a solution of compound 1 (0.967 g, 1 93 mmol) in dimethylformamide (10 mL) Sodium hydride (0 12 g, 2.89 mmol) was added TLC (10% methanol/ethyl acetate) indicated consumption of compound 1 The resulting mixture was was diluted with ethyl acetate, transferred to a separatory funnel, washed with water and brine, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel chromatography eluting with 100% ethyl acetate followed by10% methanol/ethyl acetate to give a mixture of the title compounds The title compounds were separated by preparative reverse phase HPLC YMC S5 ODS 20 X 100 mm column, 25 mL/min, 15 minute gradient eluting with 50%-100% solvent B/A (Solvent A 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA) Compound of Example 439 Rt = 11 05 min, Compound of Example 440 Rt = 11 88 min Compound of Example 439 Reverse phase LC/MS YMC S5 4 6 x 50 Ballistic column, UV detection at 220 λ, 4 min gradient 0 – 100 % Solvent B/A

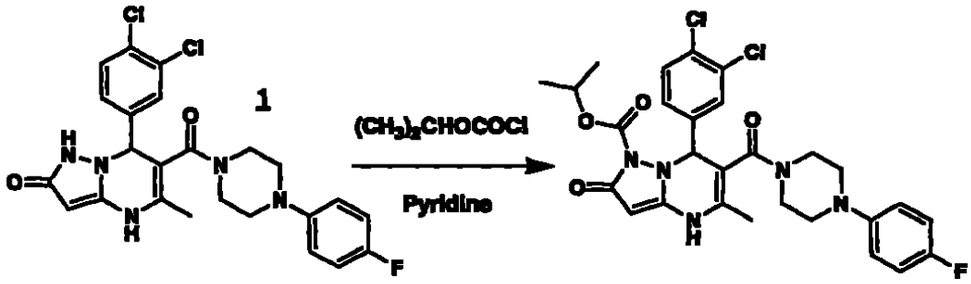
(Solvent A. 10 % MeOH/H_2O with 0 1 % TFA, Solvent B 90 % MeOH/H_2O with 0 1 % TFA), 4 mL/min. Rt = 2 87 min, 95 % pure) MS (M+H 584) Compound of Example 440 Reverse phase LC/MS YMC S5 4 6 x 50 Ballistic column, UV detection at 220 λ, 4 min gradient 0 – 100 % Solvent B/A (Solvent A. 10 % MeOH/H_2O with 0 1 % TFA, Solvent B 90 % MeOH/H_2O with 0 1 % TFA), 4 mL/min. Rt = 3 25 min, 85 % pure) MS (M+H 666)

Example 441

7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidine-1(2H)-carboxylic acid 1-methylethyl ester



Method.



Compound 1 Compound 1 was prepared in a manner similar to that described in Example 18, Method 2

Title Compound Isopropyl chloroformate (1 0 mL, 1 0 mmol, 1M in toluene) was added to a 0 °C solution of compound 1 (0.46 g, 0 92 mmol) in pyridine (5 mL) The resulting mixture was stirred at 0 °C for 30 min , the cooling bath was removed. After

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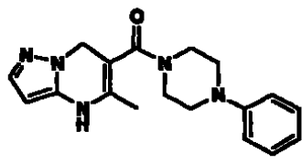
252

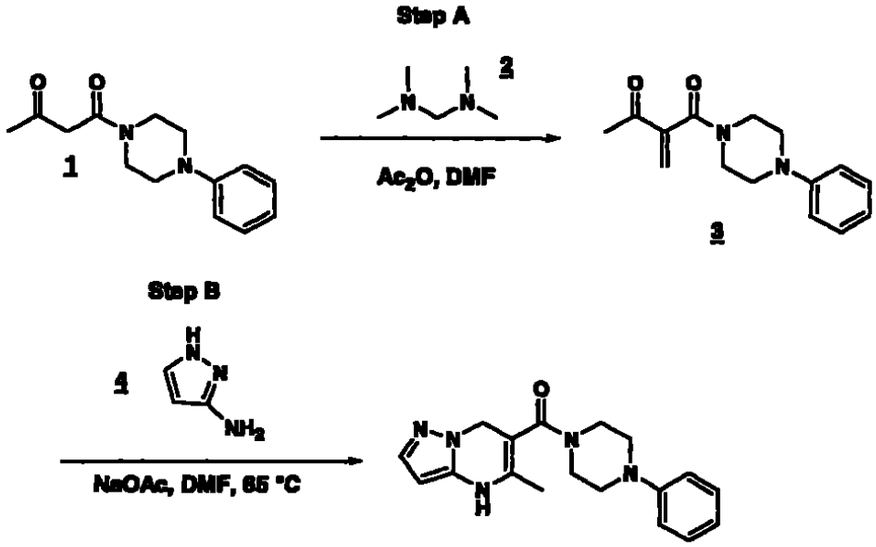
2h methanol was added to quench the reaction and the mixture was concentrated. The residue was purified by silica gel chromatography eluting with 5% methanol/ethyl acetate to afford 0 057 g (11%) of the title compound as a light pink solid Reverse phase LC/MS YMC S5 ODS 4 6 x 50 column, UV detection at 220 λ, 4 min gradient 0 – 100 % Solvent B/A (Solvent A. 10 % MeOH/H_2O with 0.1 % TFA, Solvent B 90 % MeOH/H_2O with 0 1 % TFA), 4 mL/min Rt = 3 67 min, 95 % pure) (M+H 573)

Example 442

1-[(4,7-Dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl)carbonyl]-4-phenylpiperazine



Method



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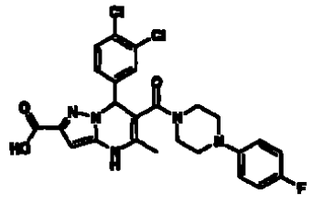
Compound 1 Compound 1 was prepared in a manner similar to that described in Example 18, Method 2.

Step A. Compound 2 (0 6 mL, 4.4 mmol) and acetic anhydride (0.83 mL, 8 8 mmol) were added to a solution of compound 1 (0 72 g, 2.9 mmol) in dimethylformamide (10 mL) The mixture was allowed to stir overnight, poured into water, extracted with dichloromethane. The extracts were combined, dried over anhydrous sodium sulfate and concentrated The residue was purified by silica gel chromatography eluting with 50% ethyl acetate/hexanes to 100% ethyl acetate/hexanes to give 0 290 g (38% yield) of compound 3 as a colorless syrup (M+H 259).

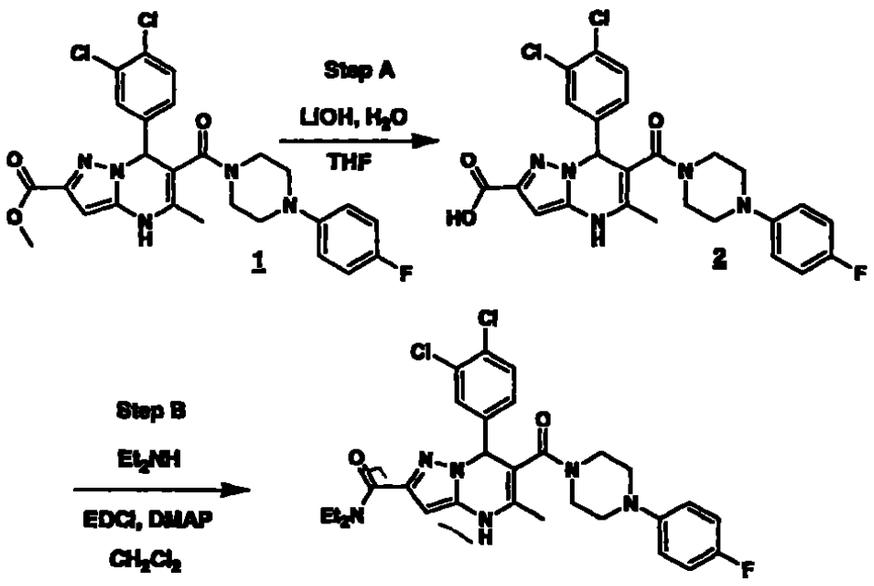
Step B Condensation of compound 3 and compound 4 as described in Example 18, Method 2 Step C provided the title compound Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4 min. gradient 0-100% Solvent B/A (Solvent A 10% MeOH/H20 with 0 1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4 mL/min. Rt = 1 96 min, (87% pure) (M+H 323)

Example 443

7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-2-carboxylic acid



Method.



Compound 1 Compound 1 was prepared in a manner similar to that described in Example 18, Method 2

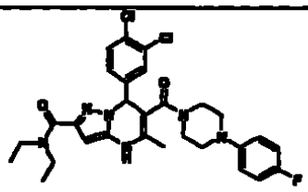
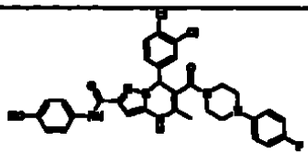
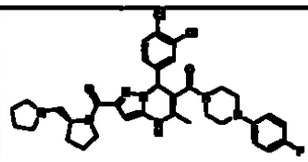
Step A Lithium hydroxide (0.43 g, 1 8 mmol) was dissolved in water (3 mL) and added slowly to a room temperature solution of compound 1 in tetrahydofuran (9 mL). The resulting mixture was stirred at room temperature for 3h. TLC indicated that all of compound 1 had been consumed. The mixture was quenched by the addition of acidic Dowex resin. The resin was filtered off The filtrate was diluted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate and concentrated to give 0.41 g (86% yield) of compound 2 as a light yellow solid Reverse phase LC/MS YMC S5 ODS 4 6 x 50 column, UV detection at 220 λ, 4 min gradient 0 – 100 % Solvent B/A (Solvent A. 10 % MeOH/H_2O with 0 1 % TFA, Solvent B 90 % MeOH/H_2O with 0 1 % TFA), 4 mL/min. Rt = 3.37 min, 96 % pure). MS (M+H 530)

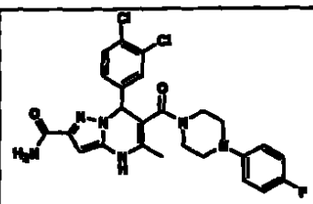
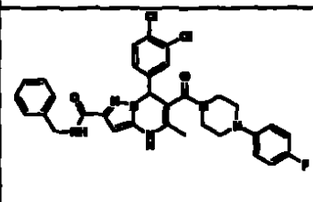
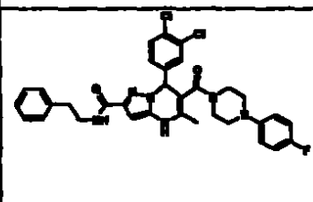
Step B. EDCI (0.025 g, 0 13 mmol), DMAP (0.003g, 0 02 mmol) were added to a solution of compound 2 (0.0508 g, 0 1 mmol) and diethylamine (0.014 mL, 0 13 mmol) in dichloromethane (3 mL) The mixture was stirred overnight. TLC indicated

some starting material remained The solvent was removed under reduced pressure. The resulting residue was purified by silica gel chromatography eluting with 5% methanol/ethyl acetate to give the title compound as a white solid. Reverse phase LC/MS YMC S5 4.6 x 50 Ballistic column, UV detection at 220 λ, 4 min gradient 0 – 100 % Solvent B/A (Solvent A 10 % MeOH/H_2O with 0.1 % TFA, Solvent B 90 % MeOH/H_2O with 0 1 % TFA), 4 mL/min Rt = 3 74 min, 91 % pure) MS (M+H. 585)

Examples 444-449

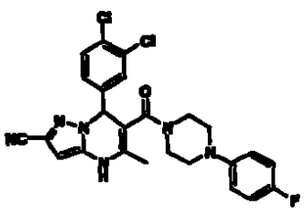
The compounds of Examples 445-450, shown in the table provided below, were prepared in a manner similar to that described in Example 443

Example	Structure	Name	(M+H)
444		7-(3,4-Dichlorophenyl)-N,N-diethyl-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-2-carboxamide	585
445		7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-N-(4-hydroxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidine-2-carboxamide	621
446		1-[[7-(3,4-Dichloro-phenyl)-4,7dihydro-5-methyl-2-[[(2S)-2-(1-pyrrolidinylmethyl)-1-pyrrolidinyl]carbonyl]-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	666

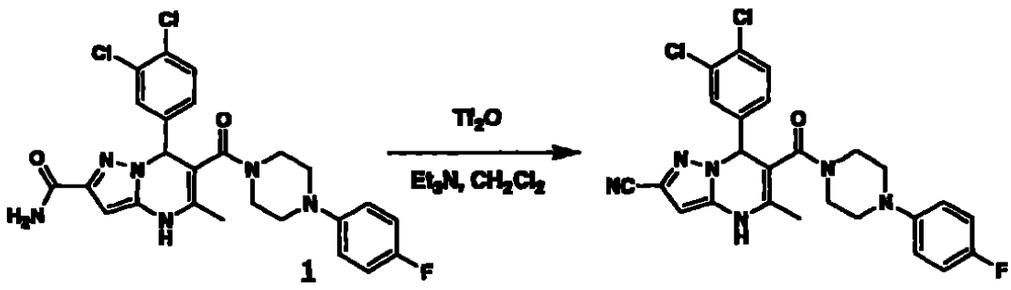
447		7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-2-carboxamide	529
448		7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-5-methyl-N-(phenylmethyl)pyrazolo-[1,5-a]pyrimidine-2-carboxamide	619
449		7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-5-methyl-N-(2-phenylethyl)-pyrazolo[1,5-a]pyrimidine-2-carboxamide	633

Example 450

1-[[2-Cyano-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine



Method

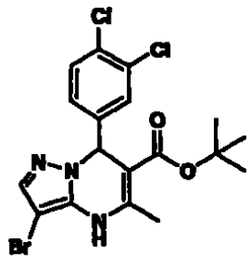


Compound 1 Compound 1 (the compound of Example 447) was prepared in a manner similar to that described in Example 443

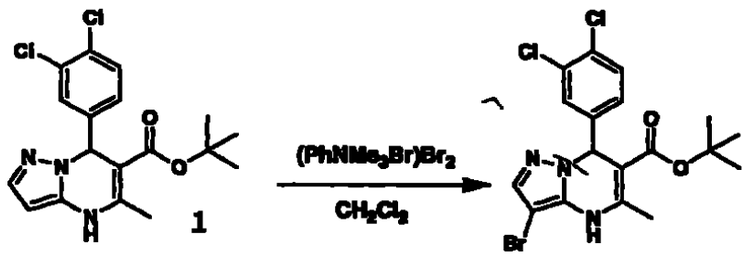
Title Compound Triflic anhydride (0 036 mL, 0.21 mmol) was added to a 0 °C solution of compound 1 (0 103 g, 0.19 mmol) and triethylamine (0.054 mL, 0.39 mmol) in dichloromethane (5 mL). After 10 min , TLC (5% methanol/ethyl acetate) indicated that compound 1 remained. Additional Triflic anhydride (0.036 mL, 0.21 mmol) and triethylamine (0.054 mL, 0.39 mmol) were added. After 10 min., TLC (5% methanol/ethyl acetate) indicated that compound 1 remained. The mixture was warmed to room temperature and stirred for an additional 30 min. The reaction was poured into saturated sodium bicarbonate, extracted with dichloromethane. The extracts were combined, dried over anhydrous sodium sulfate and concentrated. The resulting residue was purified by silica gel chromatography eluting with 2% methanol/ethyl acetate to 0.018 g (19 % yield) of the title compound as a white solid. Reverse phase LC/MS YMC S5 4.6 x 33 column, UV detection at 220 λ, 2 min gradient 0 – 100 % Solvent B/A (Solvent A 10 % MeOH/H_2O with 0 1 % TFA, Solvent B 90 % MeOH/H_2O with 0 1 % TFA), 4 mL/min. Rt = 3.60 min, 81 % pure) MS (M+H 511)

Example 451

3-Bromo-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethyl ester



Method

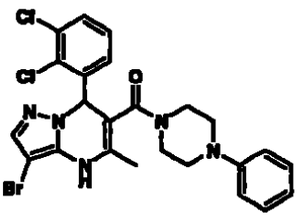


Compound 1 Compound 1 was prepared as described in Example 4

Title Compound Phenyltrimethylammonium tribromide (0.057 g, 0 14 mmol) was added to a 0 °C solution of compound 1 (0.05 g, 0 13 mmol) in dichloromethane (2 mL) The mixture was allowed to warm to room temperature over 4h. The solvent was removed under reduced pressure. The resulting residue was purified by preparative TLC (Analtech, silica gel, 20 X 20 cm, 1000μ) Elution with 25% acetone/hexane provided 0.047 g (79% yield) of the title compound as a white solid. Reverse Phase HPLC: YMC S5 ODS 4 6 x 50mm Ballistic column, UV detection at 220 λ, 4min. gradient 0-100% Solvent B/A (Solvent A. 10% MeOH/H_2O with 0.2% H_3PO_4, Solvent B 90% MeOH/H_2O with 0.2% H_3PO_4), 4mL/min. Rt = 4.67 min, (95% pure) Reverse Phase LC/MS YMC S5 ODS 4 6 x 50 mm Ballistic column, UV detection at 220 λ, 4min. gradient 0-100% Solvent B/A (Solvent A 10% MeOH/H_2O with 0.1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4mL/min Rt = 4 19 min. MS (EM, M+1 458) HMR ($CDCl_3$, 400MHz) 7.37(1H,d,J=2.0Hz), 7 36(1H,d,J=8 0Hz), 7.33(1H,s), 7 12(1H,dd,J=2.2 and 8.4Hz), 6 38(1H,s), 6 27(1H,s), 2.53(3H,s) 1.36(9H,s).

Example 452

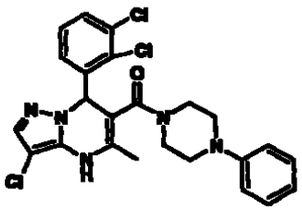
1-[[3-Bromo-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine



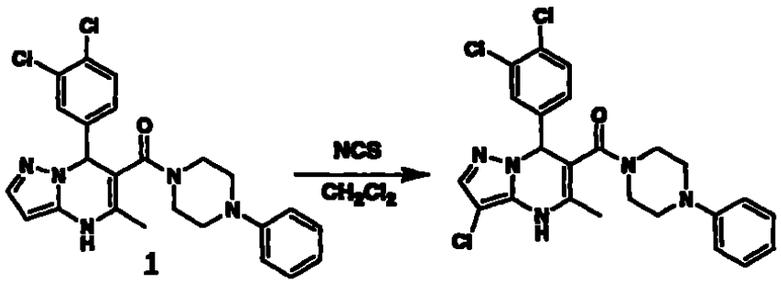
The compound of Example 452 was prepared in a manner similar to that described in Example 451 (M+H) 547

Example 453

1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine



Method.



1

Compound 1 Compound 1 was prepared in a manner similar to that described in Example 18, Method 2

Title Compound N-chlorosuccinimide (0.0102 g, 0.076 mmol) was added to a 0 °C solution of compound 1 (0.0343 g, 0 073 mmol) in dichloromethane (4 mL). The mixture was allowed to warm to room temperature over 2h. The solvent was removed under reduced pressure. The resulting residue was purified by preparative TLC (Analtech, silica gel, 20 X 20 cm, 1000μ) Elution with 50% acetone/hexane provided 0 0287g (77% yield) of the title compound as a yellow oil which solidified upon standing Reverse Phase HPLC· YMC S5 ODS 4.6 x 50mm Ballistic column, UV detection at 220 λ, 4 min. gradient 0-100% Solvent B/A (Solvent A 10% MeOH/H_2O with 0.2% PPA, Solvent B 90% MeOH/H_2O with 0.2% PPA), 4mL/min. Rt = 4 21 min, (91% pure) Reverse Phase LC/MS YMC S5 ODS 4.6 x 50mm Ballistic column, UV detection at 220 λ, 4min. gradient 0-100% Solvent B/A (Solvent A. 10% MeOH/H_2O with 0.1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4mL/min Rt = 3 72min MS (EM, M+1 501)

Examples 454-463

The compounds of Examples 454-463, shown in the table provided below, were prepared in a manner similar to that described in Example 453

Example 456 was obtained from the single enantiomer B of Example 30, and Example 457 was obtained from the single enantiomer A of Example 29 Chiralpak AD column (4 6 X 250 mm) eluting with 30% isopropanol/hexanes containing 0.1 % triethylamine at 1 mL/min), UV detection at 254λ, Example 456 Rt = 5 9 min, >99% ee. Example 457 Rt = 6 3 min, >99% ee.

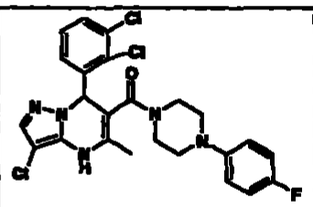
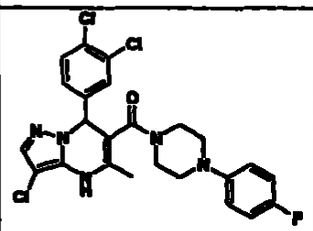
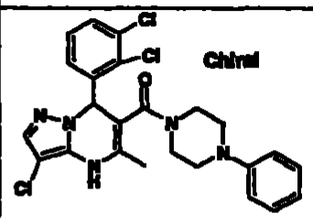
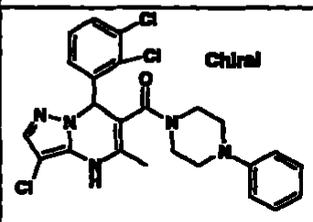
Example 458 was obtained from the single enantiomer A of Example 51, and Example 459 was obtained from the single enantiomer B of Example 52. Chiralcel OD column (4 6 X 250 mm) eluting with 30% isopropanol/hexanes containing 0 1 % triethylamine at 1 mL/min), UV detection at 254λ, Example 458 Rt = 7.8 min, >99% ee. Example 459 Rt = 8 4 min, >99% ee.

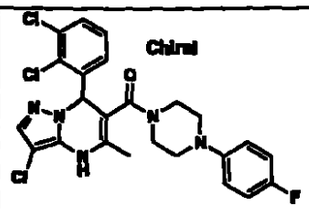
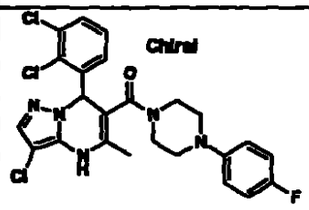
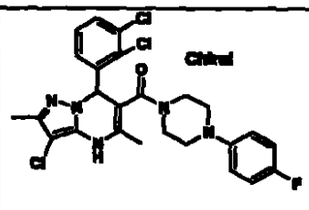
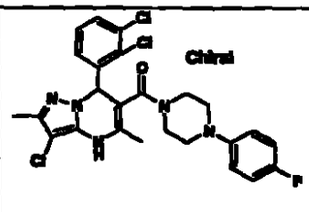
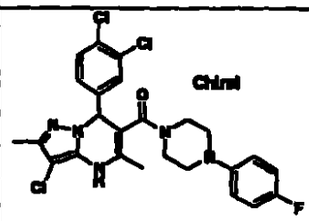
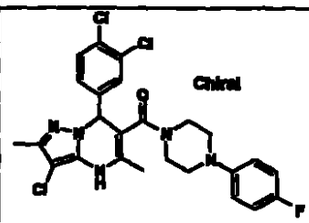
Example 460 was obtained from the single enantiomer A of Example 169, and Example 461 was obtained from the single enantiomer B of Example 168 Chiralpak

737
761

AD column (4.6 X 250 mm) eluting with 20% isopropanol/hexanes containing 0 1 % triethylamine at 1 mL/min), UV detection at 254λ, Example 461 Rt = 9.2 min, >99% ee. Example 460 Rt = 9.4 min, >99% ee.

Example 462 was obtained from the single enantiomer A of Example 81, and Example 463 was obtained from the single enantiomer B of Example 82 Chiralpak AD column (4 6 X 250 mm) eluting with 20% isopropanol/hexanes containing 0 1 % triethylamine at 1 mL/min), UV detection at 254λ, Example 462 Rt= 8 25 min, >99% ee. Example 463 Rt = 8 28 min, >99% ee.

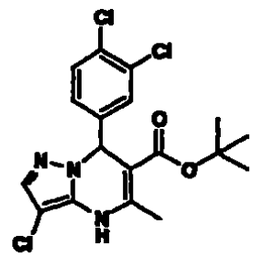
Example	Structure	Name	(M+H)
454		1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	520
455		1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	520
456		1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine, enantiomer B	502
457		1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenyl-piperazine, enantiomer A	502

458		1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer A	520
459		1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer B	520
460		1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer A	534
461		1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer B	534
462		1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer A	534
463		1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer B	534

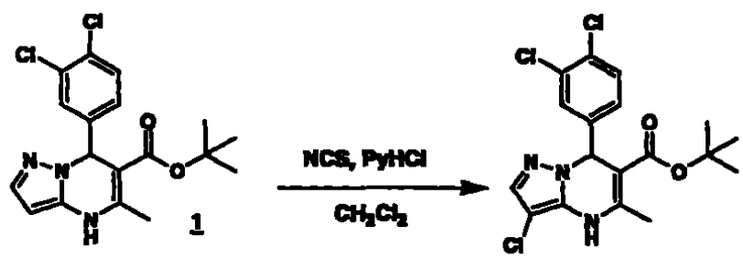
763
239

Example 464

3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethyl ester



Method.



1

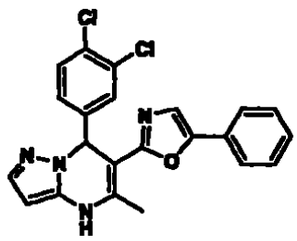
Compound 1. Compound 1 was prepared as described in Example 4

Title Compound Pyridine hydrochloride (0.020 g, 0.173 mmol) was added to a 0 °C solution of compound 1 (0.060 g, 0.158 mmol) in dichloromethane (4 mL). After 2 min, N-chlorosuccinimide (0.0231 g, 0.174 mmol) was added. The mixture was allowed to warm to room temperature and was stirred for 13h The solvent was removed under reduced pressure. The resulting residue was purified by preparative TLC (Analtech, silica gel, 20 X 20 cm, 1000μ) Elution with 20% acetone/hexane provided 0.0092g (14% yield) of the title compound as a yellow oil. Reverse Phase HPLC. YMC S5 ODS 4.6 x 50mm Ballistic column, UV detection at 220 λ, 4min. gradient 0-100% Solvent B/A (Solvent A. 10% MeOH/H_2O with 0.2% PPA, Solvent B 90% MeOH/H_2O with 0.2% PPA), 4mL/min. Rt = 4 61 min, (94% pure). Reverse

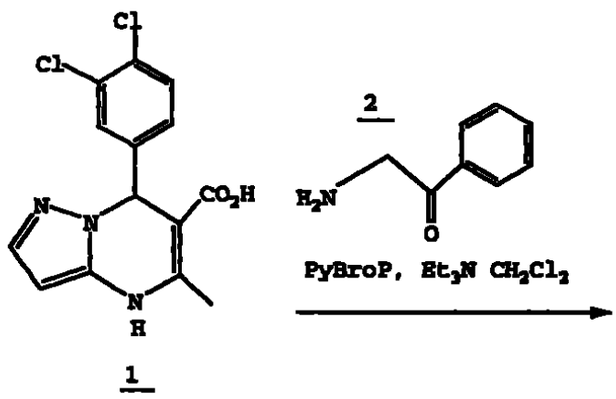
Phase LC/MS YMC S5 ODS 4 6 x 50mm Ballistic column, UV detection at 220 λ, 4min. gradient 0-100% Solvent B/A (Solvent A 10% MeOH/H_2O with 0.1% TFA, Solvent B 90% MeOH/H_2O with 0 1% TFA), 4mL/min. Rt = 4 71min MS (EM, M+1 414) HMR ($CDCl_3$, 400MHz) 7.37(1H,s) 7.36(1H,d,J=1 7Hz) 7.36(1H,d,J=8.4Hz), 7 12(1H,dd,J=2.0 and 8.4Hz), 6 45(1H,brs), 6 24(1H,s), 2 52(3H,s), 1 36(9H,s)

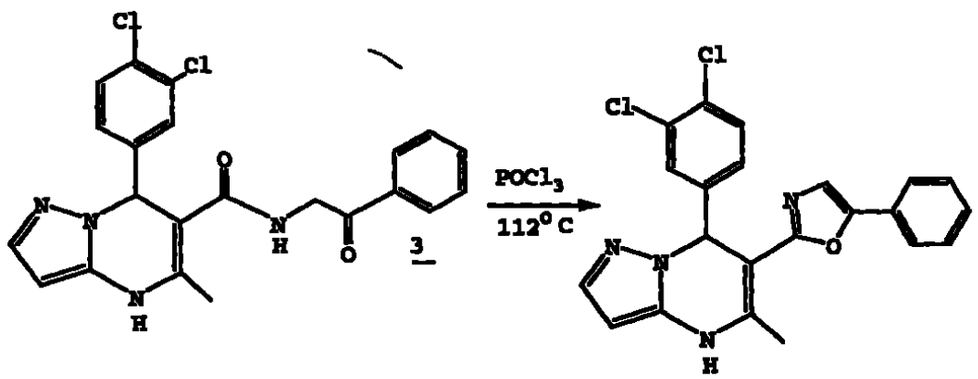
Example 465

7-(3 4 Dichlorophenyl)-4,7-dihydro-5-methyl-6-(5-phenyl-2-oxazolyl)pyrazolo[1,5-a]pyrimidine



Method





Compound 1 Compound 1 was synthesized as described in Example 16

Compound 3 Compound 1 (200 mg, 0.62 mmol) was suspended in 2 mL of dichloromethane. Triethylamine (300 µL, 2.2 mmol) and 2-aminoacetophenone 2 (116 mg, 0.68 mmol) were added followed by bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBrOP) (312 mg, 0 68 mmol) All the solid dissolved upon addition of PyBrOP and the reaction was stirred for 4 hrs The mixture was loaded onto silica gel and purified by flash chromatography on silica gel eluted with 40% acetone, hexane to yield 106 mg (39%) of a pink solid ^{1}H NMR (400 MHz, CDCl3) 44180-148-16,^{1}H COSY (400 MHz, CD3OD), ^{13}C NMR (100 MHz, $CDCl_3$), HPLC >99% at 4.0 min (YMC S5 ODS 4 6 x 50 mm column,10-90% methanol, water with 0.2% phosphoric acid gradient over 4 min., 4 mL/ min., uv detection at 220 nm)

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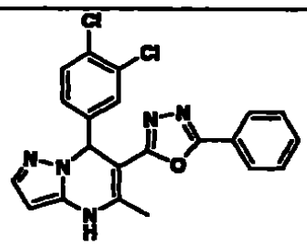
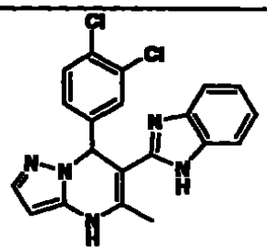
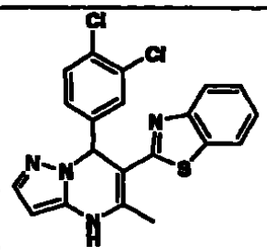
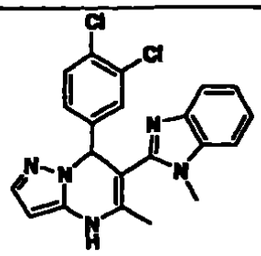
Title Compound The amide 3 (100 mg, 0 22 mmol) was dissolved in 2 mL phosphorus oxychloride and heated to 112° for 2 h The mixture was then quenched onto ice and extracted with ethylacetate. The extracts were dried over magnesium sulfate, filtered and the solvent removed to provide 339 mg of a brown oil The oil was purified by flash chromatography on silica gel eluted with 20-40% acetone, hexane to yield 50 mg (51%) of the title compound as a white powder mp 229-231° ^{1}H NMR (400 MHz, CD3OD), MS (ESI) *m/z* 423 (MH^+); HPLC >99% at 4 7 min (YMC S5 ODS 4 6 x 50 mm column, 10-90% methanol, water with 0.2% phosphoric acid gradient over 4 min. then hold at 90% methanol, water; 4 mL/ min uv detection at 220 nm)

Examples 466-469

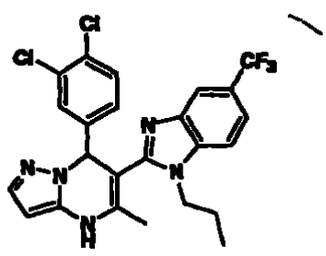
The compounds of Examples 466-473, shown in the table provided below, were prepared in a manner similar to that described in Example 465.

Example	Structure	Name	(M+H)
466		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-6-(5-phenyl-1,3,4-oxadiazol-2-yl)pyrazolo[1,5-a]pyrimidine	424
467		6-(1H-Benzimidazol-2-yl)-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine	396
468		6-(2-Benzothiazolyl)-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine	413

469		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-6-(1-methyl-1H-benzimidazol-2-yl)pyrazolo[1,5-a]pynmidine	410

Example 470

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-6-[5-(trifluoromethyl)-1-propyl-1H-benzimidazol-2-yl]pyrazolo[1,5-a]pyrimidine



Method

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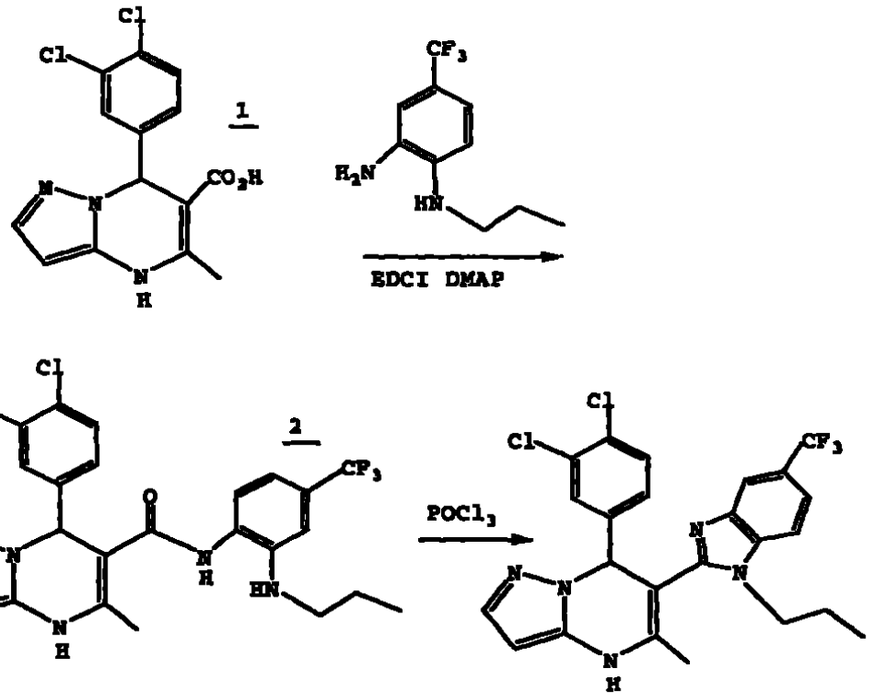


Compound 2 To a solution of acid 1, prepared as described in Example 16, (0 15g, 0.463 mmol), 2-(n-propylamino)-5-trifluoromethylaniline (0.141g, 0.648 mmol) and DMAP (5mg, cat.) EDCI (0.124g, 0.0648 mmol) was added and the solution was stirred at room temperature for 2 hours. The reaction was treated with saturated sodium bicarbonate, the organic solution was dried with magnesium sulfate and the solvent was evaporated. The crude product 2 was used without further purification.

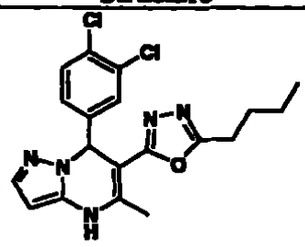
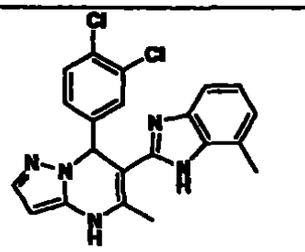
Title Compound. Compound 2 was dissolved in phosphorus oxychloride (4 mL) and heated to 80 °C for 4 h. TLC indicated the reaction was not complete. Additional phosphorus oxychloride (2 mL) was added and the mixture was heated for 2h and then left to stand at room temperature overnight. The mixture was then quenched onto ice, made basic with ammonium hydroxide, and extracted with ethyl acetate. The extracts were dried over magnesium sulfate and concentrated. The crude product was purified by preparative reversed phase chromatography (YMC PACK ODSA S3 20x 100 mm column 50-100 methanol, water with 0.1% TFA gradient over 10 min., 20 mL/min., uv detection at 220 nm.) The appropriate fractions were evaporated, the residue was partitioned between saturated sodium bicarbonate

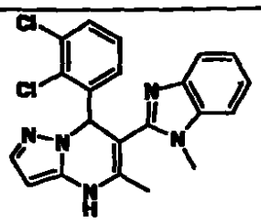
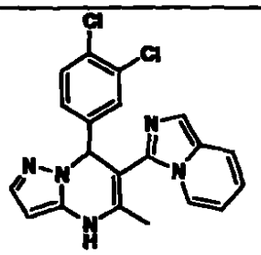
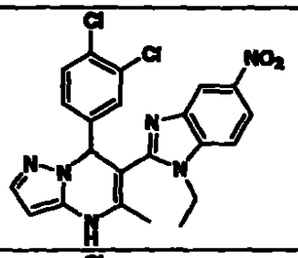
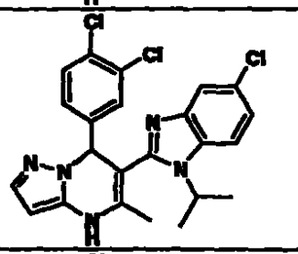
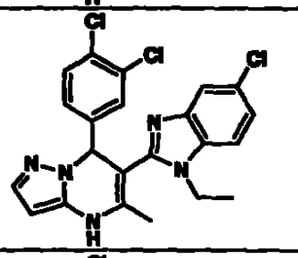
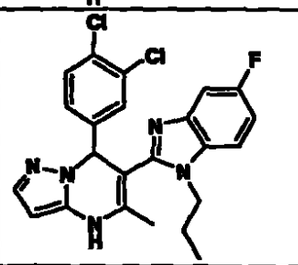
and ethyl acetate, the organic solution was dried and the solvent was removed under vacuum giving the product (27 mg, 11.5%) as a tan glass $[M+H]^+$ *m/z* 506 HPLC 91 1% at 4 6 min (YMC S5 ODS 4 6 x 50 mm column,10-90% methanol, water with 0 2% phosphoric acid gradient over 4 min 4 mL/ min , uv detection at 220 nm)

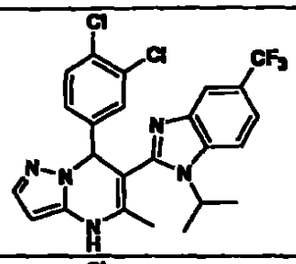
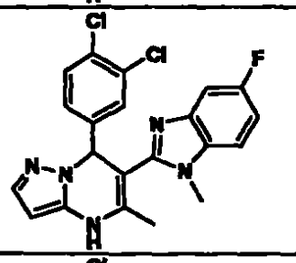
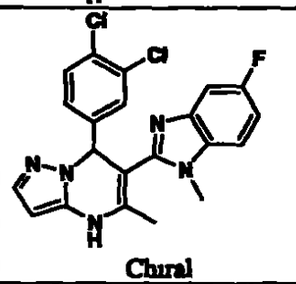
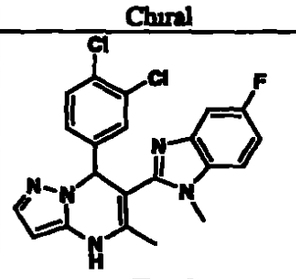
Examples 471-482

The compounds of Examples 471-482, shown in the table provided below, were prepared in a manner similar to that described in Example 470

HPLC resolution of Example 480, Chiralcel OD column (50 X 500 mm), eluting with 25% isopropanol/hexanes containing 0.1 % triethylamine at 50 mL/min), UV detection at 254 λ provided enantiomers A (Example 481) and B (Example 482) Analytical Chiralcel OD column (4 6 X 250 mm) eluting with 25% isopropanol/hexanes containing 0 1 % triethylamine at 1 mL/min), UV detection at 254 λ, enantiomer A Rt = 7 2 min, >99% ee. Enantiomer B Rt = 10.0 min, >99% ee.

Example	Structure	Name	(M+H)
471		6-(5-Butyl-1,3,4-oxadiazol-2-yl)-7-(3,4-dichlorophenyl)-4,7dihydro-5-methylpyrazolo[1,5-a]pyrimidine	404
472		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-6-(4-methyl-1H-benzimidazol-2-yl)pyrazolo[1,5-a]pyrimidine	410

473		1-[[7-(2,3-Dichloro-phenyl)-4,7-dihydro-5-methyl-6-(1-methyl-1H-benzimidazol-2-yl)pyrazolo[1,5-a]pyrimidine	410
474		7-(3,4-Dichlorophenyl)-4,7-dihydro-6-(imidazo[1,5-a]pyridin-3-yl)-5-methylpyrazolo[1,5-a]pyrimidine	510
475		7-(3,4-Dichlorophenyl)-6-(1-ethyl-5-nitro-1H-benzimidazol-2-yl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine	469
476		6-[5-Chloro-1-(1-methylethyl)-1H-benzimidazol-2-yl]-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine	472
477		6-(5-Chloro-1-ethyl-1H-benzimidazol-2-yl)-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine	458
478		7-(3,4-Dichlorophenyl)-6-(5-fluoro-1-propyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine	456.35

479		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-6-[1-(1-methylethyl)-5-(trifluoromethyl)-1H-benzimidazol-2-yl]pyrazolo[1,5-a]pyrimidine	506
480		7-(3,4-Dichlorophenyl)-6-(5-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine	428
481	 Chiral	7-(3,4-Dichlorophenyl)-6-(5-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine, enantiomer A	428
482	 Chiral	7-(3,4-Dichlorophenyl)-6-(5-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine, enantiomer B	428

Example 483

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-6-[1-(phenylmethyl)-1H-benzimidazol-2-yl]pyrazolo[1,5-a]pyrimidine

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772
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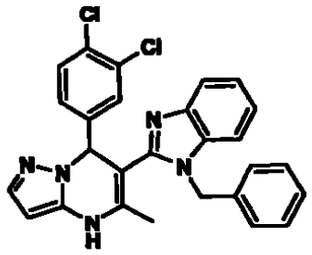
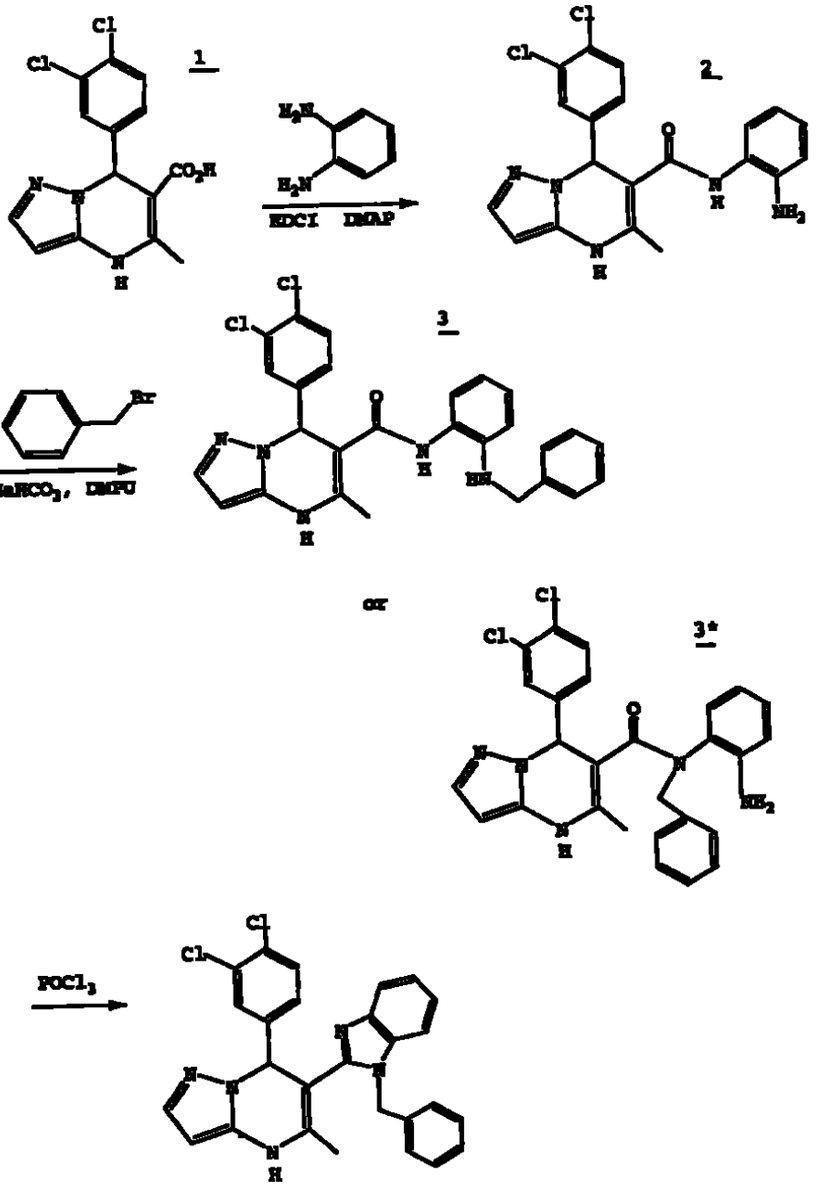


Method



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748

Compound 1 Prepared as described in Example 16

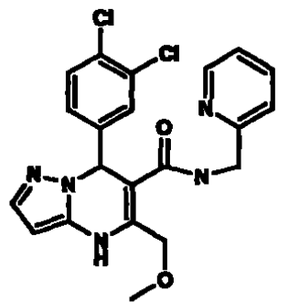
Compound 2 Prepared from compound 1 and phenylenediamine in a manner similar to that described in Example 470.

Compound 3 A suspension of 2 (50 mg 0 121mmol), $NaHCO_3$ (50 mg, 0 6 mmol) and benzyl bromide (20 mg, 0 121 mmol) in DMPU (0.5 mL) was stirred at room temp overnight. Another equivalent of benzyl bromide was added completing the reaction. The suspension was partitioned between water and ethyl acetate, the organic phase was dried ($MgSO_4$), and the solvent was evaporated. The residue was flash chromatographed through silica eluting with hexane-acetone 2 1 to provide either or both of compounds 3 and 3* (exact structure was not determined) (24.8 mg, 41%) as a white solid. Mp 135-140, $[M+H]^+$ *m/z* 504, HPLC 100% at 4 4 min (YMC S5 ODS 4 6 x 50 mm column,10-90% methanol, water with 0 2% phosphoric acid gradient over 4 min., 4 mL/ min., uv detection at 220 nm)

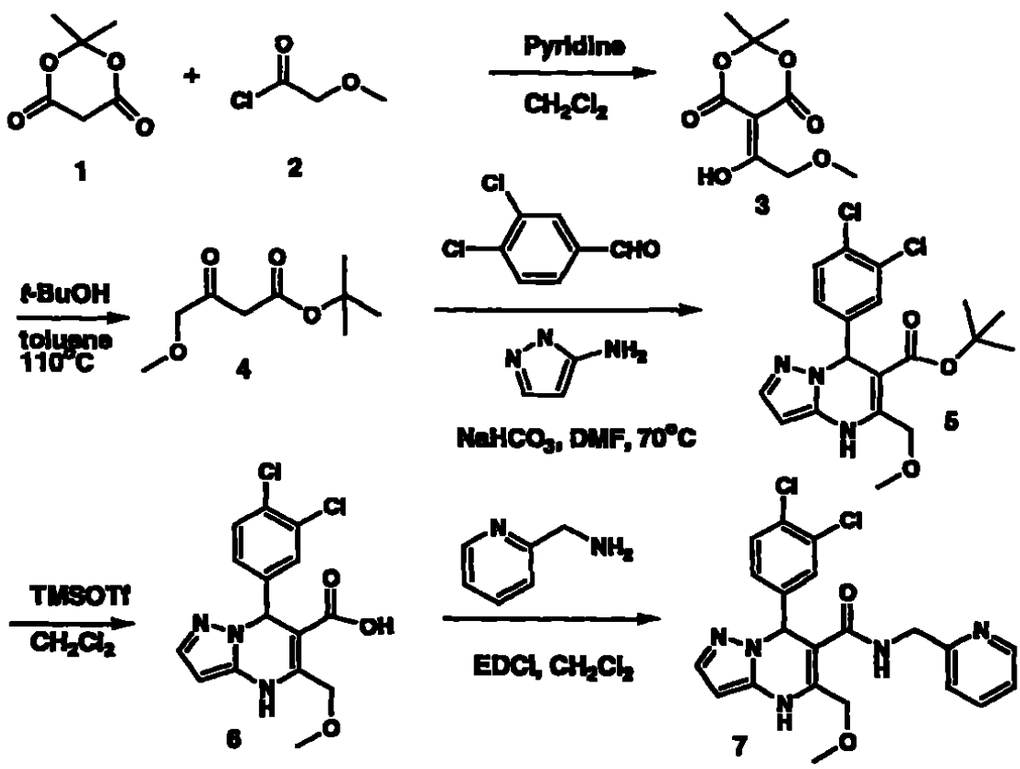
Title Compound. Compound(s) 3/3* was dissolved in phosphorus oxychloride (1.5 mL) and heated to 80 °C for 5 h. Heating was discontinued and the mixture was left to stand at room temperature overnight. The mixture was quenched onto ice, made basic with ammonium hydroxide, and extracted with ethyl acetate. The extracts were dried over magnesium sulfate and concentrated. The residue was purified by flash chromatography (silica gel, 50% acetone/hexanes) to give 6 6 mg of the title compound as a tan solid. Mp 225-230; $[M+H]^+$ *m/z* 486, HPLC 100% at 3 8 min (YMC S5 ODS 4.6 x 50 mm column,10-90% methanol, water with 0.2% phosphoric acid gradient over 4 min., 4 mL/ min., uv detection at 220 nm)

Example 484

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)-N-(2-pyridinylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide



Scheme



Synthesis of 3 A solution of recrystalized (acetone, hexane) 2,2-Dimethyl-1,3-dioxane-4,6-dione (1, 25 0 g, 173.5 mmol) in dichloromethane (350 mL) was treated with pyridine (27.4 g, 346.9 mmol) The reaction mixture was cooled to -5 1 °C. To this stirred solution was added a solution of methoxyacetyl chloride (2, 20.7 g, 190.8 mmol) in dichloromethane (150 mL) over 50 mins , maintaining the reaction temperature below 1.5 °C. The reaction mixture turned orange and a precipitate formed. The reaction mixture was allowed to warm to 17.5 °C over 40 mins. The

275
280

reaction mixture turned maroon and the solids dissolved. After TLC (100% ethyl acetate) showed the reaction was complete, the reaction was quenched with 3 7 % aqueous hydrochloric acid (500 mL) and the aqueous layer was extracted with dichloromethane) The organic extracts were combined and washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed The resulting oil was dried on high vacuum to constant weight to give 3 (33 11 g) in 88 3 % yield

Synthesis of 4. To a solution of 3 (33 1 g, 153 mmol) in 100 mL of toluene was added 2-methyl-2-propanol (100 mL, 1 05 mol) and the reaction was heated to reflux. After 1.5 h the reaction was concentrated to give 4 (30.2 g) in 100% yield

Synthesis of 5 To the solution of β-ketoester 4 (30 2 g, 160 6 mmol) in dimethylformamide (120 mL) was added 3,4 dichlorobenzaldehyde (28 13 g, 160.6 mmol), followed by 3-aminopyrazole (14.7 g, 176 7 mmol), then sodium hydrogen carbonate (54 g, 642 6 mmol) The reaction mixture was heated at 70 °C for 48 hrs. The reaction mixture was then cooled to 35 °C and transferred into rapidly stirring water (1.5 L) at RT The resulting off-white solid was filtered The filtered solid was slurried in water (1 L) and filtered again. The wet cake (165 g) was dissolved into ethyl acetate (1 L), giving a two-phase mixture. The mixture was washed with saturated aqueous sodium chloride (500 mL) The organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed. The resulting crude material was purified by column chromatography using 40 % ethyl acetate in hexane as eluent to give 5 (22.6 g, 34.3%) as a white powder

Synthesis of 6: To a solution of dihydropyrimidine tert-butyl ester 5 (10.13 g, 24.7 mmol) in dichloromethane (150 mL) was added a solution of trimethylsilyltrifluoromethanesulfonate (11 g, 49.5 mmol) in dichloromethane (11 mL) After 1 hr, hexane (300 mL) was added slowly and the reaction was concentrated to 250 mL. The product formed a gum and supernatant was decanted. Hexane (250 mL) was added and the mixture was allowed to stir for 1 hr The gum had solidified and fromed a powder The supernatant was decanted again and another

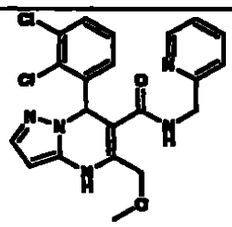
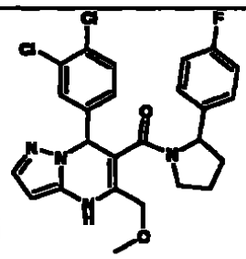
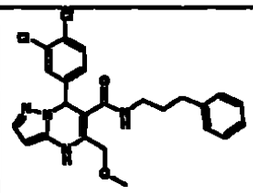
757 776

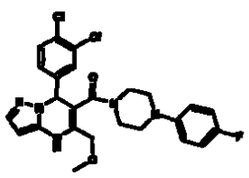
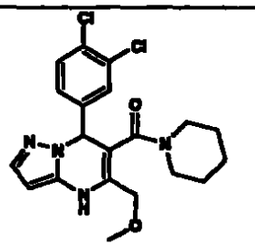
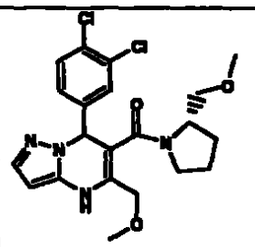
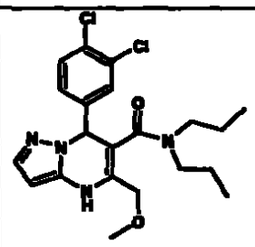
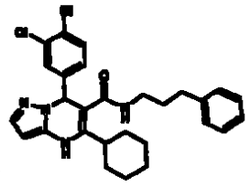
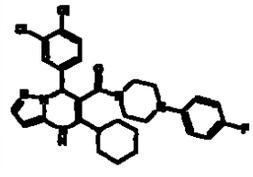
250 mL of hexane was added. The mixture was stirred for 10 min and filtered The resulting wet cake was washed with hexane (250 mL)) and a fine off-white powder 6 resulted which was allowed to suction dry

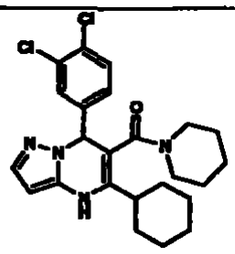
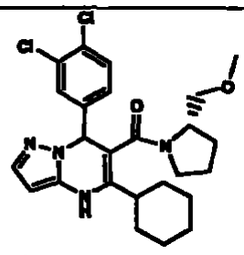
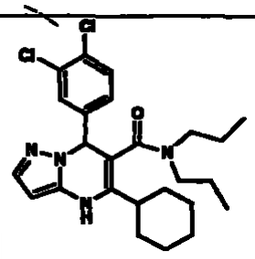
Synthesis of 7 To a suspension of dihydropyrimidine acid 6 (100 mg, 0.28 mmol) in dichloromethane (10 mL) was added EDCI (76 mg, 0.39 mmol) followed by a solution of 2-pyridylmethylamine (32.4 mg, 0.39 mmol) in dichloromethane (1mL) After 2.5 hrs, the reaction was concentrated to dryness and the crude mixture was purified by silica gel chromatography using 10% methanol in dichloromethane as eluent to give the title compound (90 mg, 72.4 %) as an off-white powder Mass Spec m/z $(M+Na)^+$ 466

Examples 485-496

The following compounds were prepared by the methods described in example 484

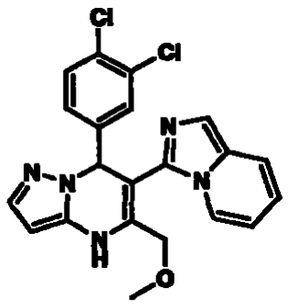
Ex. #	Structure	Name	Mass Spec (m/z)
485		7-(2,3-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)-N-(2-pyridinylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	444$(M+H)^+$
486		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(4-fluorophenyl)pyrrolidine	501$(M+H)^+$
487		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)-N-(3-phenylpropyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	471$(M+H)^+$

488		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	516(M+H)$^+$
489		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine	421(M+H)$^+$
490		(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine	451(M+H)$^+$
491		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)-N,N-dipropylpyrazolo[1,5-a]pyrimidine-6-carboxamide	437(M+H)$^+$
492		5-Cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydro-N-(3-phenylpropyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide	509 (M+H)
493		1-[[5-Cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydropyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	554 (M+H)

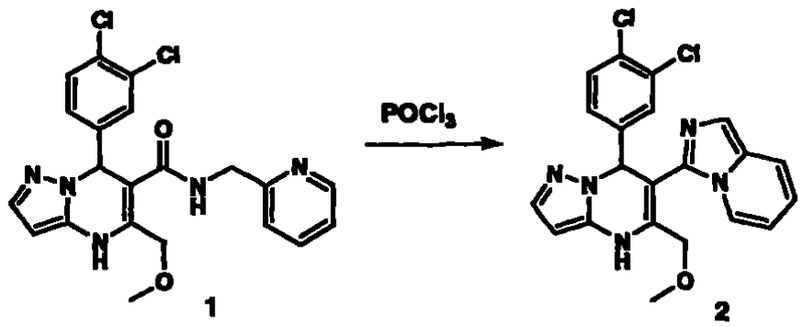
494		1-[[5-Cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydropyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine	459 (M+H)
495		(2S)-1-[[5-Cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydropyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine	489 (M+H)
496		5-Cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydro-N,N-dipropylpyrazolo[1,5-a]pyrimidine-6-carboxamide	475 (M+H)

Example 497

7-(3,4-Dichlorophenyl)-4,7-dihydro-6-(imidazo[1,5-a]pyridin-3-yl)-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine



Scheme



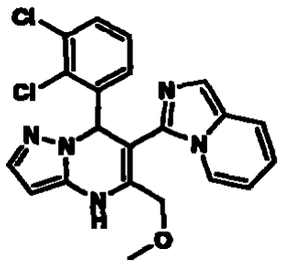
1 2

Synthesis of 1 The synthesis 1 was described in Example 484

Synthesis of 2 The title compound was synthesized in a manner described in Example 465 The product was purified by preparative TLC in 10% methanol in dichloromethane Mass Spec m/z $(M+H)^+$ 426

Example 498

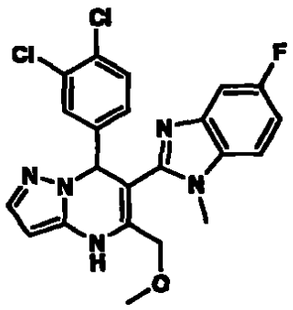
7-(2,3-Dichlorophenyl)-4,7-dihydro-6-(imidazo[1,5-a]pyridin-3-yl)-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine



The title compound was synthesized in a manner similar to that described in Example 497 Mass Spec m/z $(M+H)^+$ 426

Example 499

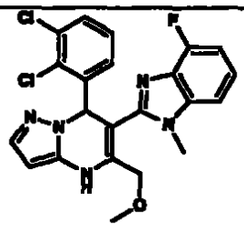
7-(3,4-Dichlorophenyl)-6-(5-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine

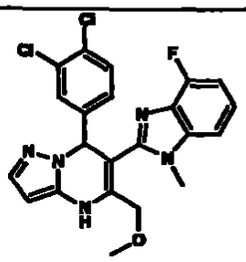
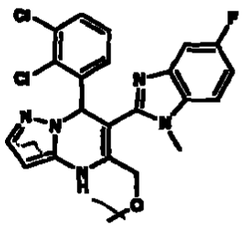
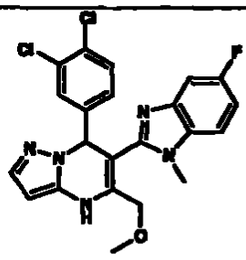
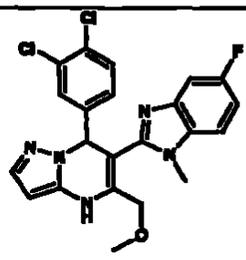


Starting with compound 6 from Example 484, the title compound was synthesized in a manner similar to that described in Example 470. Mass Spec m/z $(M+H)^+$ 458 The title compound can be separated into pure chiral form via preparative chiral HPLC (Chiralpak AD 5 cm x 50 cm column eluted with 25% isopropanol in hexane with 0 1% TEA at 50 mL/min with UV detection at 254 nM). The faster eluting isomer (example 503) is enantiomer A (HPLC retention time 6 8 min, 4.6x250mm Chiralpak AD column eluted with 25% isopropanol, hexane with 0 1% triethylamine at 1 mL/min with UV detection at 220nm) and the slower eluting isomer (example 504) is enantiomer B (HPLC retention time 12.0 min, 4 6x250mm Chiralpak AD column eluted with 25% isopropanol, hexane with 0 1% triethylamine at 1 mL/min with UV detection at 254nm).

Examples 500-504

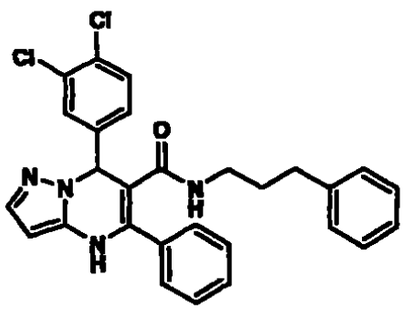
The following examples were synthesized by methods described in Example 499-

Ex.	Structure	Name	Mass Spec
500		7-(2,3-Dichlorophenyl)-6-(4-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine	458(M+H)$^+$

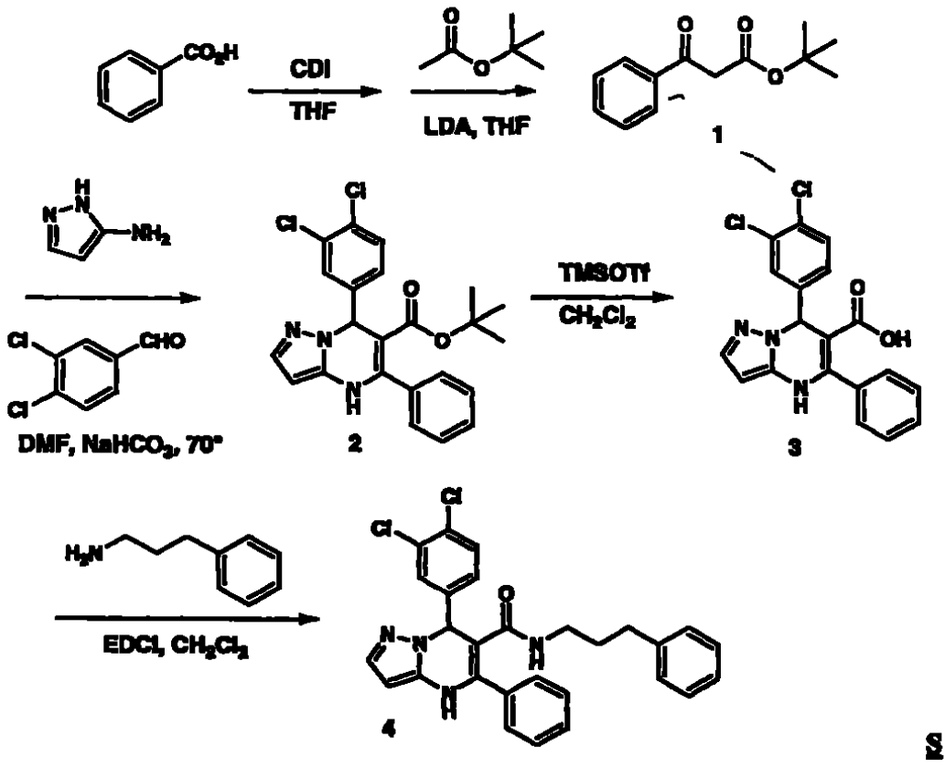
501		7-(3,4-Dichlorophenyl)-6-(4-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine	458(M+H)$^+$
502		7-(2,3-Dichlorophenyl)-6-(5-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine	458(M+H)$^+$
503		7-(3,4-Dichlorophenyl)-6-(5-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine enantiomer A	458 (M+H)
504		7-(3,4-Dichlorophenyl)-6-(5-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine enantiomer B	458 (M+H)

Example 505

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-phenyl-N-(3-phenylpropyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide



Scheme



Synthesis of 1 A solution of benzoic acid (3.05 g, 25 mmol) in tetrahydrofuran (25 mL) was treated with CDI (4 05 g, 25 mmol) at ambient temperature. In a separate flask lithiumdusopropylamide was generated at -78 °C by treatment of a tetrahydrofuran solution (40 mL) of dusopropyl amine (10 6 mL, 76 0 mmol) with 2.5 M n-butyl lithium in hexanes (30 mL, 75 0 mmol) Tert-butyl acetate was added dropwise and the reaction was stirred at -78 °C for 1 hr The enolate was transferred at -78 °C to a stirred solution of the imidazoylbenzoate prepared previously The resulting solution was cooled to -78 °C. After the addition of the enolate was

complete, a thick slurry resulted, which was broken up by shaking the reaction. The reaction mixture was allowed to stir for 1 h at -78 °C. A 1N aqueous solution of hydrochloric acid was added until the pH was 4 The reaction mixture was allowed to warm to ambient temperature with stirring. The reaction mixture was extracted with diethyl ether The combined organic layer was washed with aqueous 1N hydrochloric acid, aqueous 10% sodium hydrogen carbonate, saturated aqueous sodium chloride, dried over magnesium sulfate, and filtered. The solvent was removed to give 1 (5 0 g, 91%) as an oil.

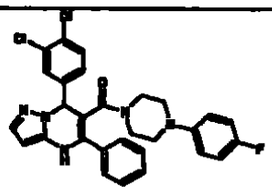
Synthesis of 2. Compound 2 was synthesized in a manner similar to that of compound 5 in example 484.

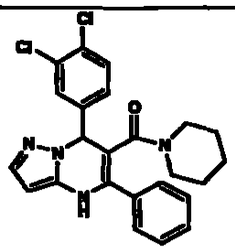
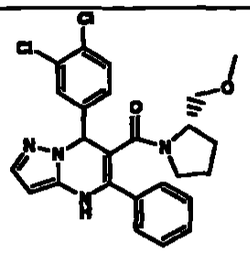
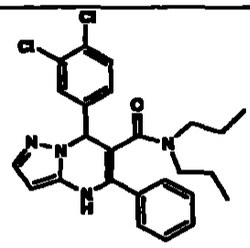
Synthesis of 3 Compound 3 was synthesized in a manner similar to that of compound 6 in example 484.

Synthesis of 4. The title compund was synthesized in a manner similar to that of compound 7 in example 484. Mass Spec m/z $(M+H)^+$ 503

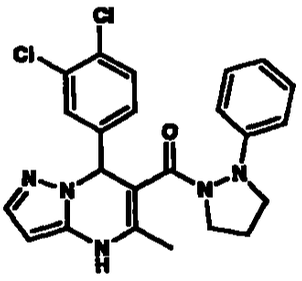
Examples 506-509

The following Examples 506-509 were synthesized in a manner similar to that described in Example 505

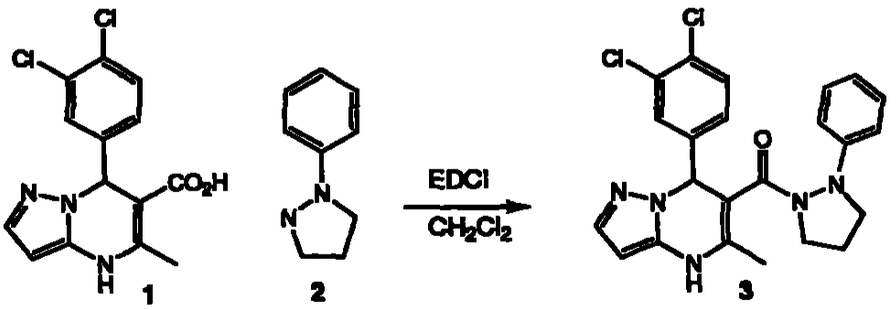
Ex.	Structure	Name	Mass Spec
506		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-phenylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine	448 $(M+H)^+$

507		1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-phenylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine	459 (M+H)$^+$
508		(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-phenylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine	489 (M+H)$^+$
509		7-(3,4-Dichlorophenyl)-4,7-dihydro-5-phenyl-N,N-dipropylpyrazolo[1,5-a]pyrimidine-6-carboxamide	475 (M+H)

Example 510

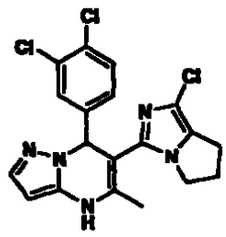


Scheme:

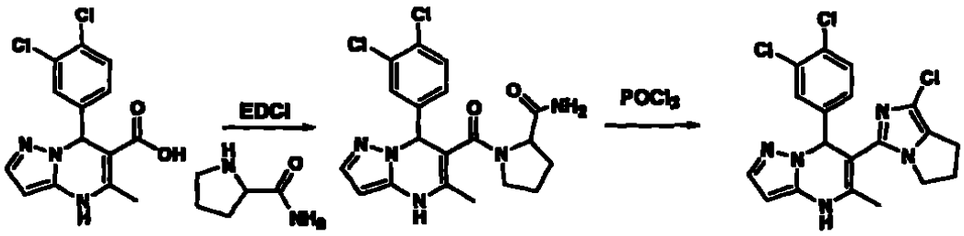


Preparation of 3. To a solution of dihydropyrimidine acid 1 (0 336 g, 1 mmol) in dichloromethane (10 mL) was added 1-phenylpyrazolidine 2 (0.215 g, 1.5 mmol, prepared using the procedure described in *Tetrahedron*, 1973, 29, 4045) followed by 1-[3 (dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.278 g, 1 5 mmol) and the mixture stirred at room temperature for 2 hours. The solvent was evaporated and the residue purified by silica gel chromatography, eluting with ethyl acetate, to give the title compound 3 (0 184 g, 39%) as a white powder $(M+H)^+ = 455$

Example 511



Scheme



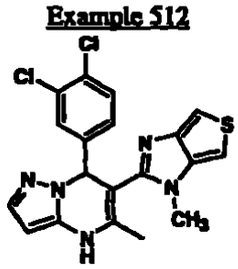
A B C

Preparation of B: At 20°C, EDCI (100mg, 0 52mmol) was added to a stirred slurry of carboxylic acid A (120mg, 0 37mmol) in CH_2Cl_2. After 5mins, proline amide was added (60mg, 0 52mmol) and the reaction mixture was stirred at ambient temperature for 3h. The resulting yellow slurry was concentrated under reduced pressure, dissolved in 2mL acetone and applied directly to a preparative silica gel TLC plate, (20x20cm, 1mm thickness, 254 nm UV indicator) eluting with 10%MeOH in CH_2Cl_2 The product B was isolated as a 1 1 ratio of diastereomers (79mg, 50% yield as a pale yellow glass) HPLC R_t 2 61 and 2 80min (YMC S5 ODS 4 6 x 50

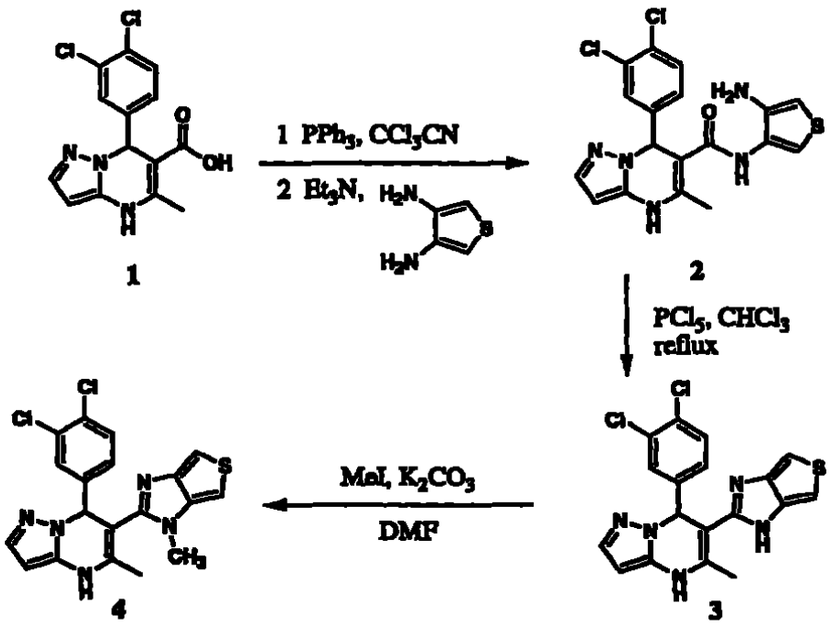
mm Ballistic column) 10-90% MeOH/water with 0 2% PPA linear gradient over 4mm, 4 mL/min, UV Detection at 220nm LCMS R_t 2 63 and 2.81min (YMC S5 ODS 4 6 x 50 mm Ballistic column) 10-90% MeOH/water with 0 1% TFA linear gradient over 4min, 4 mL/min, UV Detection at 220nm, Mass Spec m/z $(M+H)^+$ 420

Preparation of C. Phosphorus oxychloride (4mL) was added to diastereomers B (190mg, 0 46mmol) The slurry was heated to 100°C for 12h whereupon the precipitate dissolved furnishing an orange colored solution. The cooled reaction mixture was poured cautiously into saturated K_2CO_3 (ca 20mL) and extracted with EtOAc (3x30mL) The combined organic portions were dried over Na_2SO_4, decanted and concentrated yielding an orange oil which was purified directly by preparative HPLC R_t 28.40min (YMC S5 ODS 30 x 250 mm Reversed phase C18 column) 30-90% MeOH/water with 0 1% TFA linear gradient over 30min, 25 mL/min, UV Detection at 220nm Product C (96mg, 51% yield) was obtained as a free base after removal of MeOH from the HPLC fractions, addition of 1 0M NaOH and extraction into CH_2Cl_2 (3x30mL) The enantiomers were separated by chiral preparative HPLC R_t 42 4 and 59 0min (ChiralPak OD 50 x 500 mm Normal phase column) 15% EtOH/hexane Isocratic, 50 mL/min, UV Detection at 220nm Both enantiomers were isolated as pale yellow powders, (34mg of enantiomer A and 38mg enantiomer B) ChiralHPLC Enantiomer B R_t 7 36min (ChiralPak OD 4 6x250mm Normal phase column) 15% EtOH/hexane Isocratic, 2 mL/min, UV Detection at 220nm 100% ee ChiralHPLC Enantiomer A. R_t 4.94min (ChiralPak OD 4.6x250mm Normal phase column) 15% EtOH/hexane Isocratic, 2 mL/min, UV Detection at 220nm 100% ee

Example 512



Scheme



Preparation of compound 1. Compound 1 was prepared as described in example 16.

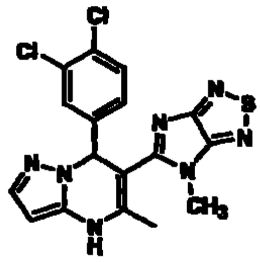
Preparation of compound 2: To a suspension of the acid (152 9 mg, 0.47 mmol) in 5 mL of anhydrous dichloromethane were added trichloroacetonitrile (57 0 µL, 0 67 mmol) and triphenylphosphine (186.2 mg, 0 71 mmol). The mixture became clear and was allowed to stir at room temperature for 1 hour The reaction mixture was transferred into a solution of 3,4-diaminothiophene hydrochloride (88 5 mg, 0 47 mmol) and triethylamine (198 0 µL, 1.42 mmol) in 5 mL of dichloromethane. The

reaction was monitored using TLC or LC/MS Upon completion of the coupling, the reaction mixture was loaded directly onto silica gel and eluted with 5% methanol/dichloromethane to yield the desired amide as a white solid (132 3 mg, 67%)

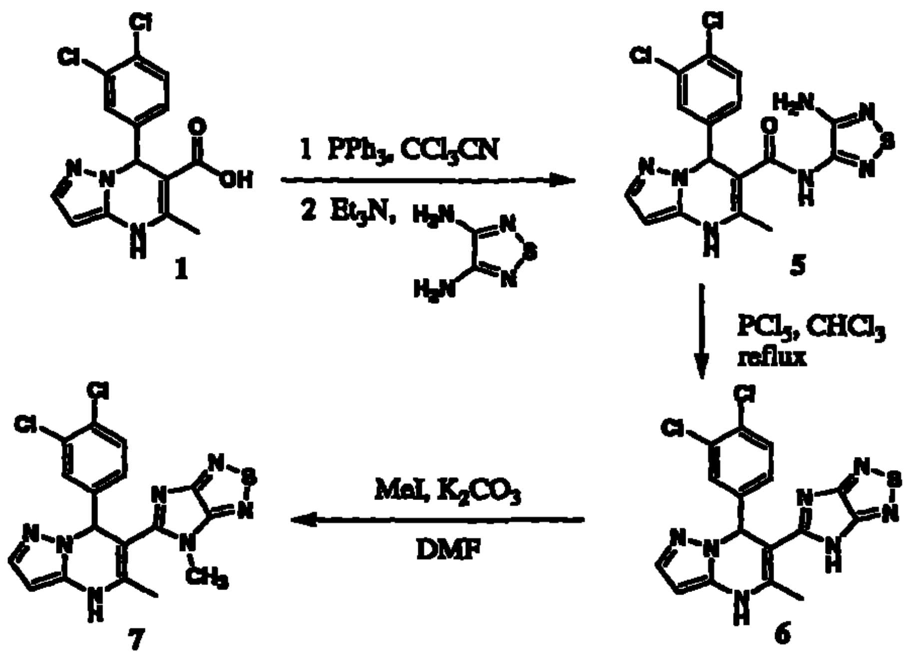
Preparation of compound 3: A suspension of the resulting amide (107 mg, 0 25 mmol) and phosphorus pentachloride (53 1 mg, 0 25 mmol) in chloroform (20 mL) was heated to reflux under anhydrous argon for 5 hours and the mixture was allowed to cool down to room temperature and stir overnight. Solvent was removed under reduced pressure, and the residue was redissolved in ethyl acetate and briefly washed with saturated aqueous sodium bicarbonate solution The organic layer was separated, dried over sodium sulfate, and concentrated to give the crude thienoimidazole, which was purified by flash chromatograph using 100 % ethyl acetate to give a brown solid (73 mg, 71 %)

Preparation of compound 4: To a solution of the thienoimidazole (22 4 mg, 0 06 mmol) in 2 mL of anhydrous DMF was added iodomethane (4.5 µL, 0 07 mmol) and potassium carbonate (15 4 mg, 0 11 mmol) The mixture was allowed to stir at room temperature overnight. The reaction was quenched using methanol. The mixture was diluted with ethyl acetate and washed with 10 % LiCl (3 x 10 mL) and brine (10 mL). The organic layer was separated and dried over sodium sulfate and concentrated to give a residue, which was further purified using flash chromatograph (5 % MeOH/ethyl acetate) and (6 % MeOH/chloroform) to give the titled compound as a white solid (4 5 mg, 20%)

Example 513



Scheme



Preparation of compound 5: To a suspension of the acid (120 mg, 0.37 mmol) in 5 mL of anhydrou dichloromethane were added trichloroacetonitrile (55 9 µL, 0 56 mmol) and triphenylphosphine (146.2 mg, 0 56 mmol). The mixture became clear and was allowed to stir at room temperature for 1 hour The reaction mixture was transferred into a solution of 3,4-diamino-1,2,5-thiadiazole (51 7 mg, 0 45 mmol, prepared according to J Heterocycl Chem 1976, *13*, 13) and triethylamine (103 6 µL, 0 74 mmol) in 5 mL of dichloromethane The reaction was monitored using TLC or LC/MS. Upon completion of the coupling, the reaction mixture was loaded directly onto silica gel and eluted with 50 % ethyl

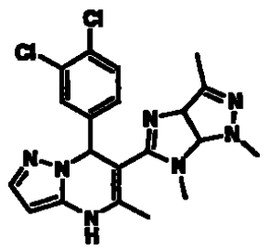
290
265

acetate/hexanes to yield the desired amide as a yellow solid (56 4 mg, 30 %)

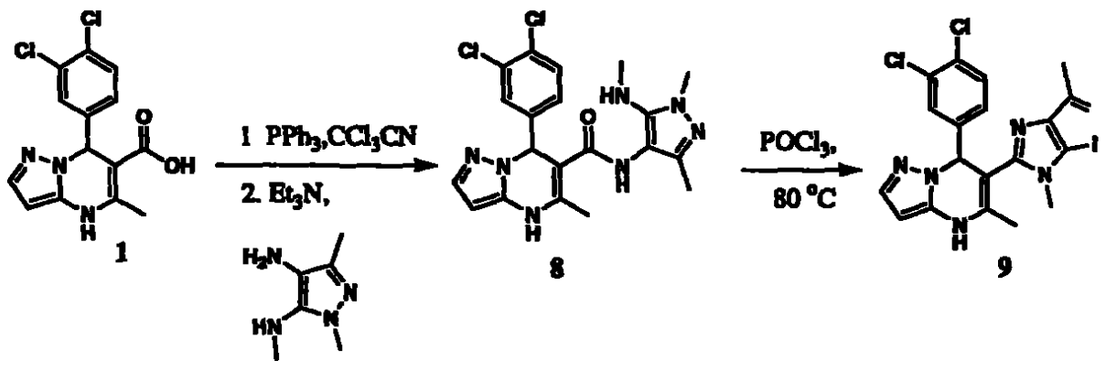
Preparation of compound 6: A suspension of the resulting amide (80 mg, 0 19 mmol) and phosphorus pentachloride (79 mg, 0 38 mmol) in chloroform (10 mL) was stirred at room temperature under anhydrous argon for one hour and then heated to reflux for 2 hours The mixture was allowed to cool down to room temperature and solvent was removed under reduced pressure The residue was redissolved in ethyl acetate and briefly washed with saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried over sodium sulfate, and concentrated to give the crude thiodiazoimidazole, which was purified by flash chromatograph using 80 % ethyl acetate/hexanes to give a yellow solid (29 mg, 38 %)

Preparation of compound 7: To a solution of the thiadiazoimidazole (29 mg, 0 07 mmol) in 2 mL of anhydrous DMF was added iodomethane (4 9 µL, 0 08 mmol) and potassium carbonate (19 9 mg, 0 14 mmol) The mixture was allowed to stir at room temperature under dry argon for 3 hours The reaction was quenched using methanol and diluted with ethyl acetate and washed with 10 % LiCl (3 x 10 mL) and brine (10 mL) The organic layer was separated and dried over sodium sulfate and concentrated to give a residue, which was purified using HPLC to give the titled compound as a white solid (1 6 mg, 5 %)

Example 514



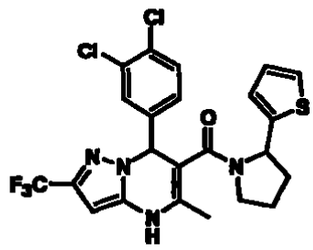
Scheme



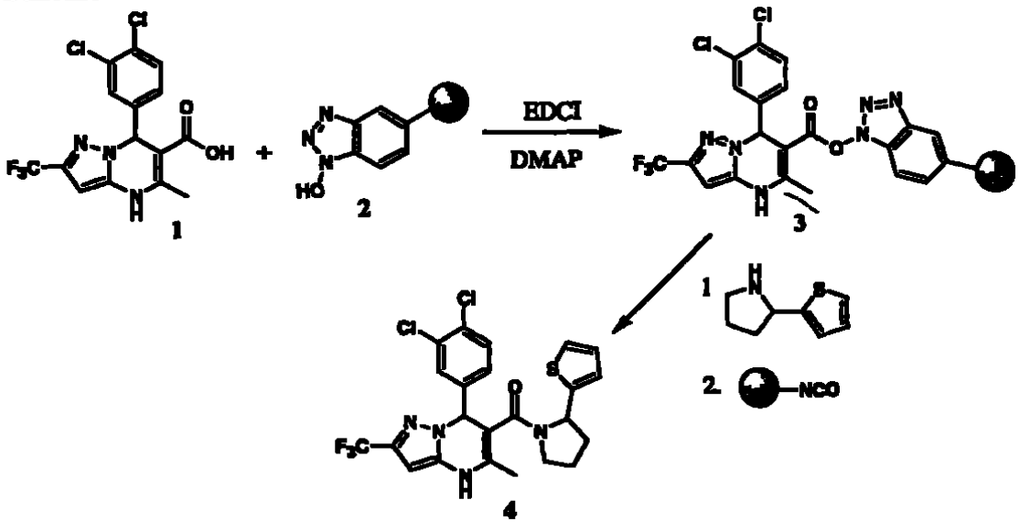
Preparation of compound 8: To a suspension of the acid (150 mg, 0 46 mmol) in 5 mL of anhydrou dichloromethane were added trichloroacetonitrile (69 8 µL, 0 70 mmol) and triphenylphosphine (182 7 mg, 0 70 mmol) The mixture became clear and was allowed to stir at room temperature for 1 hour The reaction mixture was transferred into a solution of the diaminopyrazole (prepared according to *J Med. Chem.* 1995, *38*, 3524) and triethylamine (129 5 µL, 0 93 mmol) in 5 mL of dichloromethane The reaction was monitored using TLC or LC/MS Upon completion of the coupling, the reaction mixture was loaded directly onto silica gel and eluted with 10 % methanol/ ethyl acetate to yield the desired amide as a white solid.

Preparation of compound 9: A suspension of the resulting amide (39 5 mg, 0 09 mmol) in phosphorus oxychloride (10 mL) was stirred at 80 °C under anhydrous argon overnight. The mixture was allowed to cool down to room temperature and solvent was removed under reduced pressure. The residue was redissolved in ethyl acetate and briefly washed with saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried over sodium sulfate, and concentrated to give a residue, which was purified by flash chromatograph using 10 % methanol/dichloromethane to give the desired product as a light brown solid (13 9 mg, 37 %)

Example 515



Scheme



Preparation of compound 1 Compound 1 was prepared as described in example 17

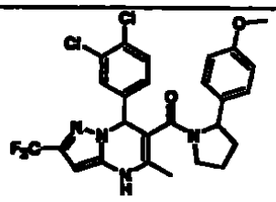
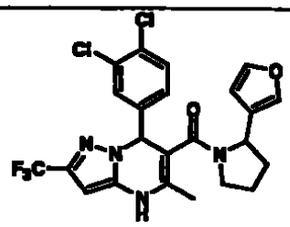
Preparation of compound 3: To a suspension of polystyrene supported HOBt reagent (5.2 g, 8 0 mmol) in 100 mL of anhydrous dichloromethane in a reaction vessel that has a fritted glass filter at the bottom was added the acid (4 7 g, 12 0 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2 3 g, 12 0 mmol), and 4-dimethylaminopyridine (98 mg, 0 8 mmol) The mixture was shook using an orbital shaker for 3 hours at room temperature Solvent was drained through filtration, and the resin washed with anhydrous DMF (3 x 30 mL), anhydrous TF (3 x 30 mL), and anhydrous dichloromethane (3 x 30 mL) The resin that contains activated ester was allowed to dry *in vacuo*

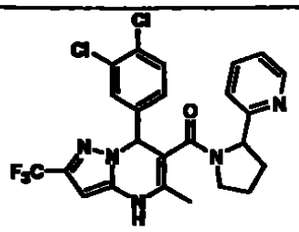
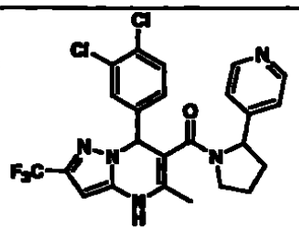
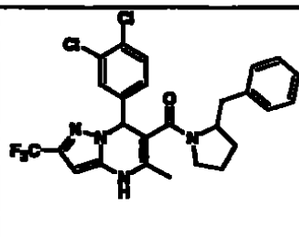
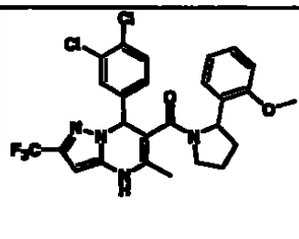
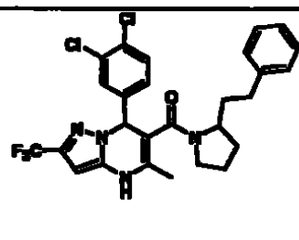
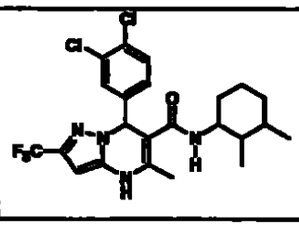
overnight The coupling yield was estimated based on the weight gain to be 84 %

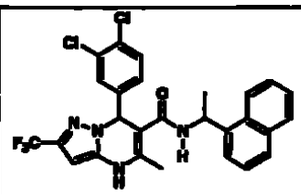
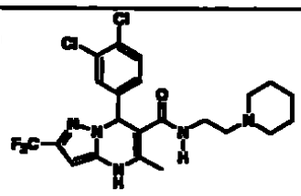
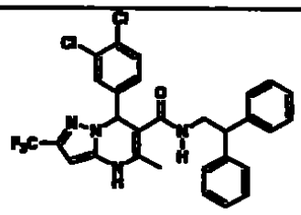
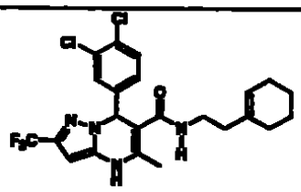
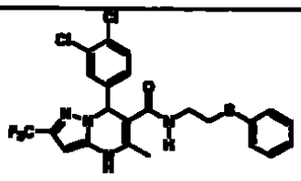
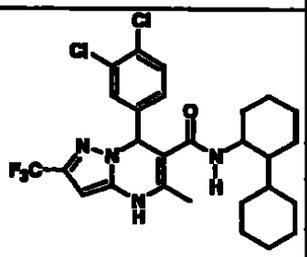
Preparation of compound 4: Resin containing the HOBt-activated ester (58 mg, 0 05 mmol) was distributed into a well, to which 2-(2'-thienyl)-pyrrolidine (80 µL of 0 5 M, 0 04 mmol) was dispensed The suspension was allowed to shake at room temperature for 3 hours, and then polystyrene-supported isocyanate reagent was added (83 mg, 0 08 mmol) and the suspension was shook for 2 hours Solvent was collected through filtration, and the resin was washed with dichloromethane (2 x 0 5 mL) All filtrates were combined and concentrated under reduced pressure to give the desired product as a white solid (18 mg) The purity of the product was checked using LC/MS to be 100 %, and m/z is 527

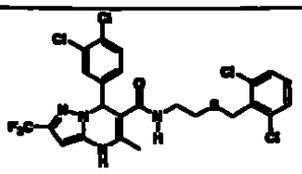
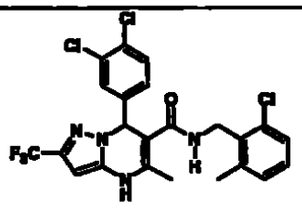
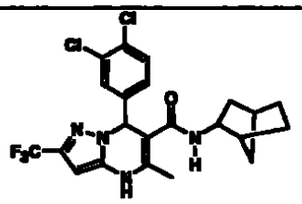
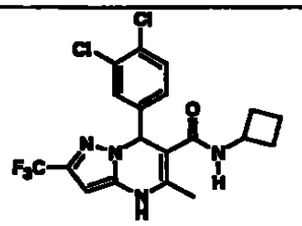
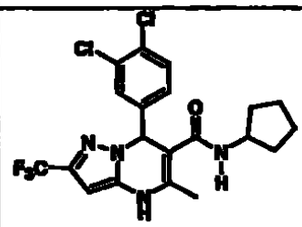
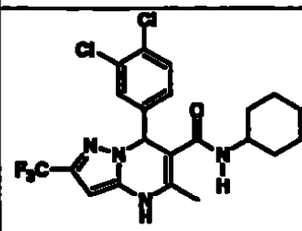
Examples 516-587

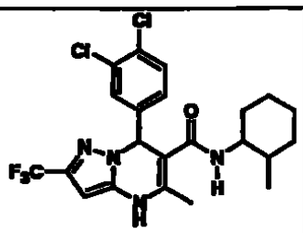
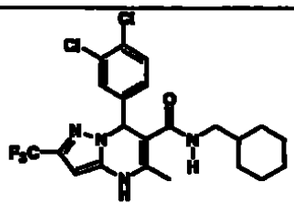
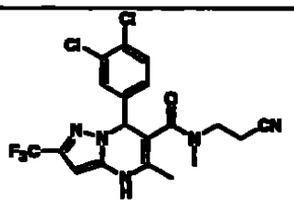
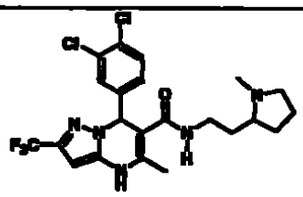
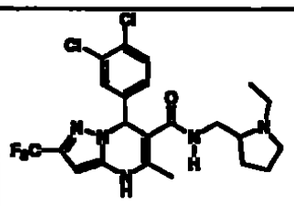
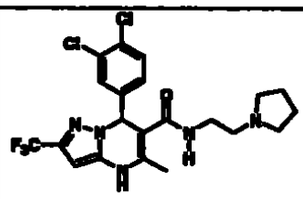
The following compounds were synthesized using the procedure as described in Example 515 Those compounds that have low purity were purified using preparative HPLC to give the corresponding desired products

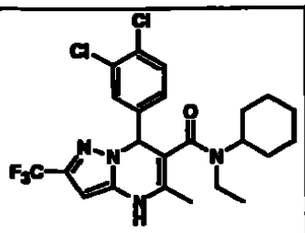
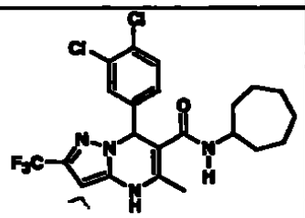
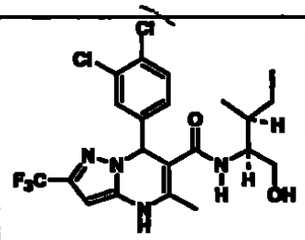
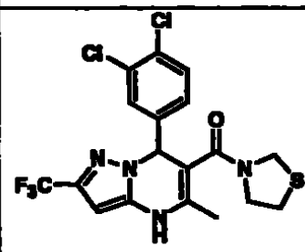
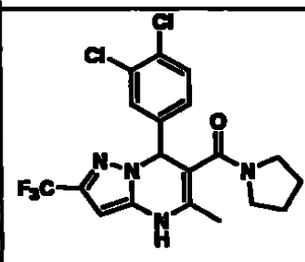
Ex.	Structure	Name	Mass Spec
516			551(M+H)$^+$
517			511(M+H)$^+$

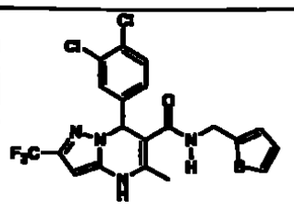
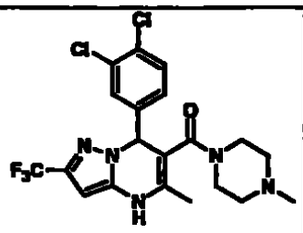
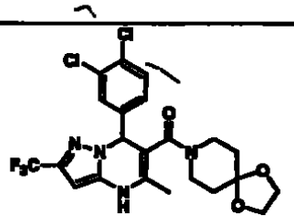
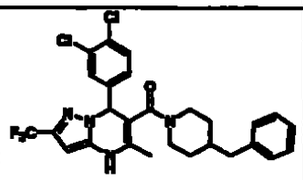
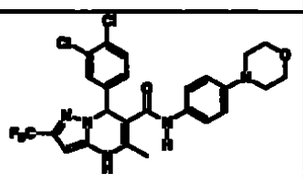
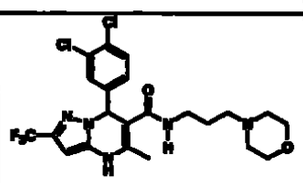
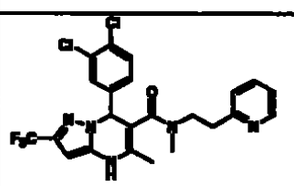
518			522(M+H)+
519			522 (M+H)
520			535 (M+H)
521			551(M+H)
522			549 (M+H)
523			501 (M+H)

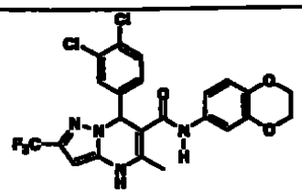
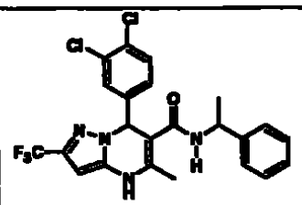
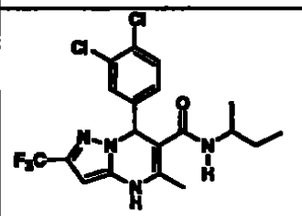
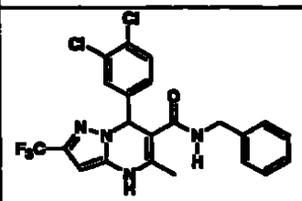
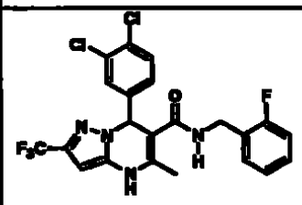
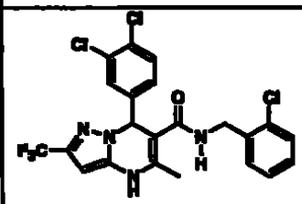
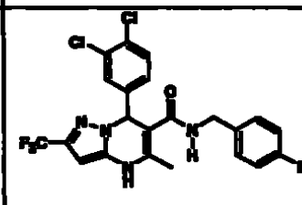
524			545 (M+H)
525			502 (M+H)
526			571 (M+H)
527			499 (M+H)
528			527 (M+H)
529			555 (M+H)

530			610 (M+H)
531			529 (M+H)
532			485 (M+H)
533			445 (M+H)
534			458 (M+H)
535			473 (M+H)

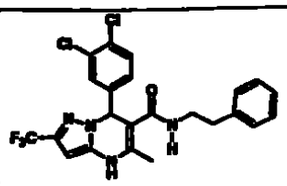
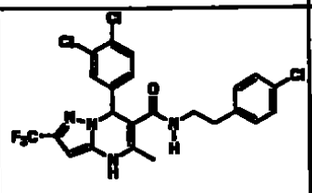
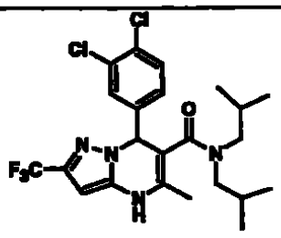
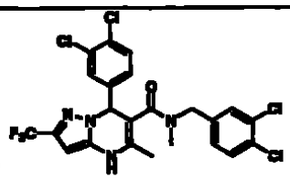
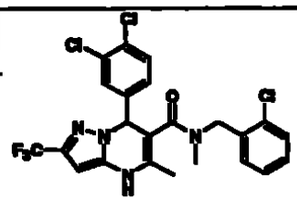
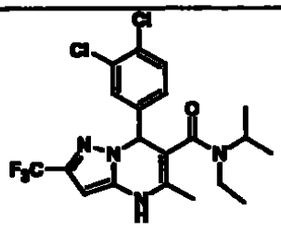
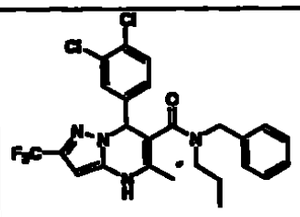
536			487 (M+H)
537			487 (M+H)
538			458 (M+H)
539			502 (M+H)
540			502 (M+H)
541			488(M+H)

542			501 (M+H)
543			487 (M+H)
544			491 (M+H)
545			463 (M+H)
546			445 (M+H)

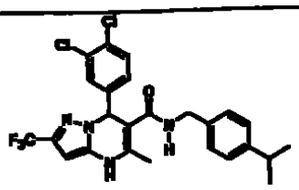
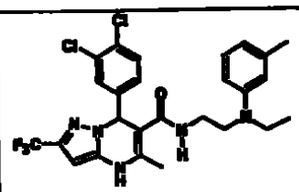
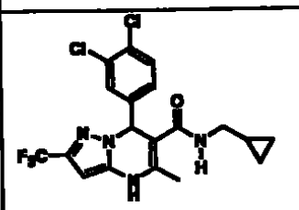
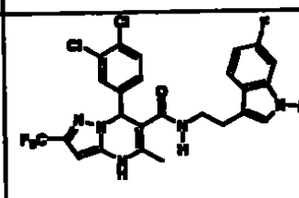
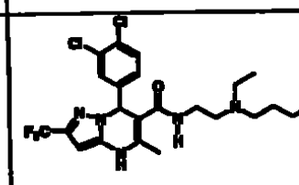
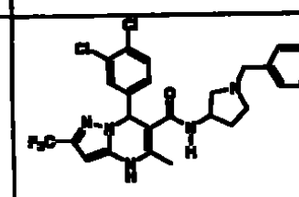
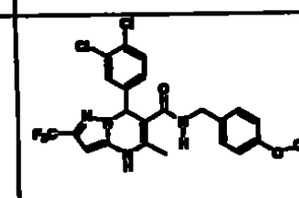
547			487 (M+H)
548			474 (M+H)
549			517 (M+H)
550			549 (M+H)
551			552 (M+H)
552			518 (M+H)
553			510 (M+H)

554			525 (M+H)
555			495 (M+H)
556			447 (M+H)
557			481 (M+H)
558			499 (M+H)
559			515 (M+H)
560			499 (M+H)

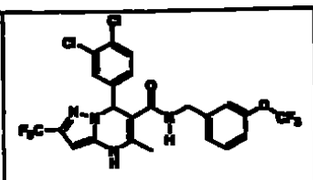
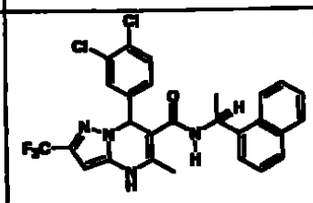
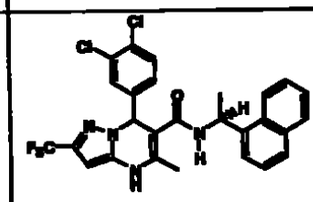
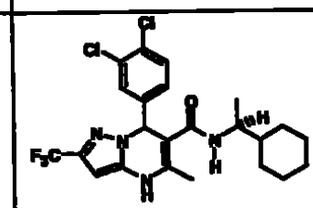
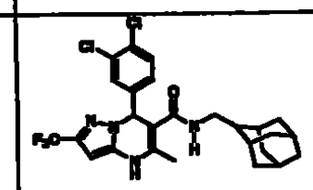
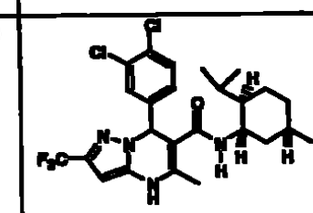
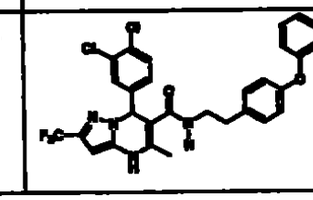
801
276

561			495 (M+H)
562			530 (M+H)
563			503 (M+H)
564			564 (M+H)
565			530 (M+H)
566			461 (M+H)
567			523 (M+H)

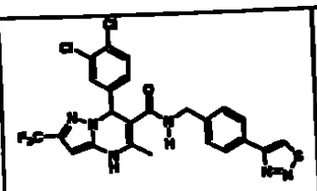
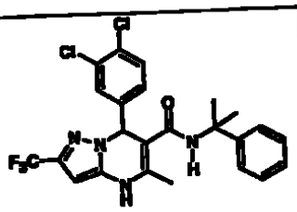
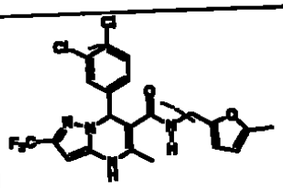
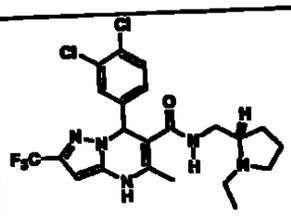
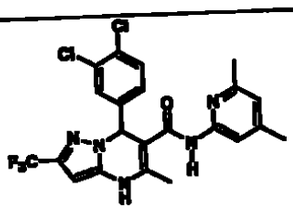
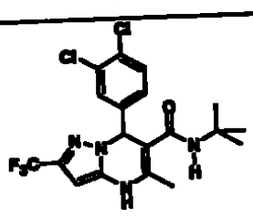
852

568			523 (M+H)
569			552 (M+H)
570			445 (M+H)
571			552 (M+H)
572			518 (M+H)
573			550 (M+H)
574			565 (M+H)

883
778

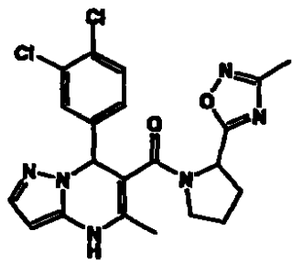
575			565 (M+H)
576			545 (M+H)
577			545 (M+H)
578			501 (M+H)
579			589 (M+H)
580			529 (M+H)
581			587 (M+H)

804

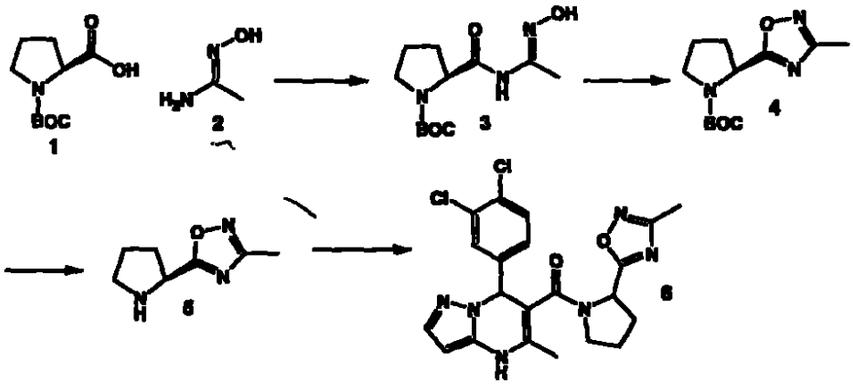
582			565 (M+H)
583			509 (M+H)
584			584 (M+H)
585			502 (M+H)
586			596 (M+H)
587			447 (M+H)

Example 588

805
780



Scheme



Synthesis of 3· A mixture of N-(tert-butoxycarbonyl)-L-proline 1 (0 5 g, 2 3 mmol), hydroxyamidine 2 (0 172 g, 2 3 mmol, prepared using the procedure outlined in *J Fluor Chem.* 1999, *95*, 127) and 1-hydroxybenzotriazole hydrate (0 323 g, 2.4 mmol) in 22% dimethyl formamide in dichloromethane (9 mL) was stirred at room temperature for 0.5 hours. Then 1-[3-(dimethylammo)propyl]-3-ethylcarbodiimide hydrochloride (0 757 g, 3 9 mmol) was added and the mixture stirred further at room temperature for 2 hours when HPLC indicated completion of the reaction. The reaction mixture was diluted with water and extracted with dichloromethane. The organic layers were washed successively with saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride solution and dried over magnesium sulfate. Evaporation of the solvent provided a white solid with an $(M+H)^+$ of 272 consistent for the coupled product 3

Preparation of 4· The solid 3 was dissolved in tetrahydrofuran (17 mL), cesium carbonate (1 6 g) added and the mixture heated at 50-70° C for 18 hours after which HPLC indicated the complete consumption of 3 The reaction was diluted with water

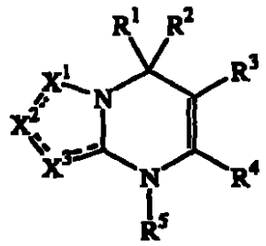
and extracted with ethyl acetate. The organic layers were dried over magnesium sulfate and evaporated to give a light-green colored oil that had an $(M+H)^+$ of 254 consistent with the desired oxadiazole 4 which was used without any further purification

Synthesis of 5 To a solution of 4 (0 288 g, 1 1 mmol) in dichloromethane (9 mL) was added 0 9 mL of trifluoroacetic acid and the solution stirred at room temperature for 18 hours when HPLC indicated the absence of 4 The reaction mixture was concentrated and the residue purified by ion-exchange chromatography (using BioRad AG-50W-X2 resin, 200-400 mesh, hydrogen form) eluting with 2N ammonia in methanol to give the deprotected pyrrolidine *5* as an oil (0 122 g, 70%) $(M+H)^+$ = 154

Synthesis of 6. To a solution of dihydropyrimidine acid (0 21 gram, 0 65 mmol) in dichloromethane (10 mL) was added pyrrolidine *5* (0 139 gram, 0.9 mmol) followed by 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.174 gram, 0 9 mmol) and the reaction stirred at room temperature for 1.5 hours The solvent was evaporated and the residue purified by silica gel chromatography, eluting with ethyl acetate, to give two diastereomers- a fast moving, less polar diastereomer-1 and a slow moving, more polar diastereomer-2 , both as white amorphous solids with an $(M+H)^+$ of 460.

We claim.

1 A method of treating atrial arrhythmias comprising administering to a patient in need thereof an effective amount of at least one compound of formula I



(I)

enantiomers, diastereomers and pharmaceutically acceptable salts thereof, wherein

X^1, X^2 and X^3 are independently selected from N, NR^6, $(CR^7)_q$, $(CHR^7)_q$, or C=O, wherein the bonds connecting X^1, X^2 and X^3 to adjacent atoms may be single or double bonds forming a 5 to 7-membered saturated, partially unsaturated or aromatic ring;

R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are independently selected from groups of the formula $-(CH_2)_x-(Z^1)_m-(CH_2)_y-Z^2$; or

R^1, R^2, R^3, R^4 and R^5 may, in one or more pairs of two, together with the atoms to which they are bonded, form a carbocyclic, substituted carbocyclic, heterocyclic or substituted heterocyclic group, or

R^6 and R^7 may, in one or more pairs of two, together with the atoms to which they are bonded, form a carbocyclic, substituted carbocyclic, heterocyclic or substituted heterocyclic group;

Z^1 is $-CZ^3Z^4-$, -O-, $-NZ^3-$, -S-, -SO-, $-SO_2-$, -C(O)-, $-C(O)Z^3-$, $-C(O)NZ^4$, -C(S)-, $-C(=NOZ^3)-$, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbocyclo, substituted carbocyclo, aryl, substituted aryl, heterocyclo, or substituted heterocyclo;

Z^2 is hydrogen, $-OZ^5$, $-OC(O)Z^5$, $-NZ^5-C(O)-Z^6$, $-NZ^5-CO_2-Z^6$, $-NZ^5(C=O)-NZ^6Z^7$, $-NZ^5Z^6$, $-NO_2$, halo, $-CN$, $-C(O)Z^5$, $-CO_2Z^5$, $-C(S)Z^5$, $-(C=NOZ^5)Z^6$, $-C(O)NZ^5Z^6$; $-C(S)NZ^5Z^6$, $-SZ^5$, $-SOZ^5$, $-SO_2Z^5$, $-SO_2NZ^5Z^6$, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbocyclo; substituted carbocyclo, aryl, substituted aryl, heterocyclo; or substituted heterocyclo,

Z^3, Z^4 Z^5, Z^6 and Z^7 are independently hydrogen, halo, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl substituted alkynyl, carbocyclo; substituted carbocyclo, aryl, substituted aryl, heterocyclo, or substituted heterocyclo; or

Z^3, Z^4, Z^5, Z^6 and Z^7 may, in one or more pairs of two, together with the atoms to which they are bonded, form a carbocyclic, substituted carbocyclic, heterocyclic or substituted heterocyclic group;

n and p are independently selected from integers from 0 to 10 wherein, when m is 0, p is also 0,

m is an integer selected from 0 or 1, and

q is an integer selected from 1 to 3

2. A method of treating atrial fibrillation comprising administering to a patient in need thereof an effective amount of at least one compound of claim 1

3 A method of treating atrial flutter comprising administering to a patient in need thereof an effective amount of at least one compound of claim 1

4 A method of selectively treating supraventricular arrhythmias comprising administering to a patient in need thereof an effective amount of at least one compound of claim 1

5 A method of treating I_{Kur}-associated conditions comprising administering to a patient in need thereof an effective amount of at least one compound of claim 1

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6 A method of treating reflux esauphagitis comprising administering to a patient in need thereof an effective amount of at least one compound of claim 1

7 A method of treating functional dispepsia comprising administering to a patient in need thereof an effective amount of at least one compound of claim 1

8 A method of treating constipation comprising administering to a patient in need thereof an effective amount of at least one compound of claim 1

9 A method of treating asthma comprising administering to a patient in need thereof an effective amount of at least one compound of claim 1

10 A method of treating diabetes comprising administering to a patient in need thereof an effective amount of at least one compound of claim 1

11 A method stimulating the secretion of growth hormone comprising administering to a patient in need thereof an effective amount of at least one compound of claim 1

12. A method of treating cell proliferative disorders comprising administering to a patient in need thereof an effective amount of at least one compound of claim 1

13 A method of treating autoimmune diseases comprising administering to a patient in need thereof an effective amount of at least one compound of claim 1

14 The method of claim 1 where in formula I

R^1 is hydrogen

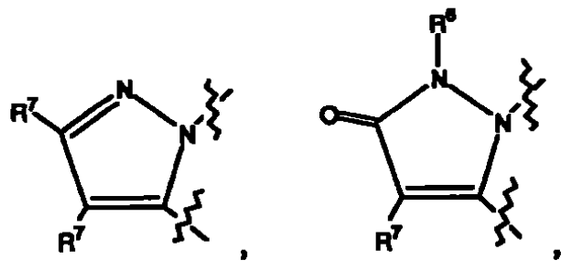
R^2 is hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo or substituted carbocyclo

R^3 is $-(CH_2)_n-Z^2$, $-(CH_2)_n-C(O)Z^3-(CH_2)_p-Z^2$, or $-(CH_2)_n-C(O)NZ^4-(CH_2)_p-Z^2$,

R^4 is alkyl or substituted alkyl,

R^5 is hydrogen or $-(CH_2)_n-Z^2$, and

X^1, X^2 and X^3, together with the atoms to which they are bonded, form a ring selected from.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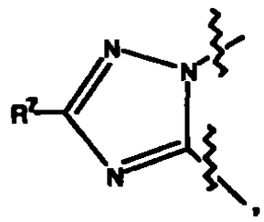
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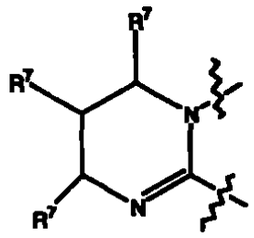
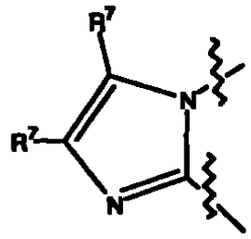



or

wherein the ring substituents are the same or different.

15 The method of claim 14 where in formula I

R^3 is $-(CH_2)_n-Z^2$, $-(CH_2)_n-C(O)Z^3-(CH_2)_p-Z^2$, or $-(CH_2)_n-C(O)NZ^4-(CH_2)_p-Z^2$ wherein

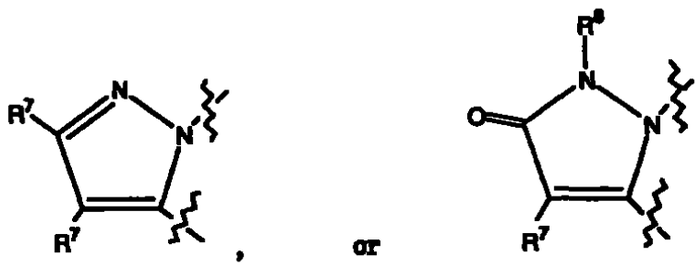
Z^2 is selected from $-C(O)NZ^5Z^6$, $-CO_2Z^5$, $-SO_2Z^5$, $-NZ^5Z^6$, $-NZ^5CO_2Z^6$, $-NZ^5C(O)Z^6$, $-OZ^5$, aryl, substituted aryl, heterocyclo, substituted heterocyclo, alkyl or substituted alkyl,

Z^3 is heterocyclo or substituted heterocyclo; and

n and p are independently selected from integers 0 to 3,

R^5 is hydrogen, or $-(CH_2)_n-Z^2$ wherein Z^2 is selected from $-C(O)NZ^5Z^6$, CO_2Z^5, $-NZ^5Z^6$, aryl, substituted aryl, alkyl, or substituted alkyl, and

X^1, X^2 and X^3, together with the atoms to which they are bonded, form a ring selected from.



16 The method of claim 15 where in formula I

R^3 is heterocyclo or substituted heterocyclo, $-C(O)NZ^5Z^6$, $-C(O)Z^3-CONZ^5Z^6$, $-C(O)Z^3-Z^2$, or $-C(O)Z^3-CO_2Z^5$, wherein Z^3 is heterocyclo or substituted heterocyclo, and Z^2 is aryl or substituted aryl

17 The method of claim 1 wherein the compound of formula I is selected from

7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid methyl ester;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid methyl ester;

7-(4-Chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid methyl ester;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethyl ester;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethyl ester;

7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethyl ester;

7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1 1-dimethylethyl ester;

7-(3 4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethylester, enantiomer A,

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1 1-dimethylethylester, enantiomer B,

7-(3,4-Dichlorophenyl)-4,7-dihydro-2,5-dimethylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethyl ester;

3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethyl ester;

7-(2,3-Dichlorophenyl)-4,7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethyl ester;

7-(3,4-Dichlorophenyl)-4,7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethyl ester;

4,7-Dihydro-5-methyl-7-(1-methylethyl)pyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethyl ester

7-Cyclopropyl-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethyl ester;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid,

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidine-6-carboxylic acid,

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine,

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-propylpyrazolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-phenyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide;

4-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]morpholine,

7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-N-propylpyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(2,3-Dichlorophenyl)-4 7-dihydro-5-methyl-N-phenylpyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(2-phenylethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(2-phenylethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-3-pyridinylpyrazolo[1,5-a]pyrimidine-6-carboxamide;

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenyl-piperazine, enantiomer A,

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenyl-piperazine, enantiomer B,

1-[[7-(4-Chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(phenyl-methyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

4-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]morpholine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-methyl-piperazine,

7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(phenylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide;

7-(4-Chlorophenyl)-4,7-dihydro-5-methyl-N-(phenylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

4-[[7-(4-Chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]morpholine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine;

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine,

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(3-phenyl-propyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

1-[[5-(3,4-Dichlorophenyl)-5,8-dihydro-7-methyl-imidazo[1,2-a]pyrimidin-6-yl]carbonyl]-4-phenyl-piperazine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(phenyl-methyl)piperidine;

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1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(phenyl-methyl)piperazine,

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N,N-dipropylpyrazolo[1,5-a]pyrimidine-6-carboxamide,

1-[[7-(3-Chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(3,4-Difluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine,

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine,

1-(4-Fluorophenyl)-4-[(4,7-dihydro-5-methyl-7-phenylpyrazolo[1,5-a]pyrimidin-6-yl)carbonyl]piperazine;

1-(4-Fluorophenyl)-4-[(4,7-dihydro-5-methyl-7-phenylpyrazolo[1,5-a]pyrimidin-6-yl)carbonyl]piperazine;

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine, enantiomer A,

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine, enantiomer A,

1-[[5-(2,3-Dichlorophenyl)-5,8-dihydro-7-methyl-imidazo[1,2-a]pyrimidin-6-yl]carbonyl]-4-phenyl-piperazine;

1-(4-Fluorophenyl)-4-[[7-(3-fluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidm-6-yl]carbonyl]-piperazine,

1-[[7-(3,5-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine;

1-[(7-Cyclohexyl-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl)carbonyl]-4-phenylpiperazine,

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-6-yl)carbonyl]-4-phenyl-piperazine,

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenyl-piperazine,

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7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-6-[(4-phenyl-1-piperazinyl)-carbonyl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

1-[[4-(2,3-Dichlorophenyl)-4,6,7,8-tetrahydro-2-methyl-1H-pyrimido[1,2-a]pyrimidin-3-yl]carbonyl]-4-phenyl-piperazine,

4-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1-piperazinecarboxylic acid 1,1-dimethylethyl ester;

4-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1-pipera-zinecarboxylic acid 1,1-dimethylethyl ester;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-phenylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine,

7-(3,4-Dichlorophenyl)-4,7-dihydro-2,5-dimethyl-N-(3-phenyl-propyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

1-[[7-(2,3-Dichlorophenyl)-2-(1,1-dimethylethyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenyl-piperidine,

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-6-[[(3-phenyl-propyl)amino]carbonyl]pyrazolo[1,5-a]pyrimidine-3-carboxylic acid ethyl ester;

7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-6-[(4-phenyl-1-piperazinyl)-carbonyl]pyrazolo[1,5-a]pyrimidine-2-carboxylic acid ethyl ester;

1-[[3-Cyano-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(3,4-Dichlorophenyl)-4 7-dihydro-5-methyl-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(2,3-Dichlorophenyl)-4,7dihydro-5-methyl-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer B

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine, enantiomer B,

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7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(3-phenylpropyl)-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-pipera-zinyl]carbonyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyri-midine-2-carboxylic acid methyl ester;

(2S)-1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine,

1-[[7-(2,3-Dichlorophenyl)-2-fluoro-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

(2S)-1-[[2-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine,

(2S)-1-[[2-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine,

(2S)-1-[[7-(2,3-Dichloro-phenyl)-2-fluoro-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxy-methyl)pyrrolidine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-2,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-2,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer A,

1-[[7-(3 4-Dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine, enantiomer B,

7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-N,N-dipropylpyrazolo[1,5-a]pyrimidine-6-carboxamide,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(2,3-Difluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

4-[6-[[4-(4-Fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-7-yl]benzoic acid methyl ester;

1-(4-Fluorophenyl)-4-[[7-(2-fluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-piperazine;

1-[[7-(2-Chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

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1-[[7-(2,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine,

1-[[4,7-Dihydro-7-(2-methoxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(2,3-Dimethoxyphenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine;

1-[[7-(2,4-Dimethoxyphenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine;

1-[[7-(2,5-Dimethoxyphenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-[2-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-(2-methylphenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-(3-phenoxyphenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(3,4-Dimethoxyphenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine,

1-[[7-(3,5-Dimethoxyphenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-[3-(phenylmethoxy)phenyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine,

1-[[4,7-Dihydro-7-(3-hydroxyphenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-[3-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-(3-methylphenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(4-Cyanophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-(4-Fluorophenyl)-4-[[7-(4-fluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-piperazine,

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N-[4-[6-[[4-(4-Fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-7-yl]phenyl]acetamide,

1-[[7-[4-(Dimethyl-amino)phenyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4,7-Dihydro-7-(4-methoxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-[4-(phenylmethoxy)phenyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine,

1-[[7-(4-Butoxyphenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-(2-thienyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-(3-thienyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-(4-methylphenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-(2-nitrophenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4 7-Dihydro-5-methyl-7-(4-nitrophenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(2,6-Difluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(2,4-Difluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(2,5-Difluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(3,5-Difluorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-[2-(phenylmethoxy)phenyl]pyra-zolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine

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1-[[7-(3,4-Dimethylphenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-[4-(trifluoromethoxy)phenyl]py-razolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-[3-(trifluoromethoxy)phenyl]py-razolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine,

1-[[7-(3-Cyanophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4 7-Dihydro-7-(3-methoxyphenyl)-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine;

1-[[7-(4-Chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-(4-phenoxyphenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-(3-nitrophenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-(5-methyl-2-furanyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4,7-Dihydro-7-(1H-imidazol-2-yl)-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-(1H-pyrrol-2-yl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-(2-pyridinyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(3-Chloro-4-methoxy-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4 7-Dihydro-7-(4-methoxy-1,3-benzodioxol-6-yl)-5-methylpyrazolo[1,5-a]pyrimidm-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4,7-Dihydro-7-[5-(hydroxymethyl)-2-furanyl]-5-methylpyrazolo[1,5-a]pyrimidm-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4,7-Dihydro-7-(1H-indol-3-yl)-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-(3-pyridinyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-(3-quinolinyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-(4-quinolinyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(2,3-Dihydro-1,4-benzodioxin-6-yl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-(2,3,5-trichloro-phenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(2,5-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-(4-Fluorophenyl)-4-[[7-(3-furanyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-piperazine,

1-[[7-(2-Benzofuranyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-(3-methylbenzo[b]thiophen-2-yl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-(2-quinolinyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-(2-thiazolyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-(4-Fluorophenyl)-4-[[7-(2-furanyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-piperazine,

1-[[4,7-Dihydro-7-[3-methoxy-4-(phenylmethoxy)phenyl]-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4,7-Dihydro-7-[4-methoxy-3-(phenylmethoxy)phenyl]-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-(2-naphthalenyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-[3 4-Bis(phenyl-methoxy)phenyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(1,3-Benzodioxol-5-yl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine,

1-[[7-[3,5-Bis(trifluoro-methyl)phenyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyri-midin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-[5-[1-methyl-3-(trifluoromethyl)-1H-pyrazol-5-yl]-2-thienyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(5-Ethyl-2-furanyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(2,3-Dihydro-5-benzofuranyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(3-Bromophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4 7-Dihydro-5-methyl-7-[4-(1-pyrrolidmyl)-phenyl]pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-(3-methyl-2-thienyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4,7-Dihydro-5-methyl-7-(5-methyl-2-thienyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(1,3-Benzodioxol-4-yl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(5-Chloro-2-thienyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(3,5-Dimethylphenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine;

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2,5-dimethylpyrazolo[1 5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine, enantiomer A,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine, enantiomer B,

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine enantiomer B,

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1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine, enantiomer A,

8-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,4-dioxa-8-azaspiro[4.5]decane,

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-(2-methoxy-phenyl)piperazine;

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]-pyrimidin-6-yl]carbonyl]-4-[3-(trifluoromethyl)-phenyl]piperazine;

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-nitrophenyl)piperazine;

1-(4-Acetylphenyl)-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine,

1-(2-Chlorophenyl)-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine,

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]-carbonyl]-4-(4-methoxy-phenyl)piperazine,

1-(3,4-Dichlorophenyl)-4-[[7-(3,4-dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]-carbonyl]piperazine,

1-(3,5-Dichlorophenyl)-4-[[7-(3,4-dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]-carbonyl]piperazine,

1-(4-Chlorophenyl)-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine,

1-(3-Chlorophenyl)-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-(3-methoxyphenyl)piperazine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-(4-methylphenyl)piperazine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5a]-pyrimidin-6-yl]car-bonyl]-4-[4-(trifluoromethyl)-phenyl]piperazine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(2-fluorophenyl)piperazine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-(3,4-dimethylphenyl)piperazine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(2-pyrimidinyl)piperazine,

7-(3,4-Dichlorophenyl)-N-[2-[(4-fluorophenyl)amino]ethyl]-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide;

4-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1-piperazinecarboxylic acid phenylmethyl ester;

7-(3,4-Dichlorophenyl)-N-ethyl-N-[(2-fluorophenyl)methyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyri-midine-6-carboxamide,

N-[(3-Chloro-4-methoxyphenyl)methyl]-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyri-midine-6-carboxamide,

1-(1,3-Benzodioxol-5-ylmethyl)-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine;

4-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1-piperazinecarboxylic acid ethyl ester;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(2-pyridinyl)piperazine,

(2*S*)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine;

1-[Bis(4-fluorophenyl)-methyl]-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine,

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-(2-furanyl-carbonyl)piperazine;

1-Cyclohexyl-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(2-methoxyethyl)piperazine;

1-[[7-(3 4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(9H-fluoren-9-yl)piperazine,

(2R)-1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-2-(methoxy-methyl)pyrrolidine,

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1-[[7-(3 4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-(2,3-dimethylphenyl)piperazine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-2-piperidinecarboxylic acid ethyl ester

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-N,N-diethyl-3-piperidinecarboxamide;

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-3-piperidine-carboxylic acid ethyl ester;

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-3-methyl-piperidine;

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-3,5-dimethyl-piperidine,

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-hydroxy-piperidine;

4-(4-Chlorophenyl)-1-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyri-midin-6-yl]carbonyl]-4-hydroxypiperidine,

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-piperidine-carboxylic acid ethyl ester;

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-methylpiperidine;

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,4-tetrahydroquinoline;

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]-pyrimidin-6-yl]carbonyl]-decahydroquinoline;

2-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1 2,3,4-tetrahydroisoquinoline,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-propylpiperidine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(hydroxydiphenylmethyl)piperidine;

7-(3,4-Dichlorophenyl)-N-[(2-fluorophenyl)methyl]-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide;

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2-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole,

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-[2-(phenylamino)-ethyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide;

(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-[(phenylamino)methyl]pyrrolidine;

N-Cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydro-N,5-dimethylpyrazolo[1,5-a]pyrimidine-6-carboxamide,

3-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]thiazole,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]pyrrolidine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3,4-dihydro-1H-indole;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]azetidine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]hexahydro-1H-azepine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]octahydroazocine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,6-tetrahydropyridine,

7-(3,4-Dichlorophenyl)-4,7dihydro-N,5-dimethyl-N-[2-(2-pyridinyl)-ethyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide,

N-[[7-(3,4-Dichlorophenyl)-4,7dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-N-(phenylmethyl)glycine ethyl ester;

trans-7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(2-phenylcyclopropyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-methylpyrrolidine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-methylaziridine,

(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-[[(2,6-dimethylphenyl)amino]methyl]pyrrolidine;

7-(3,4-Dichlorophenyl)-N-ethyl-4,7-dihydro-5-methyl-N-(4-pyridinylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-4 7-dihydro-N,5-dimethyl-N-[(1R)-1-phenylethyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(3,4-Dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-[(1S)-1-phenylethyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide,

6-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,3,3-trimethyl-6-azabicyclo[3.2.1]octane;

7-(3,4-Dichlorophenyl)-N-(hexahydro-1H-azepin-1-yl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]azinidine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]octahydro-1H-azonine,

(2R-trans)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,5-bis(methoxymethyl)-pyrrolidine,

(2S-trans)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,5-bis-(methoxymethyl)pyrrolidine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-L-prolinamide;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-D-prolinamide;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,3-dihydro-2-methyl-1H-indole;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,3-dihydro-5-nitro-1H-indole,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,3-dihydro-6-nitro-1H-indole,

4-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-thiomorpholine,

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1-[[7-(3 4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-L-proline methyl ester;

(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrro-lidine, enantiomer A,

(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine, enantiomer B,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-L-proline 1,1-dimethylethyl ester;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-N-(2-naphthalenyl)-L-prolinamide,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,4-tetrahydro-2-methylquinoline;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-6-fluoro-1,2,3,4-tetrahydro-2-methylquinoline;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidm-6-yl]carbonyl]-L-proline phenylmethyl ester;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidm-6-yl]carbonyl]-D-proline phenylmethyl ester

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-hydroxy-L-proline phenylmethyl ester;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)-2-methylpiperazine,

3-Chloro-N-cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydro-N,5-dimethyl-pyrazolo[1,5-a]pyri-midine-6-carboxamide;

4-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-thiomorpholine,

1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,3-dihydro-1H-indole,

1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]hexahydro-1H-azepine;

1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-octahydroazocine,

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1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,6-tetrahydropyridine;

3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-[(1S)-1-phenylethyl]-pyrazolo[1,5-a]pyrimidine-6-carboxamide,

3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-[(1R)-1-phenylethyl]-pyrazolo[1,5-a]pyrimidine-6-carboxamide,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]-carbonyl]-2-(methoxy-methyl)piperidine;

[(3R)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-pyrrolidinyl]carbamic acid 1,1-dimethylethyl ester;

[(3S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-pyrrolidinyl]carbamic acid 1,1-dimethylethyl ester;

(3R)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-(dimethylamino)pyrrolidine,

N-[1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-pyrrolidinyl]acetamide,

N-[1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-pyrrolidinyl]-N-methylacetamide;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N,N-dipentylpyrazolo[1,5-a]pyri-midine-6-carboxamide,

7-(3,4-Dichlorophenyl)-N,N-dihexyl-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide,

1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine;

3-Chloro-7-(3-chlorophenyl)-N-cyclohexyl-4,7-dihydro-N,5-dimethyl-pyrazolo[1,5-a]pyrimidine-6-carboxamide;

(2*S*)-1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxy-methyl)pyrrolidine;

1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-decahydroquinoline,

2-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,4-tetrahydroisoquinoline,

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4-[[3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-thiomorpholine,

N-Cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydro-N,5-dimethyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(3,4-Dichlorophenyl)-N,N-diethyl-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide;

N,N-Dibutyl-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-N,N-diheptyl-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-azacyclotridecane;

9-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-dodecahydro-1H-fluorene,

(2S)-1-[[7-(3,4-Di-chlorophenyl)-4,7-dihydro-5-methyl-2-(tri-fluoromethyl)pyrazolo-[1,5-a]pyrimidm-6-yl]car-bonyl]-2-(methoxy-methyl)pyrrolidine;

1-[[3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]piperidine;

1-[[3-Chloro-7-(3-chloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]hexahydro-1H-azepine,

1-[[3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-octahydroazocine,

1-[[3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,6-tetrahydropyridine;

3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-N,5-dimethyl-N-[(1S)-1-phenyl-ethyl]pyrazolo[1,5-a]pyrimidine-6-carboxamide;

(2S)-1-[[3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine,

1-[[3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-decahydroquinoline;

2-[[3-Chloro-7-(3-chlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,4-tetrahydroisoquinoline,

1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]hexahydro-1H-azepine;

1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,6-tetrahydropyridine,

(2S)-1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimi-din-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine;

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methyl-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,3-dihydro-1H-indole,

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methyl-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]hexahydro-1H-azepine;

7-(3,4-Dichlorophenyl)-4,7-dihydro-N,5-di-methyl-N-[(1S)-1-phenylethyl]-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-[(1R)-1-phenylethyl]-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(3,4-Dichlorophenyl)-4,7-dihydro-N,N-bis(2-methoxyethyl)-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-N,N-bis(2-ethoxyethyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-4,7-dihydro-N-(2-methoxyethyl)-N,5-dimethylpyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(3,4-Dichlorophenyl)-4,7-dihydro-N-(2-methoxyethyl)-5-methyl-N-propylpyrazolo[1,5-a]pyrimidine-6-carboxamide;

1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine;

2-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,4-tetrahydroisoquinoline;

1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-octahydroazocine,

3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-[(1S)-1-phenylethyl]-pyrazolo[1,5-a]pyrimi-dine-6-carboxamide,

3-Chloro-N-cyclohexyl-7-(2,3-dichlorophenyl)-4,7-dihydro-N,5-dimethyl-pyrazolo[1,5-a]pyrimdine-6-carboxamide,

3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-N-(phenylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(3,4-Dichlorophenyl)-N-ethyl-4,7-dihydro-N-(2-methoxyethyl)-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide;

N-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-N-methylglycine ethyl ester

N-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-N-methylglycine 1,1-dimethylethyl ester;

N-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-N-(2-ethoxy-2-oxoethyl)glycine ethyl ester;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(3-pyridinyl)piperidine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,4-tetrahydro-6-methylquinoline;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-propylpiperidine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-[(diethylamino)methyl]piperidine;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(2-phenoxyethyl)-pyrazolo[1,5-a]pyrimidine-6-carboxamide;

1-[(7-Cyclopropyl-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl)carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[4,7-Dihydro-5-methyl-7-(1-methylethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

(2S)-1-[[4,7-Dihydro-5-methyl-7-(1-methyl-ethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine,

1-[[4,7-Dihydro-5-methyl-7-(1-methyl-ethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2,3-dihydro-1H-indole;

1-[[4,7-Dihydro-5-methyl-7-(1-methylethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1,2,3,6-tetrahydropyridine,

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3-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]thiazolidine, enantiomer A,

3-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]thiazolidine, enantiomer B,

7-(3,4-Dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-(phenylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-(2-phenylethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(2-phenylethyl)-N-(phenylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(phenoxymethyl)pyrrolidine,

(2R)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(phenoxymethyl)pyrrolidine;

(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-[(4-fluorophenoxy)methyl]pyrrolidine;

(2R)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-[(4-fluorophenoxy)methyl]-pyrrolidine;

7-(3,4-Dichlorophenyl)-N-ethyl-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide;

N-Butyl-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-pentylpyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(3,4-Dichlorophenyl)-4,7-dihydro-N-(2-methoxyethyl)-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxamide;

(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(hydroxydiphenylmethyl)pyrrolidine;

(2R)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(hydroxydiphenylmethyl)pyrrolidine;

1-[[7-(3,4-Dichlorophenyl)-4 7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(3-pyridinyl)pyrrolidine,

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(2S)-1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-phenylpyrrolidine,

3-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-phenylthiazolidine,

3-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-thiazolidinecarboxylic acid methyl ester;

7-(3,4-Dichlorophenyl)-4,7-dihydro-N,5-dimethyl-N-(3-phenyl-propyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(3,4-Dichlorophenyl)-N-ethyl-4,7-dihydro-5-methyl-N-(3-phenyl-propyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(3-phenylpropyl)-N-propylpyrazolo[1,5-a]pyrimidine-6-carboxamide,

N-Butyl-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-N-(3-phenyl-propyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

2-(4-Chlorophenyl)-3-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]thiazolidine

N-(Cyclopropylmethyl)-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-N-propylpyrazolo[1,5-a]pyrimidine-6-carboxamide;

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(2,3-dihydro-2-oxo-1H-benzimidazol-1-yl)piperidine;

8-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-1-phenyl-1,3,8-triazaspiro[4 5]decan-4-one,

4-(4-Chlorophenyl)-1-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methy-lpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-1,2,3,6-tetrahydropyridine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(2-phenylethyl)pyrrolidine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(4-methoxyphenyl)pyrrolidine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(2-methoxyphenyl)pyrrolidine,

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1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(4-fluoro-phenyl)pyrrolidine;

(3R)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-phenoxypyrrolidine,

(2S)-2-[(Cyclohexyloxy)methyl]-1-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]pyrrolidine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(phenylmethyl)pyrrolidine,

(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(phenoxymethyl)pyrrolidine, diastereomer A,

(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(phenoxymethyl)pyrrolidine, diastereomer B,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(3-methoxyphenyl)pyrrolidine;

(2S)-2-(Butoxymethyl)-1-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]pyrrolidine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(2-thienyl)pyrrolidine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(4-pyridinyl)pyrrolidine;

(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-[(methoxymethoxy)-methyl]pyrrolidine;

(2S)-2-(1H-Benzimidazol-1-ylmethyl)-1-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]pyrrolidine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(3-furanyl)pyrrolidine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(2-pyridinyl)pyrrolidine,

(3S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-phenoxypyrrolidine,

(3S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-3-phenoxypyrrolidine,

(2S)-1-[[7-(3 4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine, enantiomer A,

(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoro-methyl)pyrazolo[1,5-a]-pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine, enantiomer B

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-L-proline;

7-(3 4-Dichlorophenyl)-4 7-dihydro-N-[(1R)-2,3-dihydro-1H-inden-1-yl]-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(3,4-Dichlorophenyl)-N-(2,3-dihydro-1H-inden-2-yl)-4,7-dihydro-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide;

N-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-D-phenylalanine methyl ester;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(1,2,3,4-tetrahydro-1-naphthalenyl)-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-4 7-dihydro-5-methyl-N-[3-(2-oxo-1-pyrrolidinyl)propyl]-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-N-(2-furanylmethyl)-4,7-dihydro-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(3,4-Dichlorophenyl)-N-[(3,4-dichlorophenyl)methyl]-4,7-dihydro-5-methyl-2-(trifluoromethyl)pyra-zolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-4,7-dihydro-N-[(2R)-2-(methoxymethyl)-1-pyrrolidmyl]-5-methyl-2-(trifluoromethyl)pyra-zolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-N-[(tetrahydro-2-furanyl)-methyl]-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(3,4-Dichlorophenyl)-4,7-dihydro-N-[(1S)-2,3-dihydro-1H-inden-1-yl]-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-N-[2-(3,4-dichloro-phenyl)ethyl]-4,7-dihydro-5-methyl-2-(trifluoromethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-2-(trifluoromethyl)-N-[[4-[(trifluoromethyl)thio]-phenyl]methyl]pyrazolo-[1,5-a]pyrimidine-6-carboxamide,

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(2S)-1-{[7-(3,4-Dichlorophenyl)-4,7di-hydro-5-methyl-2-(trifluoro-methyl)pyra-zolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(1-pyrrolidinylmethyl)-pyrrolidine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(1-naphthalenylsulfonyl)piperazine,

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-[(4-ethylphenyl)sulfonyl]-piperazine,

1-[(4-Bromo-5-chloro-2-thienyl)sulfonyl]-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimi-din-6-yl]carbonyl]-piperazine;

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-[[2-(trifluoro-methoxy)phenyl]sulfonyl]piperazine,

1-[(5-Chloro-3-methyl-benzo[b]thiophen-2-yl)sulfonyl]-4-[[7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyra-zolo[1,5-a]pyrimidin-6-yl]carbonyl]piperazine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-[(3-methoxyphenyl)carbonyl]piperazine;

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(1-oxo-3-phenyl-2-propenyl)-piperazine,

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-pyridinylcarbonyl)piperazine;

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine,

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine,

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(2,3-Dichloro-phenyl)-4,7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(2,3-Dichloro-phenyl)-4,7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer B,

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-4,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer A,

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1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-2,4,5-trimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(2,3-Dichlorophenyl)-4-[(4-fluorophenyl)methyl]-4,7dihydro-2,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

7-(2,3-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-N,N,2,5-tetramethylpyrazolo[1,5-a]pyrimidine-4(7H)-acetamide;

7-(2,3-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-N,N,2,5-tetramethylpyrazolo[1,5-a]pyrimidine-4(7H)-acetamide;

1-[[7-(2,3-Dichlorophenyl)-4-[2-(dimethylamino)ethyl]-4,7-dihydro-2,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[4-(Cyclopropylmethyl)-7-(2,3-dichlorophenyl)-4,7-dihydro-2,5-dimethylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

7-(2,3-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-N,N,2,5-tetramethylpyrazolo[1,5-a]pyrimidine-4(7H)-carboxamide;

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-4-methyl-5-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(2,3-Dichlorophenyl)-4,7-dihydro-5-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine,

1-[[7-(2,3-Dichloro-phenyl)-4,7-dihydro-2-methyl-5-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-(4-fluoro-phenyl)piperazine;

1-[[7-(2,3-Dichloro-phenyl)-4,7-dihydro-2,4-dimethyl-5-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(2,3-Dichloro-phenyl)-4,7-dihydro-2,4-dimethyl-5-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine, enantiomer B,

1-[[7-(3,4-Dichlo-rophenyl)-4,7-dihydro-5-(trifluoromethyl)pyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-2-methyl-5-(trifluoro-methyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine,

1-[[1-Benzoyl-7-(2,3-dichlorophenyl)-1,2,4 7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine,

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1-[[1-Benzoyl-7-(3,4-dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-phenylpiperazine;

1-[[1-Acetyl-7-(3,4-dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-phenylpiperazine;

1-[[7-(3,4-Dichloro-phenyl)-1,2,4 7-tetrahydro-5-methyl-2-oxo-1-(1-oxobutyl)-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine,

1-[[1-(Cyclopropyl-carbonyl)-7-(3,4-dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-phenylpiperazine;

1-[[1-(Cyclopropyl-carbonyl)-7-(2,3-dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]car-bonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(2,3-Dichloro-phenyl)-1,2,4,7-tetra-hydro-5-methyl-1-(3-methyl-1-oxobutyl)-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)-piperazine

1-[[7-(2,3-Dichloro-phenyl)-(2,2-dimethyl-1-oxopropyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidm-6-yl]carbonyl]-4-phenyl-piperazine;

1-[[1-(Cyclopropyl-carbonyl)-7-(3,4-dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine,

1-[[1-(Cyclobutyl-carbonyl)-7-(3,4-dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluoro-phenyl)piperazine,

1-[[7-(3,4-Dichloro-phenyl)-1,2,4,7-tetrahydro-5-methyl-1-(2-methyl-1-oxopropyl)-2-oxopyrazolo[1,5-a]pyrimidm-6-yl]car-bonyl]-4-(4-fluoro-phenyl)piperazine;

1-[[7-(2,3-Dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-1-[(1-methylethyl)sulfonyl]-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine;

1-[[7-(3,4-Dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-1-[(1-methylethyl)sulfonyl]-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-N-(1-methylethyl)-2-oxo-6-[(4-phenyl-1-piperazinyl)carbonyl]pyrazolo[1,5-a]pyrimidine-1(2H)-carboxamide;

7-(2,3-Dichlorophenyl)-4,7-dihydro-N,5-dimethyl-2-oxo-6-[(4-phenyl-1-piperazinyl)-carbonyl]pyrazolo[1,5-a]pyrimidine-1(2H)-carboxamide;

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7-(2,3-Dichlorophenyl)-4,7-dihydro-5-methyl-2-oxo-6-[(4-phenyl-1-piperazinyl)carbonyl]-pyrazolo[1,5-a]pyri-midine-1(2H)-carboxamide;

7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-N,N,5-trimethyl-2-oxopyrazolo[1,5-a]pyrimidine-1(2H)-carboxamide,

1-[[1-(3-Butenyl)-7-(3,4-dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(3,4-Dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxo-1-(2,2,2-trifluoroethyl)pyrazolo-[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(3,4-Dichlorophenyl)-1,2,4,7-tetrahydro-5-methyl-2-oxo-1,4-bis(2,2,2-trifluoroethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-5-methyl-2-oxopyrazolo[1,5-a]pyrimidine-1(2H)-carboxylic acid 1-methylethyl ester;

1-[(4,7-Dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl)carbonyl]-4-phenylpiperazine;

7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-2-carboxylic acid,

7-(3,4-Dichlorophenyl)-N,N-diethyl-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-2-carboxamide,

7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-N-(4-hydroxyphenyl)-5-methylpyrazolo[1,5-a]pyrimidine-2-carboxamide,

1-[[7-(3,4-Dichloro-phenyl)-4,7dihydro-5-methyl-2-[[(2S)-2-(1-pyrrolidinylmethyl)-1-pyrrolidinyl]carbonyl]-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-2-carboxamide,

7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-5-methyl-N-(phenylmethyl)pyrazolo-[1,5-a]pyrimidine-2-carboxamide,

7-(3,4-Dichlorophenyl)-6-[[4-(4-fluorophenyl)-1-piperazinyl]carbonyl]-4,7-dihydro-5-methyl-N-(2-phenylethyl)-pyrazolo[1,5-a]pyri-midine-2-carboxamide,

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1-[[2-Cyano-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

3-Bromo-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethyl ester;

1-[[3-Bromo-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine,

1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine,

1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenylpiperazine, enantiomer B,

1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-phenyl-piperazine, enantiomer A,

1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer A,

1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer B,

1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer A,

1-[[3-Chloro-7-(2,3-dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer B,

1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer A,

1-[[3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine, enantiomer B,

3-Chloro-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine-6-carboxylic acid 1,1-dimethylethyl ester;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-6-(5-phenyl-2-oxazolyl)pyrazolo[1,5-a]pyrimidine;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-6-(5-phenyl-1,3,4-oxa-diazol-2-yl)pyrazolo[1,5-a]pyrimidine,

6-(1H-Benzimidazol-2-yl)-7-(3,4-dichloro-phenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidine,

6-(2-Benzothiazolyl)-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine,

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-6-(1-methyl-1H-benzimi-dazol-2-yl)pyrazolo[1,5-a]pyrimidine;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-6-[5-(trifluoromethyl)-1-propyl-1H-benzimidazol-2-yl]pyrazolo[1,5-a]pyrimidine;

6-(5-Butyl-1,3,4-oxadiazol-2-yl)-7-(3,4-dichlorophenyl)-4,7dihydro-5-methylpyrazolo[1,5-a]pyrimidine,

1-[[7-(3,4-Dichloro-phenyl)-4,7-dihydro-5-methyl-6-(4-methyl-1H-benzimidazol-2-yl)pyra-zolo[1,5-a]pyrimidine;

1-[[7-(2,3-Dichloro-phenyl)-4,7-dihydro-5-methyl-6-(1-methyl-1H-benzimidazol-2-yl)pyra-zolo[1,5-a]pyrimidine;

7-(3,4-Dichlorophenyl)-4,7-dihydro-6-(imida-zo[1,5-a]pyridin-3-yl)-5-methylpyrazolo[1,5-a]pyrimidine,

7-(3,4-Dichlorophenyl)-6-(1-ethyl-5-nitro-1H-benzimidazol-2-yl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine,

6-[5-Chloro-1-(1-methylethyl)-1H-benzimidazol-2-yl]-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine,

6-(5-Chloro-1-ethyl-1H-benzimidazol-2-yl)-7-(3,4-dichlorophenyl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine;

7-(3,4-Dichlorophenyl)-6-(5-fluoro-1-propyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-methylpyra-zolo[1,5-a]pyrimidine;

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-6-[1-(1-methylethyl)-5-(trifluoromethyl)-1H-benzimidazol-2-yl]pyrazolo[1,5-a]pyrimidine,

7-(3,4-Dichlorophenyl)-6-(5-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyrimidine,

7-(3,4-Dichlorophenyl)-6-(5-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyri-midine, enantiomer A,

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7-(3,4-Dichlorophenyl)-6-(5-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-methyl-pyrazolo[1,5-a]pyri-midine, enantiomer B

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methyl-6-[1-(phenylmethyl)-1H-benzimidazol-2-yl]pyrazolo[1,5-a]pyrimidine,

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)-N-(2-pyridinylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(2,3-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)-N-(2-pyridinylmethyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(4-fluorophenyl)pyrrolidine,

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)-N-(3-phenylpropyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine;

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine,

(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine,

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-(methoxymethyl)-N,N-dipropylpyrazolo[1,5-a]pyrimidine-6-carboxamide;

5-Cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydro-N-(3-phenylpropyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

1-[[5-Cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydropyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[5-Cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydropyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine,

(2S)-1-[[5-Cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydropyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine,

5-Cyclohexyl-7-(3,4-dichlorophenyl)-4,7-dihydro-N,N-dipropylpyrazolo[1,5-a]pyrimidine-6-carboxamide,

7-(3,4-Dichlorophenyl)-4,7-dihydro-6-(imidazo[1,5-a]pyridin-3-yl)-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine,

7-(2,3-Dichlorophenyl)-4,7-dihydro-6-(imidazo[1,5-a]pyridin-3-yl)-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine,

7-(3,4-Dichlorophenyl)-6-(5-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine,

7-(2,3-Dichlorophenyl)-6-(4-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine,

7-(3,4-Dichlorophenyl)-6-(4-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine,

7-(2,3-Dichlorophenyl)-6-(5-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine,

7-(3,4-Dichlorophenyl)-6-(5-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine enantiomer A,

7-(3,4-Dichlorophenyl)-6-(5-fluoro-1-methyl-1H-benzimidazol-2-yl)-4,7-dihydro-5-(methoxymethyl)pyrazolo[1,5-a]pyrimidine enantiomer B,

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-phenyl-N-(3-phenylpropyl)pyrazolo[1,5-a]pyrimidine-6-carboxamide,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-phenylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-4-(4-fluorophenyl)piperazine,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-phenylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]piperidine,

(2S)-1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-phenylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(methoxymethyl)pyrrolidine,

7-(3,4-Dichlorophenyl)-4,7-dihydro-5-phenyl-N,N-dipropylpyrazolo[1,5-a]pyrimidine-6-carboxamide,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(4-fluorophenyl)pyrrolidine diastereomer 1,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(4-fluorophenyl)pyrrolidine diastereomer 2,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(4-fluorophenyl)pyrrolidine enantiomer A,

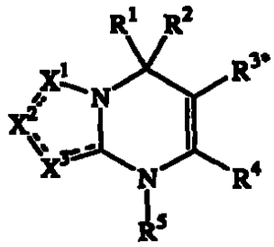
1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(4-fluorophenyl)pyrrolidine enantiomer B,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(4-fluorophenyl)pyrrolidine enantiomer C,

1-[[7-(3,4-Dichlorophenyl)-4,7-dihydro-5-methylpyrazolo[1,5-a]pyrimidin-6-yl]carbonyl]-2-(4-fluorophenyl)pyrrolidine enantiomer D

enantiomers, diastereomers and pharmaceutically acceptable salts thereof

18 A compound of the formula I*



(I*)

enantiomers, diastereomers and pharmaceutically acceptable salts thereof, wherein

X^1, X^2 and X^3 are independently selected from N, NR^6, $(CR^7)_q$, $(CHR^7)_q$, or C=O, wherein the bonds connecting X^1, X^2 and X^3 to adjacent atoms may be single or double bonds forming a 5 to 7-membered saturated, partially unsaturated or aromatic ring,

R^1, R^2, R^4, R^5, R^6 and R^7 are independently selected from groups of the formula $-(CH_2)_n-(Z^1)_m-(CH_2)_p-Z^2$, or

R^1, R^2, R^4 and R^5 may, in one or more pairs of two, together with the atoms to which they are bonded, form a carbocyclic, substituted carbocyclic heterocyclic or substituted heterocyclic group, or

R^6 and R^7 may, in one or more pairs of two, together with the atoms to which they are bonded, form a carbocyclic, substituted carbocyclic, heterocyclic or substituted heterocyclic group;

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Z^1 is $-CZ^3Z^4-$, $-O-$, $-NZ^3-$, $-S-$, $-SO-$, $-SO_2-$, $-C(O)-$, $-C(O)Z^3-$, $-C(O)NZ^4$, $-C(S)-$, $-C(=NOZ^3)-$, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbocyclo, substituted carbocyclo; aryl, substituted aryl, heterocyclo, or substituted heterocyclo;

Z^2 is hydrogen, $-OZ^5$, $-OC(O)Z^5$, $-NZ^5-C(O)-Z^6$, $-NZ^5-CO_2-Z^6$, $-NZ^5(C=O)-NZ^6Z^7$, $-NZ^5Z^6$, $-NO_2$, halo, $-CN$, $-C(O)Z^5$, $-CO_2Z^5$, $-C(S)Z^5$, $-(C=NOZ^5)Z^6$ $-C(O)NZ^5Z^6$, $-C(S)NZ^5Z^6$, $-SZ^5$, $-SOZ^5$, $-SO_2Z^5$, $-SO_2NZ^5Z^6$, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbocyclo, substituted carbocyclo, aryl, substituted aryl, heterocyclo, or substituted heterocyclo;

Z^3, Z^4, Z^5, Z^6 and Z^7 are independently hydrogen, halo, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbocyclo, substituted carbocyclo, aryl, substituted aryl, heterocyclo; or substituted heterocyclo, or

Z^3, Z^4, Z^5 Z^6 and Z^7 may, in one or more pairs of two, together with the atoms to which they are bonded, form a carbocyclic, substituted carbocyclic, heterocyclic or substituted heterocyclic group,

R^{3*} is $-OZ^5$, $-OC(O)-Z^5$, $-NZ^5-C(O)_2-Z^6$, $-NZ^5(C=O)-NZ^6Z^7$, $-NZ^5Z^6$, $-(C=NOZ^5)Z^6$, $-C(O)NZ^{5*}Z^{6*}$, $-C(S)NZ^{5*}Z^{6*}$, $-SZ^5$, $-SOZ^5$, $-SO^2Z^5$, $-SO_2NZ^5Z^6$ $-C(O)Z^{3*}$-Z^{2*}, halo, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbocyclo; substituted carbocyclo; aryl, substituted aryl, heterocyclo or substituted heterocyclo,

Z^{2*} is other than hydrogen when Z^{3*} is heterocyclo,

Z^{3*} is heterocyclo or substituted heterocyclo

Z^{5*} is substituted alkyl alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbocyclo, substituted carbocyclo, aryl, substituted aryl, heterocyclo, or substituted heterocyclo, and

Z^{6*} is hydrogen, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, carbocyclo, substituted carbocyclo, aryl, substituted

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aryl, heterocyclo, or substituted heterocyclo, provided that Z^{6*} is not hydrogen when Z^{5*} is unsubstituted cycloalkyl, unsubstituted aryl, or unsubstituted benzyl,

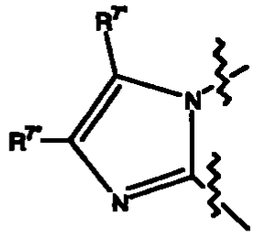
or Z^{5*} and Z^{6*} may together with the nitrogen atom to which they are bonded form a heterocyclic group or substituted heterocyclic group, provided that Z^{5*} and Z^{6*} do not together form unsubstituted piperidinyl unsubstituted pyrrolidinyl, or unsubstituted morpholinyl, and further provided that when

(i) R^1 and R^5 are each hydrogen, and

(ii) R^2 is aryl or substituted aryl, and

(iii) R^4 is heterocyclo-substituted aryl, and

(iv) X^1, X^2 and X^3 form the ring



where R^{7*} is H or alkyl,

Z^{5*} and Z^{6*} do not together form unsubstituted piperazinyl or N-alkyl-substituted piperazinyl,

n and p are independently selected from integers from 0 to 10 wherein, when m is 0, p is also 0;

m is an integer selected from 0 or 1, and

q is an integer selected from 1 to 3

19 A compound of claim 18 wherein

R^{3*} is heterocyclo, substituted heterocyclo, $-C(O)NZ^{5*}Z^{6*}$, $-C(O)Z^{3*}$-$C(O)NZ^5Z^6$, $-C(O)Z^{3*}$-CO_2Z^5, $-C(O)Z^{3*}$-(aryl), $-C(O)Z^{3*}$-(substituted aryl), $-C(O)Z^{3*}$-(heterocyclo) or $-C(O)Z^{3*}$-(substituted heterocyclo)

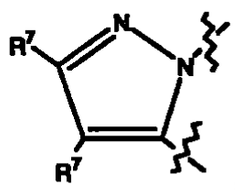
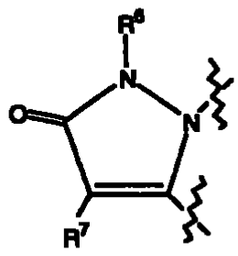
20 A compound of claim 19 wherein

R^1 is H,

R^2 is aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo or substituted carbocyclo,

R^4 is alkyl or substituted alkyl, and

X^1, X^2 and X^3, together with the atoms to which they are bonded, form a ring selected from.

where the ring substituents are the same or different

21 A compound of claim 18 wherein R^{3a} is heterocyclo or substituted heterocyclo

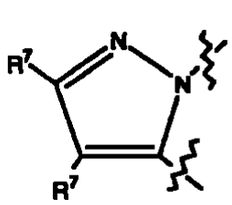
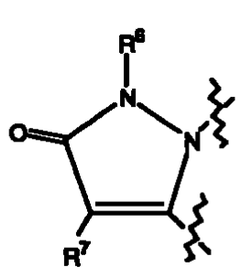
22 A compound of claim 21 wherein

R^1 is H,

R^2 is aryl, substituted aryl, heterocyclo, substituted heterocyclo, carbocyclo or substituted carbocyclo,

R^4 is alkyl or substituted alkyl, and

X^1, X^2 and X^3, together with the atoms to which they are bonded, form a ring selected from.

where the ring substituents are the same or different.

23 A compound of claim 18 selected from the title compounds of examples 18, 19, 25-30, 33, 39-42, 44-82, 84-221, 223-273, 277-282, 286-288, 290-307, 309-312, 314-336, 340-400, 402-450, 452-463, 465-483, 484-488, 490, 492, 493, 495, 497-506, 508, 510-545, 547-555 557-562, 564, 565, 567-586, and 588

24 A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 18 and a pharmaceutically acceptable vehicle or carrier thereof

25 A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 19 and a pharmaceutically acceptable vehicle or carrier thereof

26 A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 20 and a pharmaceutically acceptable vehicle or carrier thereof

27 A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 21 and a pharmaceutically acceptable vehicle or carrier thereof

28 A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 22 and a pharmaceutically acceptable vehicle or carrier thereof.

29 A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 23 and a pharmaceutically acceptable vehicle or carrier thereof

30 A method of treating arrhythmias comprising administering to a patient in need thereof an effective amount of at least one compound of claim 18

31 A method of treating arrhythmias comprising administering to a patient in need thereof an effective amount of at least one compound of claim 19

32 A method of treating arrhythmias comprising administering to a patient in need thereof an effective amount of at least one compound of claim 20

33 A method of treating arrhythmias comprising administering to a patient in need thereof an effective amount of at least one compound of claim 21

34 A method of treating arrhythmias comprising administering to a patient in need thereof an effective amount of at least one compound of claim 22.

35 A method of treating arrhythmias comprising administering to a patient in need thereof an effective amount of at least one compound of claim 23

HETEROCYCLIC DIHYDROPYRIMIDINE COMPOUNDS

Abstract of the Disclosure

Novel heterocyclic dihydropyrimidine compounds, methods of using such compounds in the prevention and treatment of arrhythmia and I_{Kur}-associated conditions, and pharmaceutical compositions containing such compounds.

ESTADOS UNIDOS DE AMERICA

A QUIENES PUEDA LLEGAR LA PRESENTE

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Patentes y Marcas de los Estados Unidos

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Febrero 08, 2001

LA PRESENTE ES PARA CERTIFICAR QUE ANEXA A LA MISMA SE ENCUENTRA UNA COPIA AUTENTICA DE LOS REGISTROS DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS, DE LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE ABAJO IDENTIFICADA, QUE CUMPLE CON LOS REQUISITOS PARA QUE SE LE CONCEDA UNA FECHA DE PRESENTACION CONFORME A LA 35 USC 111

NUMERO DE SOLICITUD *60/236,037*
FECHA DE PRESENTACION *Septiembre 28 2000*

(SELLO)

Por Autoridad del
COMISIONADO DE PATENTES Y MARCAS

(Rubrica)
L EDELEN
Oficial de Certificaciones

Número de Documento	HA726 PSP1

ENVIADO POR "CORREO EXPRESS" BAJO EL 37 CFR 1.10

EL600707943US	Septiembre 28, 2000
Número de Etiqueta de Correo Express	Fecha del Depósito

8/28

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Dirigido a Assistant Commissioner for Patents
Box Provisional Patent Application
Washington, DC 20231

HOJA DE CUBIERTA DE LA SOLICITUD PROVISIONAL

Es la SOLICITUD PROVISIONAL para patentes transmitida junto con esta, para su presentación bajo el 37 CFR &1 53(c) en

INVENTOR(ES)

Nombre dado (primero e intermedio[(si hay])	Apellido o Subnombre	Residencia (Ciudad y ya sea Estado o País Extranjero)
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TITULO DE LA INVENCION (280 caracteres máx)

COMPUESTOS DE DIHIDROPIRIMIDINA HETEROCICLICOS

DIRECCION PARA CORRESPONDENCIA

Dirija toda la correspondencia a la dirección abajo la cual está actualizada

Burton Rodney
Bristol Myers Squibb Company
Patent Department
P O Box 4000
Princeton, NJ 08543-4000

PARTES DE LA SOLICITUD ADJUNTAS (*verificar todas las que se aplican*)

- ☒ Especificación (incluyendo cualquera de las reivindicaciones y Resumen) 90 páginas
- ☐ Dibujos – hojas
- ☐ Otros (especificar) Poder del Abogado y Firmas

METODO DE PAGO (*verificar uno*)

El comisionado está con ello, autorizado a cargar el cálculo de tasas y cualquier calculo adicional requerido al Número de Cuenta del Depósito 19-3880 en nombre de Bristol Myers Squibb Company	CALCULO DE TASAS PROVISIONAL $ 150

☐ Agencia Gubernamental Estadounidense y número de contrato (Si se elabora la invencion por una agencia del Gobierno de los Estados Unidos o bajo un contrato con una agencia del Gobierno de los Estados Unidos)

Respetuosamente,
Ronald S. Hermenau
Abogado para los Solicitantes
Reg. No. 34,620
Tel No. (609) 252-5781

Fecha 9/28/00

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COMPUESTOS DE DIHIDR PIRIMIDINA HETEROCICLICOS

Campo de la Invención

La presente invención se refiere a compuestos de dihidropirimidina heterocíclicos, para métodos de compuestos tales como los empleados en el tratamiento de arritmia, alteraciones asociadas con I_{Kur} y para composiciones que contiene tales compuestos

Antecedentes de la Invención

La fibrilación del atrio y el palpitar son las arritmias más comunes encontradas en la práctica clinica Aunque algunos fármacos antiarrítmicos actualmente disponibles pueden convertir la fibrilación sostenida a ritmo del seno, son solamente efectivos en la fibrilación aguda del atrio y aún asi su eficacia es baja Además, estos fármacos son de uso limitado debido a una variedad de efectos potencialmente adversos, incluyendo proarritmia ventricular

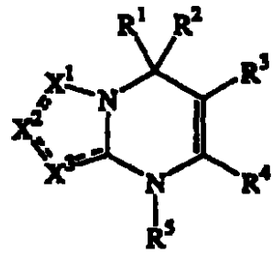
Así, existe actualmente una necesidad médica no satisfecha para un tratamiento seguro y eficaz de la fibrilación del atrio y otras arritmias supraventriculares

La corriente de potasio rectificadora de liberación ultra rápida (I_{Kur}), es una corriente sostenida de activación rápida que ha sido identificada en los miocitos del atrio humano, pero está aparentemente ausente de los miocitos ventriculares humanos (Konarzewska et al , *Circulation J Physiol , 491,* 13 (1996)) Los datos farmacológicos y biofísicos, biológicos moleculares considerables, indican que el I_{Kur} es codificado por el gen del canal de potasio Kv1 5 El I_{Kur} juega un papel significante en la repolarización de la inhibición potencial y selectiva de la acción del atrio de esta corriente, en los miocitos del atrio humano prolonga la duración de la acción potencial por mas del 50% (Wang et al , *Circ Res 73,* 1061 (1993)) La prolongacion de la acción potencial, consecuentemente prolonga el periodo refractorio efectivo del atrio, esto es, la inhibición del I_{Kur} produce un efecto antiarrítmico de clase

III De manera importante, un inhibidor de I_{Kur} puede tener utilidad contra la fibrilación atrial sin tener el riesgo proarrítmico ventricular concomitante asociado con otros agentes de clase III que tienen canales de calcio objetivo expresados en ambos, atrio y ventriculo

Breve Descripción de la Invención

La presente invención proporciona compuestos de dihidropirimidina heterociclicos de la siguiente formula I, incluyendo enantiómeros, diastereómeros, y sales de los mismos, para el tratamiento de alteraciones tal como la arritmia y alteraciones asociadas con I_{Kur}



(I)

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donde

X^1, X^2 y X^3 son independientemente seleccionados de N, NR^6, $(CR^7)_q$, $(CHR^7)_q$, o C=O, en donde los enlaces que conectan X^1, X^2 y X^3 a los átomos adyacentes, pueden ser enlaces unicos o dobles que forman un anillo aromático de 5 a 7 elementos saturados o parcialmente insaturados,

R^1, R^2, R^3, R^4, R^5, R^6 y R^7 son los mismos o diferentes y son seleccionados de manera independiente de los grupos de la fórmula $-(CH_2)_n-(Z^1)_m-(CH_2)_p-Z^2$, o

R^1, R^2, R^3, R^4 y R^5 pueden, en uno o más pares de dos (tal como R^1 y R^2, R^1 y R^3, R^2 y R^3, R^3 y R^4 o R^4 y R^5), junto con los átomos a los cuales están enlazados, formar un grupo carbociclico, carbociclico substituido, heterociclico o heterociclico substituido, o

R^6 y R^7 pueden, en uno o mas pares de dos (tal como R^6 y R^7, R^6 y R^6, o R^7 y R^7), junto con los átomos a los cuales estan unidos, formar

un grupo carbocíclico, carbocíclico substituido, heterocíclico o heterocíclico substituido,

Z^1 es $-CZ^3Z^4-$, $-O-$, $-NZ^3-$, $-S-$, $-SO-$, $-SO_2-$, $-C(O)-$, $-C(O)Z^3-$, $-C(O)NZ^4$, $-C(S)-$, $-C(=NOZ^3)-$, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, carbociclo, carbociclo substituido, arilo, arilo substituido, heterociclo, o heterociclo substituido,

Z^2 es hidrógeno, $-OZ^5$, $-OC(O)Z^5$, $-NZ^5-C(O)-Z^6$, $-NZ^5-CO_2-Z^6$, $-NZ^5(C=O)-NZ^6Z^7$, $-NZ^5Z^6$, $-NO_2$, halo, $-CN$, $-C(O)Z^5$, $-CO_2Z^5$, $-C(S)Z^5$, $-(C=NOZ^5)Z^6$, $-C(O)NZ^5Z^6$, $-C(S)NZ^5Z^6$, $-SZ^5$, $-SOZ^5$, $-SO_2Z^5$, $-SO_2NZ^5Z^6$, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, carbociclo, carbociclo substituido, arilo, arilo substituido, heterociclo (tal como heteroarilo), o heterociclo substituido

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Z^3, Z^4, Z^5, Z^6 y Z^7 son independientemente hidrógeno, halo, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, carbociclo, carbociclo substituido, arilo, arilo substituido, heterociclo, o heterociclo substituido, o

Z^3, Z^4, Z^5, Z^6 y Z^7 pueden, en uno o más pares de dos (tal como Z^3 y Z^4, Z^5 y Z^6 o Z^6 y Z^7), junto con los átomos de carbono a los cuales están unidos, formar un grupo carbocíclico carbocíclico substituido, heterocíclico o heterocíclico substituido,

n y p son independientemente seleccionados de los enteros a partir de 0 a 10 en donde m es 0, p es también 0,

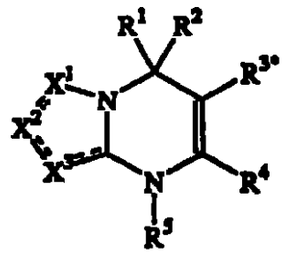
m es un entero seleccionado de 0 o 1, y

q es un entero seleccionado de 1 a 3

La presente invencion proporciona nuevos metodos para la prevención y tratamiento de la

arritmia y alteraciones asociadas con I_{Kur}, empleando uno o más compuestos de la fórmula I, enantiómeros, diastereómeros o sales del mismo farmacéuticamente aceptables En particular, la presente invención proporciona un nuevo método para la prevención selectiva y tratamiento de arritmias supraventriculares

Además, los compuestos dentro de la fórmula I, así como también enantiómeros, diastereómeros y sales de los mismos son compuestos nuevos, incluyendo compuestos de la fórmula I* y sales de los mismos



(I*)

en donde

X^1, X^2, X^3, R^1, R^2, R^4 y R^5 son como se definen anteriormente,

860
836

R^{3*} es $-OZ^5$, $-OC(O)Z^5$, $-NZ^5-C(O)_2-Z^6$, $-NZ^5(C=O)-NZ^6Z^7$, $-NZ^5Z^6$, $-(C=NOZ^5)Z^6$, $-C(O)NZ^{5*}Z^{6*}$, $-C(S)NZ^{5*}Z^{6*}$, $-SZ^5$, $-SOZ^5$, $-SO^2Z^5$, $-SO_2NZ^5Z^6$, $-C(O)Z^{3*}Z^{2*}$, halo, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, carbociclo, carbociclo substituido, arilo, arilo substituido, heterociclo o heterociclo substituido,

Z^{2*} es otro hidrógeno cuando Z^{3*} es heterociclo,

Z^{3*} es heterociclo o heterociclo substituido,

Z^{5*} es alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, carbociclo, carbociclo substituido, arilo, arilo substituido, heterociclo, o heterociclo substituido, y

Z^{6*} es hidrógeno, alquilo, alquilo

861
837

substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, carbociclo, carbociclo substituido, arilo, arilo substituido, heterociclo, o heterociclo substituido, con la condición de que Z^{6*} no sea hidrógeno cuando Z^{5*} es cicloalquilo insubstituido, arilo insubstituido, o bencilo insubstituido,

o Z^{5*} y Z^{6*} pueden, junto con el átomo de nitrógeno al cual están unidos, formar un grupo heterociclico o un grupo heterociclico substituido, con la condición de que Z^{5*} y Z^{6*} no formen juntos piperidinilo insubstituido, pirrolidinilo insubstituido, o morfolinilo insubstituido, y demás, con la condición de que

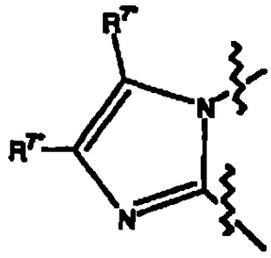
(i) R^1 y R^5 sean cada uno hidrógeno, y

(ii) R^2 sea arilo o arilo substituido, y

(iii) R^4 sea heterocíclico-arilo substituido, y

862

(iv) X^1, X^2 y X^3 formen el anillo



donde R^{7*} es H o alquilo

Z^{5*} y Z^{6*} no forman juntos el piperazinilo insubstituido o piperazinilo N-alquil-substituido,

Compuestos Preferidos

Los compuestos de la fórmula I y las sales del mismo, en donde uno o mas, y especialmente todos, de X^1, X^2, X^3, R^1, R^2, R^3, R^4 y R^5 se seleccionan a partir de las siguientes definiciones, son compuestos preferidos de la presente invención

863

R^1 es hidrógeno,

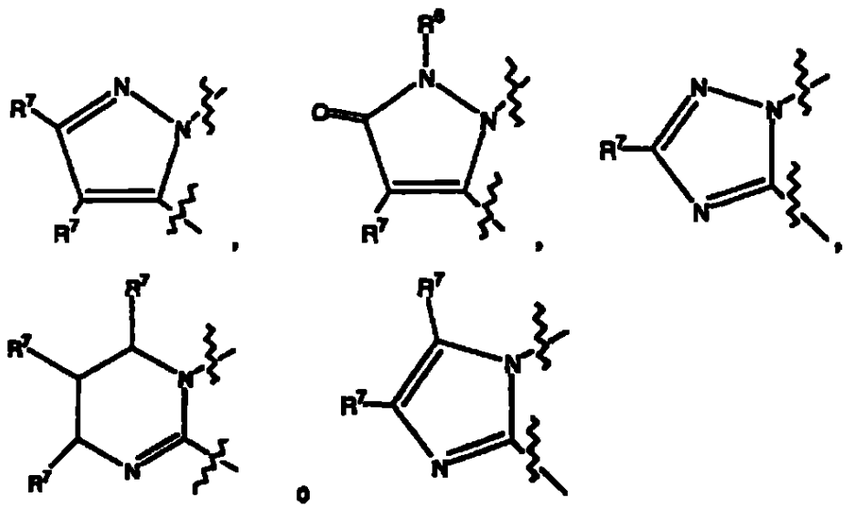
R^2 es hidrógeno, alquilo, alquilo substituido, arilo, arilo substituido, heterociclo, heterociclo substituido, carbociclo o carbociclo substituido,

R^3 es $-(CH_2)_n-Z^2$, $-(CH_2)_n-C(O)Z^3-(CH_2)_p-Z^2$, o $-(CH_2)_n-C(O)NZ^4-(CH_2)_p-Z^2$,

R^4 es alquilo o alquilo substituido, y

R^5 es hidrógeno, o $-(CH_2)_n-Z^2$, y

X^1, X^2 y X^3, junto con los átomos a los cuales están unidos, forman un anillo, seleccionado de



donde R^6 y/o R^7 son los mismos o diferentes, como se definen anteriormente

Los compuestos de la fórmula I y las sales de los mismos, en donde uno o más, y especialmente, todos de X^1, X^2, X^3, R^1, R^2, R^3, R^4 y R^5 se seleccionan a partir de las siguientes definiciones, son más preferidos los compuestos de la presente invención

R^1 es hidrógeno,

R^2 es arilo (especialmente cuando arilo es

865

847

fenilo), arilo substituido, heterociclo, heterociclo substituido, carbociclo o carbociclo substituido,

R^3 es $-(CH_2)_n-Z^2$, $-(CH_2)_n-C(O)Z^3-(CH_2)_p-Z^2$, o $-(CH_2)_n-C(O)NZ^4-(CH_2)_p-Z^2$, en donde Z^2 se selecciona a partir de $-C(O)NZ^5Z^6$, $-CO_2Z^5$, $-SO_2Z^5$, $-NZ^5Z^6$, $-NZ^5CO_2Z^6$, $-NZ^5C(O)Z^6$, $-OZ^5$, arilo, arilo substituido, heterociclo, heterociclo substituido, alquilo o alquilo substituido,

Z^3 es heterociclo o heterociclo substituido, y

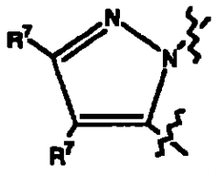
n y p son independientemente, seleccionados a partir de los enteros 0 a 3,

R^4 es alquilo, o alquilo substituido,

R^5 es hidrógeno, o $-(CH_2)_n-Z^2$, en donde Z^2 se selecciona a partir de $-C(O)NZ^5Z^6$, $-CO_2Z^5$, $-NZ^5Z^6$, arilo, arilo substituido, alquilo o alquilo substituido, y

866
842

X^1, X^2 y X^3, junto con los átomos a los cuales están unidos, forman un anillo seleccionado de



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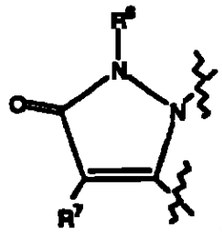

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Los compuestos de la fórmula I y las sales de los mismos, en donde uno o más, y especialmente, todos de X^1, X^2, X^3, R^1, R^2, R^3, R^4 y R^5 se seleccionan a partir de las siguientes definiciones, son más preferidos, los compuestos de la presente invención

R^1 es hidrógeno,

R^2 es arilo (especialmente cuando arilo es fenilo), arilo substituido, heterociclo,

867
843

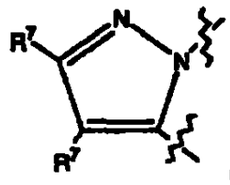
heterociclo substituido, carbociclo o carbociclo substituido,

R^3 es heterociclo o heterociclo substituido, $-C(O)NZ^5Z^6$, $-CO_2Z^3$-$CONZ^5Z^6$, $-C(O)Z^3Z^2$, o $-C(O)Z^3$-CO_2Z^5, en donde Z^3 es heterociclo o heterociclo substituido, y Z^2 es arilo o arilo substituido,

R^4 es alquilo (especialmente alquilo inferior) o alquilo substituido (especialmente haloalquilo substituido),

R^5 es hidrógeno, alquilo o alquilo substituido, y

X^1, X^2 y X^3, junto con los átomos a los cuales están unidos, forman un anillo seleccionado a partir de



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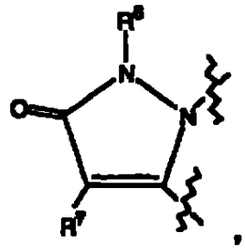

,

en donde

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R^6 es H o $C(O)Z^5$, en donde Z^5 es alquilo o carbociclo, y

R^7 es independientemente seleccionado a partir de H, alquilo, alquilo substituido (especialmente halo substituido), halo, o CN

Descripción Detallada de la Invención

Las siguientes son definiciones de los términos usados en esta especificacion La definición inicial proporcionada para un grupo o término aqui aplica a tal grupo o término a traves de toda la especificación, individualmente o como parte de otro grupo, a menos que se indique de otro modo

Los término "alq" o "alquilo" se refieren a grupos hidrocarburos de cadena lineal o recta o ramificada, que tienen de 1 a 12 átomos de carbono, preferiblemente, 1 a 8 átomos de carbono, tal como metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo, t-butilo, pentilo, hexilo, heptilo, octilo, etc Los

grupos alquilo inferior, esto es, los grupos alquilo de 1 a 6 átomos de carbono, son generalmente más preferidos El término "alquilo substituido" se refiere a grupos alquilo substituidos con uno o más grupos (tal como por grupos descritos anteriormente en la definición de R^1), preferiblemente se seleccionan de arilo, arilo substituido, heterociclo, heterociclo substituido, carbociclo, carbociclo substituido, halo, hidroxi, alcoxi (opcionalmente substituido), ariloxi (opcionalmente substituido), alquiléster (opcionalmente substituido), arilester (opcionalmente substituido), alcanoilo (opcionalmente substituido), ariol (opcionalmente substituido), ciano, nitro, amino, amino substituido, amido, lactama, urea, uretano, sulfonilo, etc

El término "alquenilo" se refiere a grupos hidrocarburos de cadena lineal o recta o ramificada, que tienen de 2 a 12 átomos de carbono, preferiblemente 2 a 4 atomos de carbono, y al menos, un doble carbono para el enlace de carbono (ya sea cis o trans), tal como etenilo El término "alquenilo substituido" se

870
840

refiere a grupos alquenilos substituidos con uno o más grupos (tal como por los grupos descritos anteriormente en las definiciones de R^1), preferiblemente, seleccionados de arilo, arilo substituido, heterociclo, heterociclo substituido, carbociclo, carbociclo substituido, halo, hidroxi, alcoxi (opcionalmente substituido), ariloxi (opcionalmente substituido), alquiléster (opcionalmente substituido), arilester (opcionalmente substituido), alcanoilo (opcionalmente substituido), ariol (opcionalmente substituido), ciano, nitro, amino, amino substituido, amido, lactama, urea, uretano, sulfonilo, etc

El término "alquinilo" se refiere a grupos hidrocarburos de cadena lineal o recta o rafimicada, que tienen de 2 a 12 átomos de carbono, preferiblemente 2 a 4 átomos de carbono y al menos, un triple carbono para el enlace de carbono, tal como etinilo El término "alquinilo substituido" se refiere a grupos alquinilo substituidos con uno o más grupos (tal como por grupos descritos anteriormente en la definición de R^1), preferiblemente seleccionados de arilo,

871
847

arilo substituido, heterociclo, heterociclo substituido, carbociclo, carbociclo substituido, halo, hidroxi, alcoxi (opcionalmente substituido), ariloxi (opcionalmente substituido), alquiléster (opcionalmente substituido), ariléster (opcionalmente substituido), alcanoilo (opcionalmente substituido), ariol (opcionalmente substituido), ciano, nitro, amino, amino substituido, amido, lactama, urea, uretano, sulfonilo, etc

Los terminos "ar" o "arilo" se refieren a grupos que contienen anillos homociclicos aromáticos (por ejemplo, hidrocarburos), mono, bi o triciclicos, preferiblemente tienen 6 a 12 elementos, tal como fenilo, naftilo y bifenilo Fenilo es un grupo arilo preferido El termino "arilo substituido" se refiere a grupos arilo substituidos con uno o más grupos (tal como por grupos descritos anteriormente en la definición de R^1), preferiblemente seleccionados de alquilo, alquilo substituido, alquenilo (opcionalmente substituido), arilo (opcionalmente substituido), heterociclo (opcionalmente substituido), halo, hidroxi, alcoxi (opcionalmente substituido),

arıloxı (opcıonalmente substituıdo), alcanoılo (opcıonalmente substituıdo), aroılo (opcıonalmente substituıdo), alquiléster (opcıonalmente substituıdo), arıléster (opcıonalmente substituıdo), cıano, nıtro, amıno, amıno substituıdo, amıdo, lactama, urea, uretano, sulfonılo, etc , donde opcionalmente, uno o mas pares de substituyentes junto con los átomos a los cuales están enlazados, forman un anıllo de 3 a 7 elementos,

Los términos "cicloalquılo" y "cıcloalquenılo" se refıeren a grupos de anıllos mono, bı o trı- homocıclıcos de 3 a 15 atomos de carbono, los cuales son, respectivamente, completamente saturados y parcıalmente saturados El término "cıcloalquenılo" ıncluye sıstemas de anıllos bı y trıcíclıcos que no son aromátıcos como un total, pero contienen porcıones aromátıcas (por ejemplo, fluoreno, tetrahıdronaftaleno, dıhıdroındeno y sımılares) Los términos "cıcloalquılo substituıdo" y "cıcloalquenılo substituıdo" se refıeren, respectıvamente, a grupos cıcloalquılo y cıcloalquenılo, substituıdos con uno o más

873
849

grupos (tal como por grupos descritos anteriormente en la definición de R^1), preferiblemente seleccionados de arilo, arilo substituido, heterociclo, heterociclo substituido, carbociclo, carbociclo substituido, halo, hidroxi, alcoxi (opcionalmente substituido), ariloxi (opcionalmente substituido), alquiléster (opcionalmente substituido), ariléster (opcionalmente substituido), alcanoilo (opcionalmente substituido), ariol (opcionalmente substituido), ciano, nitro, amino, amino substituido, amido, lactama, urea, uretano, sulfonilo, etc

Los terminos "carbociclo", "carbociclico" o "grupo carbocíclico" se refiere a ambos grupos cicloalquilo y cicloalquenilo Los términos "carbociclo substituido", "carbocíclico substituido" o "grupo carbocíclico substituido", se refieren a los grupos carbociclo o carbocíclico, substituidos con uno o más grupos como se describen en la definición de cicloalquilo o cicloalquenilo

374
870

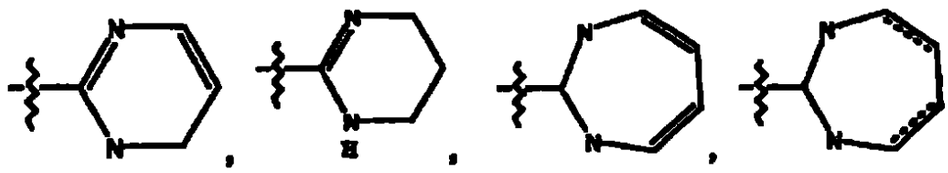
Los términos "halógeno" y "halo" se refieren a flúor, cloro, bromo y yodo

Los términos "heterociclo", "heterocíclico", "grupo heterocíclico" o "heterociclo", se refieren a grupos cíclicos completamente o parcialmente saturados o completamente insaturados, incluyendo grupos cíclicos aromáticos ("heteroarilo"), o no aromáticos (por ejemplo, sistemas de anillos 3 a 13 elementos monocíclicos, 7 a 17 elementos bicíclicos, o 10 a 20 elementos tricíclicos, preferiblemente que contienen un total de 3 a 10 átomos de anillos), los cuales tienen al menos un heteroátomo, en al menos un anillo que contiene un átomo de carbono Cada uno de los anillos del grupo heterociclico que contiene un heteroátomo, puede tener 1, 2, 3 o 4 heteroátomos seleccionados a partir de átomos de nitrógeno, átomos de oxigeno y/o átomos de azufre, en donde los heteroátomos de nitrógeno y azufre pueden opcionalmente ser oxidados y los heteroátomos de nitrógeno pueden ser opcionalmente cuaternizados El grupo heterocíclico puede estar unido a cualquier

875
851

heteroátomo o átomo de carbono del anillo o sistema de anillo Los anillos de los heterocíclos de anillos múltiples, pueden estar ya sea fusionados, en puentes y/o unidos a través de una o más uniones espiro

Los grupos heterocíclicos monocíclicos ejemplares incluyen, azetidinilo, pirrolidinilo, pirrolilo, pirazolilo, oxetanilo, pirazolinilo, imidazolilo, imidazolinilo, imidazolidinilo, oxazolilo, oxazolidinilo, isoxazolinilo, isoxazolilo, tiazolilo, tiadiazolilo, tiazolidinilo, isotiazolilo, isotiazolidinilo, furilo, tetrahidrofurilo, tienilo, oxadiazolilo, piperidinilo, piperazinilo, 2-oxopiperazinilo, 2-oxopiperidinilo, 2-oxopirrolidinilo, 2-oxoazepinilo, azepinilo, 4-piperidonilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, triazinilo, tetrahidropiranilo, tetrazolilo, triazolilo, morfolinilo, tiamorfolinilo, sulfoxido de tiamorfolinilo, sulfona de tiamorfolinilo, 1,3-dioxolano y tetrahidro-1,1-dioxotienilo,

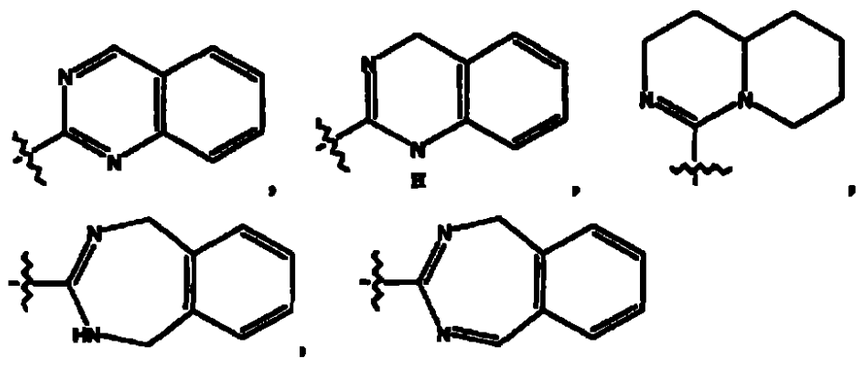


y similares

Los grupos heterocíclicos bicíclicos ejemplares incluyen indolilo, benzotiazolilo, benzoxazolilo, benzotienilo, quinuclidinilo, quinolinilo, tetra-hidroisoquinolinilo, isoquinolinilo, bencimidazolilo, benzopiranilo, indolizinilo, benzofurilo, benzofuranilo, dihidrobenzofuranilo, cromonilo, cumarinilo, benzodioxolilo, dihidrobenzodioxolilo, benzodioxinilo, cinolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridinilo (tal como furo[2,3-c]piridinilo, furo[3,2-b]piridinilo] o furo[2,3-b]piridinilo), dihidroisoindolilo, dihidroquinazolinilo (tal como 3,4-dihidro-4-oxo-quinazolinilo), tetrahidroquinolinilo, azabicicloalquilos (tal como 6-azabiciclo[3 2 1]octano), azaspiroalquilos (tal como 1,4-dioxa-8-azaespiro[4 5]decano), imidazopiridinilo (tal como imidazo[1,5-a]piridin-3-il),

877
~~853~~

triazolopiridinilo (tal como 1,2,4-triazolo[4,3-a]piridin-3-il), y hexahidroimidazopiridinilo (tal como 1,5,6,7,8,8a-hexahidroimidazo[1,5-a]piridin-3-ilo),



y similares

Los grupos heterocíclicos tricíclicos ejemplares incluyen carbazolilo, bencidolilo, fenantrolinilo, acridinilo, fenantridinilo, xantenilo y similares

Los términos "heterociclo substituido", heterocíclico substituido", "grupo heterocíclico substituido" y "heterociclo substituido" se

878
854

refieren a grupos heterociclo, heterocíclico y heterociclo substituidos con uno o más grupos (tal como por los grupos descritos anteriormente en la definición de R^1), preferiblemente seleccionado de alquilo, alquilo substituido, alquenilo, oxo, arilo, arilo substituido, heterociclo, heterociclo substituido, carbociclo (opcionalmente substituido), halo, hidroxi, alcoxi (opcionalmente substituido) ariloxi (opcionalmente substituido), alcanoilo (opcionalmente substituido), aroilo (opcionalmente substituido), alquiléster (opcionalmente substituido), ariléster (opcionalmente substituido), ciano, nitro, amido, amino, amino substituido, lactama, urea, uretano, sulfonilo, etc , en donde uno o más pares de substituyentes junto con los átomos a los cuales están unidos, forman un anillo de 3 a 7 elementos

El término "alcanoilo" se refiere al grupo alquilo (el cual puede ser opcionalmente substituido como se describe anteriormente) ligado a un grupo carbonilo (es decir, -C(O)-alquilo) De manera similar, el término "aroilo"

879
855

se refiere a un grupo arilo (el cual puede ser opcionalmente substituido como se define anteriormente) ligado a un grupo carbonilo (es decir, -C(O)-arilo)

A través de la especificación, los grupos y substituyentes de los mismos, pueden ser seleccionados para proporcionar porciones y compuestos estables

Los compuestos de fórmula I forman sales, las cuales están tambien dentro del ámbito de esta invencion La referencia a un compuesto de la fórmula I aquí se entiende incluye la referencia a las sales de los mismos, a menos que se indique de otro modo El término "sal(es)", como se emplea aquí, denota sales acidicas y/o básicas formadas con ácidos y bases inorgánicas y/o orgánicas Además, cuando un compuesto de fórmula I contiene ambas, una porción básica y una porción acidica, los zwitteriones ("sales inertes") pueden ser formados y están incluidos dentro del término "sal(es)" como se usó aquí Se prefieren las sales farmacéuticamente aceptables (es decir, no

tóxicas, fisiológicamente aceptables), aunque otras sales son también empleados, por ejemplo, en etapas de aislamiento o purificación, las cuales pueden ser empleadas durante la preparacion Las sales de los compuestos de fórmula I pueden ser formadas, por ejemplo, al hacer reaccionar un compuesto I con una cantidad de ácido o base, tal como una cantidad equivalente, en un medio tal como uno en el cual, la sal precipita en un medio acuoso seguido por liofilización

Los compuestos de fórmula I los cuales contienen una porción básica pueden formar sales con una variedad de sales orgánicas e inorgánicas Las sales de adición ejemplares incluyen acetatos (tal como aquellos formados con ácido acético o acido trihaloacético, por ejemplo, ácido trifluoroacético), adipatos, alginatos, ascorbatos, aspartatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, canforatos, canforsulfonatos, ciclopentanopropionatos, digluconatos, dodecilsulfatos, etanosulfonatos, fumaratos, glucoheptanoatos, glicerofosfatos,

hemisulfatos, heptanoatos, hexanoatos, clorhidratos (formados con ácido clorhídrico), bromhidratos (formados con bromuro de hidrógeno), yodohidratos, 2-hidroxietanosulfonatos, lactatos, maleatos (formados con ácido maléico), metanosulfonatos (formados con ácido metanosulfónico), 2-naftalenosulfonatos, nicotinatos, nitratos, oxalatos, pectinatos, persulfatos, 3-fenilpropionatos, fosfatos, picratos, pivalatos, propionatos, salicilatos, succinatos, sulfatos (tal como aquellos formados con ácido sulfurico), sulfonatos (tal como aquellos mencionados aquí), tatratos, tiocianatos, toluensulfonatos tal como tosilatos, undecanoatos y similares

Los compuestos de fórmula I los cuales contienen una porción acídica pueden formar sales con una variedad de bases orgánicas e inorgánicas Las sales básicas ejemplares incluyen sales de amonio, sales de metal álcali tal como sales de sodio, litio y potasio, sales de metales alcalino térreos tal como sales de calcio y magnesio, sales con bases orgánicas

(por ejemplo, aminas orgánicas) tal como benzatinas, diciclohexilaminas, hidrabaminas (formadas con N,N-bis(deshidroabietil)etilendiamina), N-metil-D-glucaminas, N-metil-D-glucamidas, t-butil-aminas y sales con aminoácidos tal como arginina, lisina y similares

Los grupos que contienen nitrógeno básico pueden ser cuaternizados con agentes tal como haluros de alquilo inferior (por ejemplo, metilo, etilo, propilo y cloruros, bromuros y yoduros de butilo), sulfatos dialquilo (por ejemplo dimetilo, dietilo, dibutilo, y sulfatos de diamino), haluros de cadena larga (por ejemplo, cloruros, bromuros y yoduros de decilo, laurilo, miristilo y estearilo), haluros de aralquilo (por ejemplo bromuros de bencilo y fenetilo), y otros

Los profármacos y solvatos de los compuestos de la invención están también contemplados aqui El termino "profármaco" como se empleó aquí, denota un compuesto el cual, después de la administración a un sujeto, se

somete a conversión química mediante el proceso metabólico o químico para proporcionar un compuesto de la fórmula I, o una sal y/o solvato del mismo Los solvatos de los compuestos de fórmula I son preferiblemente hidratos

Hasta cierto punto tales compuestos de fórmula I, y sales del mismo, pueden existir en su forma tautomérica, todas las tales formas tautoméricas están contempladas aquí como parte de la presente invención

Todos los estereoisómeros de los presentes compuestos, tales como aquellos los cuales pueden existir debido a los carbonos asimetricos en los varios substituyentes R y Z, incluyendo formas enantioméricas (las cuales pueden existir aún en la ausencia de carbonos asimétricos) y formas diastereoméricas, están contempladas dentro del ambito de esta invención Los estereoisómeros individuales de los compuestos de la invención pueden, por ejemplo, estar substancialmente libres de otros isómeros, o pueden ser mezclados, por ejemplo, como racematos o con todos los otros, u otros

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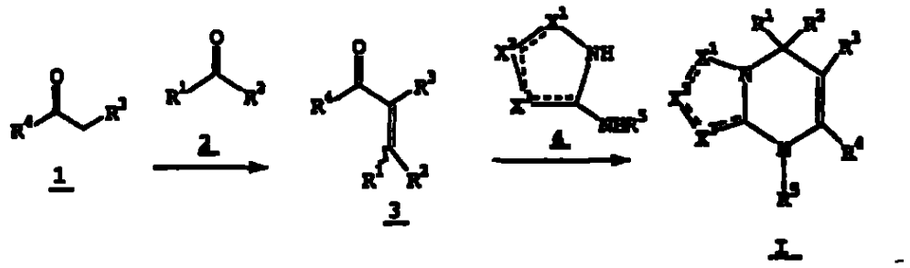
estereoisómeros seleccionados Los centros quirales de la presente invención pueden tener la configuración S o R como se define por las recomendaciones IUPAC 1974

Los términos "incluyendo", "tal como", "por ejemplo" y similares, están propuestos para referirse a las modalidades ejemplares y no limitan el ámbito de la presente invención

Esquemas

Los compuestos de fórmula I pueden ser preparados usando la secuencia de las etapas resumidas abajo



Los compuestos 1, 2 y 4 usados en esta preparación, están comercialmente disponibles o

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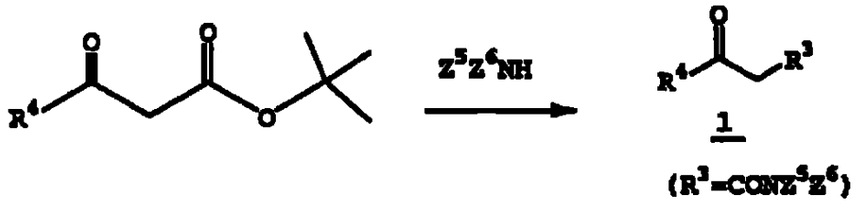
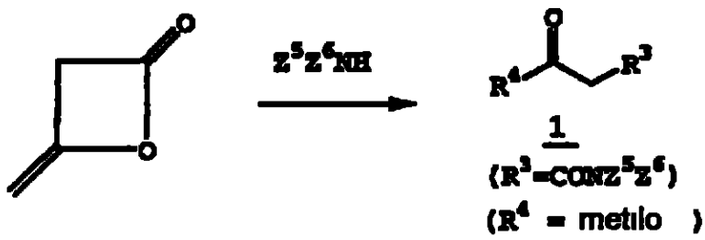
son fácilmente preparados por métodos bien conocidos por aquellos expertos en la técnica Por ejemplo, los compuestos de fórmula 1, donde R^3 = $CONZ^5Z^6$ pueden ser preparados por el método de Witzeman (JOC 1991, 56(5), 1713), el cual involucra el calentamiento de una amina y un t-butoxi-β-cetoéster puro o en un solvente adecuado (xilenos, toluenos, etc)



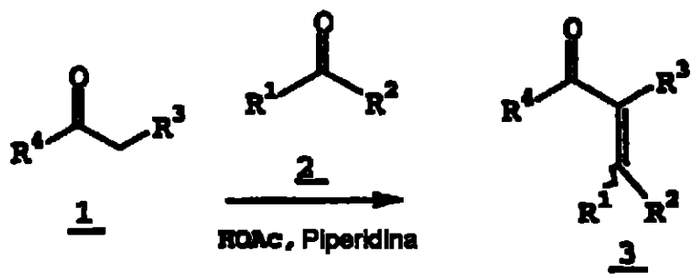
1

(R^3=$CONZ^5Z^6$)

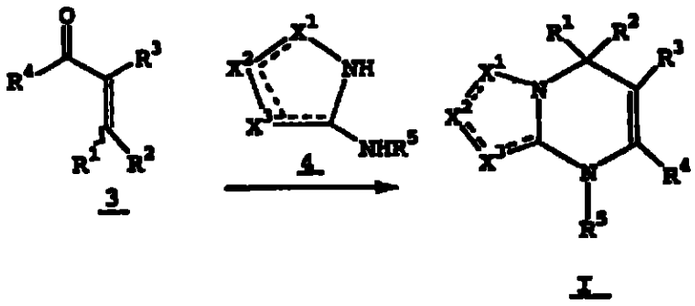
Alternativamente, los compuestos de fórmula 1, donde R^4 = metilo y R^3 =$CONZ^5Z^6$ pueden ser preparados mediante la reacción de una amina con diceteno en un solvente adecuado tal como diclorometano a temperaturas entre -100-22 °C



Los compuestos de fórmula 3, pueden ser preparados mediante la modificación de la condensación Knovenagel Por ejemplo, la condensación de un compuesto de fórmula 1, y un compuesto de fórmula 2 a temperaturas entre 22-170°C en solventes tal como tolueno o dimetilformamida en la presencia de un ácido tal como ácido acético y una base tal como piperidina con remocion de agua generada durante la reacción por el uso de tamices moleculares secos de 4Å o una trampa Dean-Starl proporcionando compuestos de fórmula 3 como una mezcla de estereoisómeros cis y trans



Los compuestos de fórmula I pueden también, ser preparados mediante la condensación de compuestos de fórmula 3 con compuestos de fórmula 4 por el calentamiento a temperaturas entre 30-150 °C en solventes alcohólicos tal como etanol o propanol o mediante el calentamiento entre 30-150°C en un solvente tal como dimetilformamida y en la presencia de una base tal como acetato de sodio



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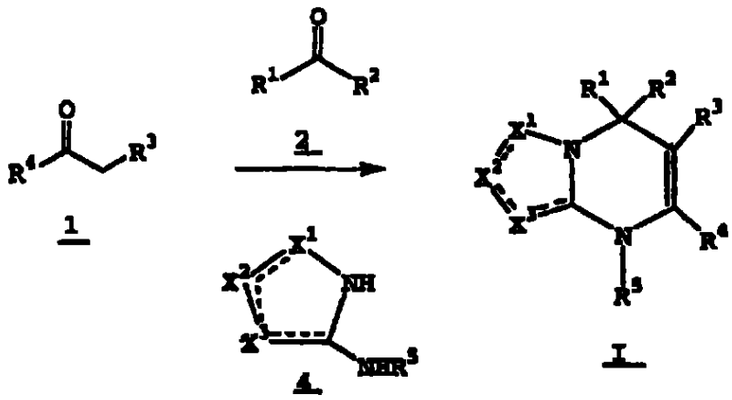
Los compuestos de fórmula I en donde R^3 = éster, pueden ser preparados por la condensación de compuestos de fórmula 1, fórmula 2 y heterociclos de fórmula 4 mediante el calentamiento entre temperaturas de 30-150°C en la presencia de una base tal como carbonato de sodio o bicarbonato de sodio en un solvente adecuado tal como dimetilformamida



Los compuestos de fórmula I donde R^3 = amida, pueden ser preparados por el tratamiento de los compuestos de fórmula I donde R^3 = éster con una amina adecuada y trietilaluminio en un solvente tal como tolueno a temperaturas entre 0-150°C

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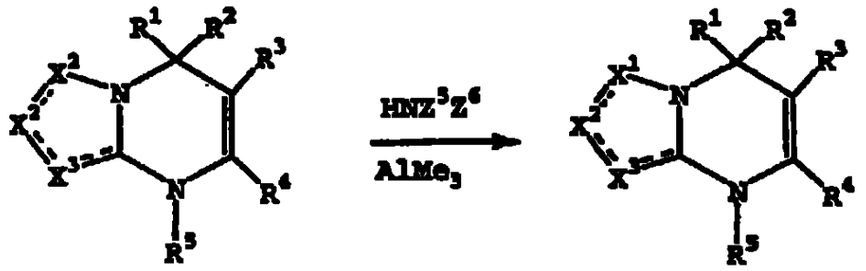
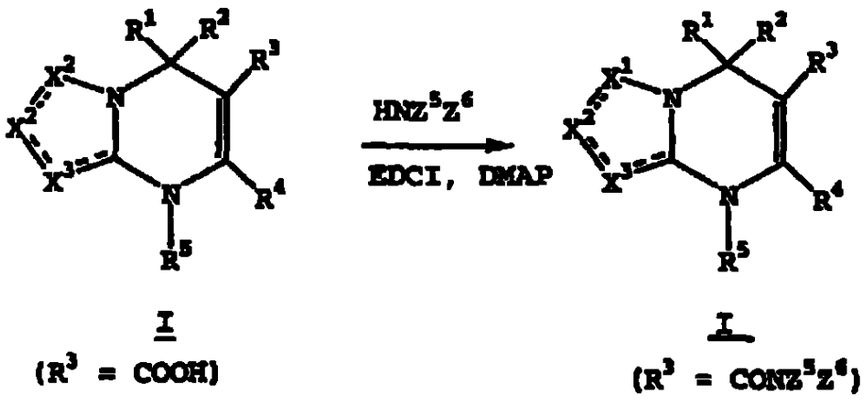


I
(R^3 = Ester)

I
(R^3 = $CONZ^5Z^6$)

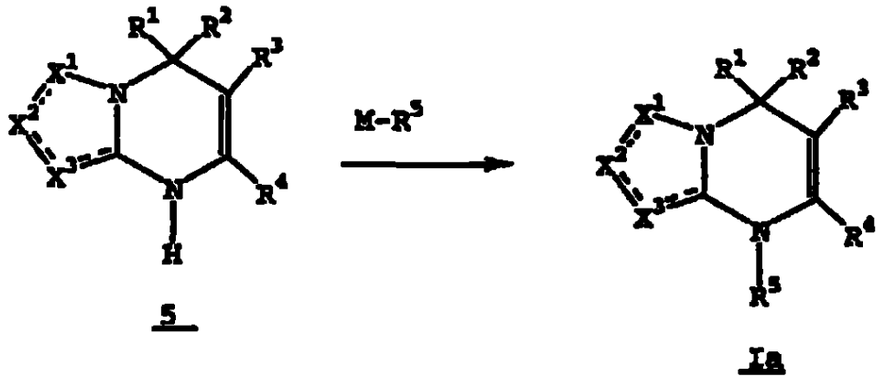
Los compuestos de fórmula I donde R^3 = amida, pueden ser preparados mediante la condensación de los compuestos de fórmula I donde R^3 = COOH con una amina adecuada mediante los métodos de amidación, bien conocidos por aquellos expertos en la técnica Para el tratamiento ejemplo de un compuesto de fórmula I donde R^3 = COOH, con clorhidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (EDCI) y dimetilaminopiridina (DMAP) en un solvente tal como diclorometano proporciona compuestos de fórmula I donde R^3 = amida



I
(R^3 = COOH)

I
(R^3 = $CONZ^5Z^6$)

Los compuestos de fórmula I donde R^5 es un substituyente preferentemente hidrógeno, pueden ser formados al hacer reaccionar un compuesto de fórmula 5 con una especie reactiva $M-R^5$, de manera tal que se obtiene un compuesto de fórmula Ia, donde M es Cl, Br, OR, etc , y R^5 es como se define anteriormente (preferentemente hidrógeno)



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Ia

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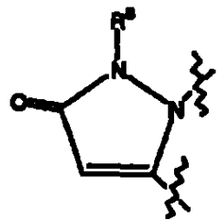
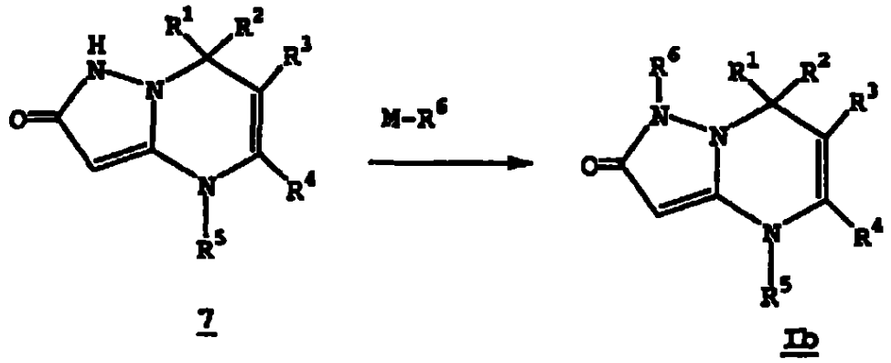
Los compuestos de fórmula I, donde X^1, X^2 y X^3 forman un anillo de la estructura

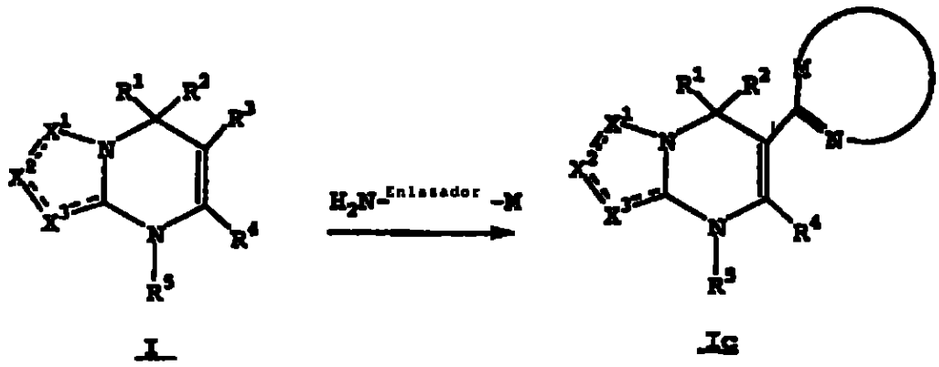


en donde R^6 es un substituyente preferentemente hidrógeno, puede ser formado al hacer reaccionar un compuesto de fórmula 7 con una especie reactiva $M-R^6$ de manera tal que se obtiene un compuesto de fórmula Ib, donde M es Cl, Br, OR, etc y R^6 es como se define anteriormente



7 Ib

Los compuestos de fórmula Ic donde R^3 es un amino, que contienen un heterociclo, pueden ser formados mediante la condensación de compuestos de fórmula I donde R^3 es un ácido o éster con una amina la cual está unida a través de un enlazador a M M puede ser NH_2, NHR, SH o OH La unidad enlazadora puede ser seleccionada de manera tal que se forman los heterociclos insubstituidos, substituidos o fusionados



I Ic

R^3= Ester o ácido

Los compuestos adicionales dentro del ámbito de la presente invención, pueden ser

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preparados a partir de los compuestos obtenidos por los métodos descritos anteriormente a través de la conversión de los grupos substituyentes a otra funcionalidad mediante los métodos usuales de síntesis química, como se ilustra en los siguientes ejemplos

Los compuestos de fórmula I que contienen centros quirales pueden ser obtenidos en formas no racémicas mediante la síntesis o resolución no racémica por métodos bien conocidos por aquellos expertos en la técnica Los compuestos que no son racémicos, son designados como "quirales" en los ejemplos

En los ejemplos descritos abajo, puede ser necesario proteger la funcionalidad reactiva tal como grupos hidroxi, amino, tio o carboxi, cuando estos se desean en el producto final, para evitar su participación indeseada en las reacciones La introducción y remoción de los grupos protectores son bien conocidas por aquellos expertos en la técnica, véase por ejemplo (Gree, T W en "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991)

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Utilidad

Los compuestos de la presente invención, son agentes antiarrítmicos los cuales son empleados en la prevención y tratamiento (incluyendo alivіación parcial o cura) de arritmias Los presentes compuestos son particularmente usados en la prevención y tratamiento de arritmias supraventriculares tales como fibrilación atrial, y palpito atrial Mediante "prevención selectiva y tratamiento de arritmias supraventriculares", se sugiere la prevención o tratamiento de arritmias supraventriculares, en donde la relación de la prolongación del periodo retractorio efectivo atrial hasta la prolongación del periodo refractorio efectivo ventricular es mayor que 1 1 Esta relación es preferiblemente mayor que 4 1, más preferiblemente mayor que 10 1, y más preferiblemente de manera tal que la prolongación del periodo de respuesta refractorio efectivo atrial se alcanza sin prolongación significantemente detectable del periodo refractorio efectivo ventricular

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Además, los compuestos dentro del ámbito de la presente invención bloquean el I_{Kur}, y así, pueden ser empleados en la prevención y tratamiento de todas las condiciones asociadas con I_{Kur} "Una condición asociada con I_{Kur}" es una alteración la cual se puede prevenir, parcialmente aliviar o curar mediante la administración de un bloqueador I_{Kur} El gen $K_v1.5$ se conoce por estar expresado en el tejido estomacal, tejido intestinal/colón, la arteria pulmonar, y las células beta pancreáticas Así, la administración de un bloqueador I_{Kur} podrá proporcionar tratamiento util para las alteraciones tales como esofagitis con reflujo, dispepsia funcional, constipación, asma y diabetes Adicionalmente, el $K_v1.5$ se conoce por estar expresado en la pituitaria anterior Además, la administracion de un bloqueador I_{Kur} podrá estimular la secreción de la hormona de crecimiento Los inhibidores de I_{Kur} pueden adicionalmente, ser empleados en las alteraciones proliferativas celulares tales como leucemia, y padecimientos autoinmunes tales como artritis rehumatoide y rechazo al transplante

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La presente invención además, proporciona métodos para la prevención o tratamiento de una o más alteraciones mencionadas anteriormente, que comprenden la etapa de administrar a un sujeto en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la fórmula I Otros agentes terapéuticos tal como aquellos descritos abajo, pueden ser empleados con los compuestos inventivos en los presentes métodos En los métodos de la presente invención, tales otros agente(s) terapéuticos pueden ser administrados antes de, simultáneamente con o después de la administración de los compuesto(s) de la presente invención

La presente invención también proporciona composiciones farmacéuticas que comprenden al menos, uno de los compuestos de la formula I o sales de los mismos, capaces de prevenir o tratar una o más de las alteraciones mencionadas anteriormente en una cantidad efectiva del mismo, y un vehiculo o diluyente farmacéuticamente aceptable Las composiciones de la presente invención pueden contener otros

agentes terapéuticos tal como se describe abajo, y pueden ser formuladas por ejemplo, mediante el empleo de vehículos o diluyentes sólidos o líquidos convencionales, así como también aditivos farmacéuticos de un tipo apropiado al modo de administración deseado (por ejemplo, excipientes, atadores, preservativos, estabilizadores, saborizantes, etc) de conformidad con las técnicas así como tambien aquellas conocidas en la técnica de formulación farmacéutica

Los compuestos de la fórmula I pueden ser administrados por cualquier medio adecuado, por ejemplo, oralmente, tal como en la forma de tabletas, cápsulas, gránulos o polvos, sublingualmente, bucalmente, parenteralmente, tal como por técnicas de infusión o inyección subcutánea, intravenosa, intramuscular o inyección intrasternal (por ejemplo, como soluciones o suspensiones acuosas o no acuosas estériles inyectables), nasalmente tal como por atomización para inhalación, tópicamente, tal como en la forma de crema o ungüento, o rectalmente tal como en la forma de

supositorios, en formulaciones de dosificaciones unitarias que contienen vehículos o diluyentes farmacéuticamente aceptables no tóxicos Los presentes compuestos pueden, por ejemplo, ser administrados en una forma adecuada para liberación inmediata o liberación prolongada La liberación inmediata o liberación prolongada puede ser alcanzada por el uso de composiciones farmaceuticas adecuadas que comprenden los presentes compuestos, o, particularmente en el caso de liberación prolongada, por el uso de dispositivos tal como implantes subcutáneos o bombas osmóticas En el caso en donde los compuestos de la formula I están siendo administrados para prevenir o tratar arritmias, los compuestos pueden ser administrados para alcanzar la conversión química a ritmo del seno normal, o pueden ser opcionalmente usados en conjunto con cardioconversión eléctrica

Las composiciones ejemplares para la administración oral incluyen suspensiones, las cuales pueden contener, por ejemplo, celulosa microcristalina para impartir volumen, ácido algínico o alginato de sodio como un agente de

suspensión, metilcelulosa como un incrementador de la viscosidad, y agentes endulzadores o saborizantes tal como aquellos conocidos en la técnica, y tabletas de liberación inmediata las cuales pueden contener, por ejemplo, celulosa microcristalina, fosfato dicálcico, almidón, estearato de magnesio y/o lactosa y/o otros excipientes, atadores, extendedores, desintegradores, diluyentes y lubricantes tal como aquellos conocidos en la técnica. Los compuestos de fórmula I pueden también ser liberados a través de la cavidad oral mediante la administración sublingual y/o bucal. Las tabletas moldeadas, tabletas comprimidas o tabletas secadas por congelamiento, son formas ejemplares las cuales pueden ser usadas. Las composiciones ejemplares incluyen aquellas que formulan el presente compuesto(s) con diluyentes de disolución rápida, tal como manitol, lactosa, sucrosa y/o ciclodextrinas. También incluidas en tales formulaciones pueden ser excipientes de peso molecular alto, tal como celulosas (avicel) o polietilenglicoles (PEG). Tales formulaciones pueden también incluir un excipiente para ayudar a la adhesión de la mucosa tal como

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hidroxipropilcelulosa (HPC), hidroxipropilmetilcelulosa (HPMC), carboximetilcelulosa de sodio (SCMC), copolímero de anhídrido maléico (por ejemplo, Gantrez), y agentes para el control de la liberación tal como un polimero poliacrílico (por ejemplo, Carbopol 934) Lubricantes, deslizantes, saborizantes, agentes colorantes y estabilizadores pueden también ser agregados para facilidad de fabricación y uso

Las composiciones ejemplares para la administración por inhalación o aerosol nasal, incluyen soluciones en salina, la cual puede contener por ejemplo, alcohol bencilico u otros preservativos adecuados, promotores de la absorción para incrementar la biodisponibilidad, y/o otros agentes de solubilización o dispersión tal como aquellos conocidos en la técnica

Las composiciones ejemplares para la administración parenteral incluyen soluciones o suspensiones inyectables las cuales pueden contener, por ejemplo, diluyentes o solventes parenteralmente aceptables, no tóxicos

adecuados, tal como manitol, 1,3-butandiol, agua, solución Ringer, una solución de cloruro de sodio isotónico, u otros agentes de suspensión y humectación o dispersión adecuados, incluyendo mono o diglicéridos sintéticos, y ácidos grasos, incluyendo ácido oléico

Las composiciones ejemplares para la administración rectal incluyen supositorios, los cuales pueden contener, por ejemplo, un excipiente no irritante adecuado, tal como manteca de cacao, ésteres glicéridos sintéticos o polietilenglicoles, los cuales son sólidos a temperaturas ordinarias, pero se licúan y/ disuelven en la cavidad rectal para liberar el fármaco

Las composiciones ejemplares para la administración tópica incluyen un portador tópico tal como Plastibase (aceite mineral gelificado con polietileno)

La cantidad efectiva de un compuesto de la presente invención puede ser determinada por un experto ordinario en la técnica, e incluye

cantidades de dosificaciones ejemplares para un humano adulto desde aproximadamente 0 001 hasta 100 mg/kg de peso corporal de un compuesto activo por día, el cual puede ser administrado en una dosis única o en la forma de dosis divididas, tal como de 1 a 4 veces por dia Se entenderá que el nivel de dosis especifica y la frecuencia de dosificación para cualquier sujeto particular puede variarse y dependerá de una variedad de factores que incluyen la actividad del compuesto específico empleado, la estabilidad metabólica y la longitud de acción de tal compuesto, las especies, edad, peso corporal, salud general, sexo y dieta de sujeto, el modo y tiempo de administración, relación de excreción, combinacion del fármaco y severidad de la condición particular Los sujetos preferidos para el tratamiento incluyen animales, más preferiblemente especies de mamíferos tal como humanos, y animales domésticos tal como perros, gatos y similares, sometidos a las alteraciones mencionadas anteriormente

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Los compuestos de la presente invención pueden ser empleados solos o en combinación con cada uno de los otros y/o otros agentes terapéuticos adecuados empleados en el tratamiento de las alteraciones mencionadas anteriormente, tales como otros agentes antirrítmicos, bloqueadores del canal de calcio, inhibidores de la ciclooxigenasa, inhibidores de agregación de plaquetas, antagonistas de fibrinógeno, diuréticos, inhibidores de enzima que convierte la angiotesina, antagonistas de la angiotesina II, agentes trombóticos, antagonista del receptor de tromboxano, memeticos de la prostaciclina, o imhibidores de la fosfodiesterasa Otros agentes ejemplares antirritmicos incluyen gentes Clase I (tal como propafenona y quinidina), agentes Clase II (tal como sotalol), y agentes Clase III (tal como dofetilido y amiodarona) Los bloqueadores del canal de calcio ejemplares, incluyen diltiazem, verapamil, nifedipina, y amlodipina Los inhibidores de la ciclooxigenasa ejemplares incluyen aspirina o indometacina Los inhibidores de la agregación de plaquetas ejemplares incluyen clopidogrel, ticlopideno o

aspirina Los diuréticos ejemplares incluyen clorotiazida, clorhidrotiazida, flumetiazida, hidroflumetiazida, bendroflumetiazida, metilcorotiazida, triclorometiazida, politiazida, benztiazida, tricrinafeno de ácido etacrínico, clortalidona, furosemida, musolimina, bumetanida, triametrereno, amilorido o espironolactona Los inhibiodres de enzima que convierten la angiotensina ejemplares incluyen captoprilo, zofenoprilo, fosinoprilo, enalaprilo, ceranoprilo, cilazoprilo, delaprilo, pentoprilo, quinaprilo, ramipirilo, lisinopirilo o sales de tales compuestos Los antagonistas de la angiotensina II ejemplares incluyen, losartan, irbesartan o valsartan Los agentes trombilíticos ejemplares incluyen al activador del plasminógeno del tejido (tPA), tPA recombinante, estreptocinasa, urocinasa, prourocinasa, complejo activador de la estreptocinasa del plasminógeno anisoilado (APSAC, Eminase, Beecham Laboratories) o activadores del plasminógeno de la glandula salival animal Los antagonistas del receptor tromboxano ejemplares incluyen ifetrobano

Los otros agentes terapéuticos anteriores, cuando se emplean en combinación con los compuestos de la presente invención, pueden ser usados, por ejemplo, en tales cantidades indicadas en la Physician's Desk Reference (PDR) o como de otro modo se determina por uno de los expertos ordinarios en la técnica

Los ensayos para determinar el grado de actividad de un compuesto como un inhibidor I_{Kur} son bien conocidos en la técnica y se describen en referencias tal como *J Gen Physiol* Apr, 101(4) 513-43, y *Br J Pharmacol* 1995 Mayo, 115(2) 267-74

Todos los documentos citados en la presente especificación, están incorporados aquí para referencia en su totalidad

Los siguientes ejemplos y preparaciones describen la manera y proceso de elaboración y uso de la invención, y son ilustrativos en lugar de limitativos Se entenderá que pueden ser otras modalidades las cuales caen dentro del espíritu y ámbito de la invención como se define

por las reivindicaciones adjuntas a estos Las abreviaciones empleadas aqui están definidas abajo

CDI= carbonildiimidazol

DCM= diclorometano

DMPA= dimetilaminopiridina

DMF= dimetilformamida

DMPU= 1,3-dimetil-3,4,5,6-tetrahidro-2(1*H*)-pirimidinona

EDCI (o EDC) = clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida

M + H = masa monoisotópica más un protón

Et = etilo

h = horas

HPLC = cromatografia liquida de alta resolucion

HOBT = hidroxibenzotriazol

LC/MS = cromatografia líquida/espectrometría de masas

Me = metilo

min = minutos

MS = espectrometria de masas

NaOAc = acetato de sodio

Ph = fenilo

PPA = ácido polifosfórico

Pr = propilo

Py = piridina

PyBrOP= hexafluorofosfato de bromo-tris-pirrolidino-fosfonio

TA = temperatura ambiente

Rt = tiempo de retención

TEA = trietilamina

TFA = ácido trifluoroacético

TLC = cromatografia de capa delgada

THF = tetrahidrofurano

TMSOTf = trifluorometanosulfonato de trimetilsililo

Ejemplo 1

Ester metílico del ácido 7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico

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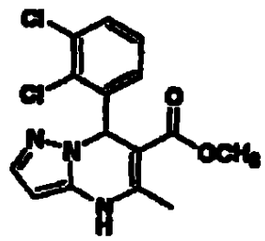
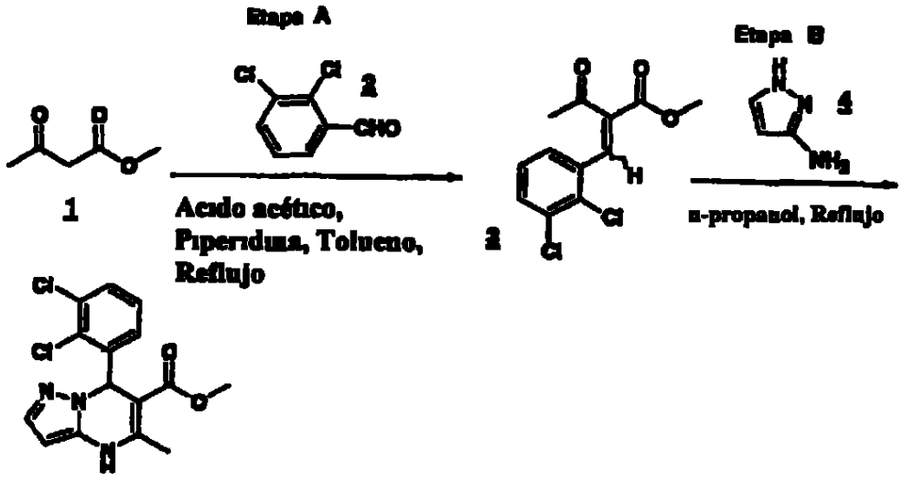


Método



Etapa A Una mezcla de acetoacetato de metilo 1 (5 mL, 46 mmol), 2,3-diclorobenzaldehido 2 (8 1 g, 46 mmol), piperidina (1 1 ml, 12 mmol), y ácido acético (0 6 mL, 11 mmol) en tolueno (200 mL) se sometió

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a reflujo durante la noche con remoción azeotrópica del agua vía una Trampa Dean-Stark La mezcla se enfrió a temperatura ambiente, se enfrió rápidamente con agua, se transfirió a un embudo separador, se diluyó con acetato de etilo, se lavó con NaOH (1M), acuoso, HCl(1M) acuoso, agua y salmuera y se concentró in vacuo El residuo se purificó por cromatografia instantánea (gel de sílice, acetato de etilo/hexanos al 33%) para proporcionar 10 8 g (85% de rendimiento) del compuesto **3** como una mezcla de diasterómeros Columna Balística LC/MS de Fase Inversa YMC S5 ODS 4 6 x 50 mm, detección UV a 220λ, gradiente 4 minutos ($MeOH/H_2O$ al 10% con TFA al 0 1% - $MeOH/H_2O$ al 90% con TFA al 0 1%), 4 mL/min Diastereomero A, Rt= 3 51 min, (53%) Diastereómero B, Rt= 3 70 min (45%) MS (M+H 273)

Etapa B Una mezcla del compuesto **3** (5g, 18 3 mmol), 3-aminopirazol **4** (1 5 g, 18 3 mol) en 1-propanol (60 mL) se sometió a reflujo por 6 horas La mezcla se enfrió a temperatura ambiente se concentró y recristalizó de acetato de etilo/hexanos para dar 1 25 g (20%) del

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compuesto del título como un sólido amarillo El licor madre se concentró y purificó por cromatografía instantánea (gel de sílice, metanol/diclorometano al 5%) para dar una adicional de 1 62 g (26%) del compuesto del título Rendimiento combinado 2 87 g (46%) Columna Balística LC/MS de Fase Inversa YMC S5 ODS 4 6 x 50 mm, detección UV a 220λ, gradiente 4 minutos ($MeOH/H_2O$ al 10% con TFA al 0 1% - $MeOH/H_2O$ al 90% con TFA al 0 1%), 4 mL/min Rt= 3 38 min, (96% puro) MS (M+H 338) HMR ($CDCl_3$, 400 MHz), 7 98 (1H, app s), 7 15 (3H, m), 6 91 (1H, s), 5 52 (1H, app s), 3 61 (3H, s), 2 39 (3H, s)

Ejemplos 2 y 3

Los compuestos de los Ejemplos 2 y 3, mostrados en la tabla proporcionada abajo, se prepararon de una manera similar a aquella descrita en el Ejemplo 1

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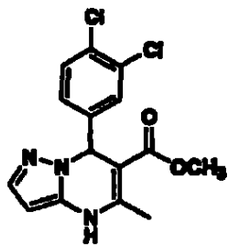
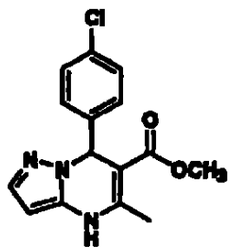
Ejemplo	Estructura	Nombre	(M+H)
2		Éster metílico del ácido 7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico	338
3		Éster metílico del ácido 7-(4-clorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico	303

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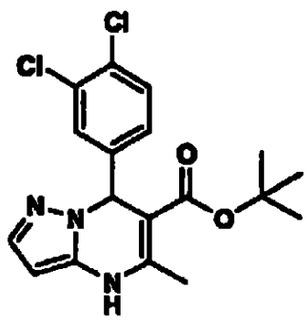
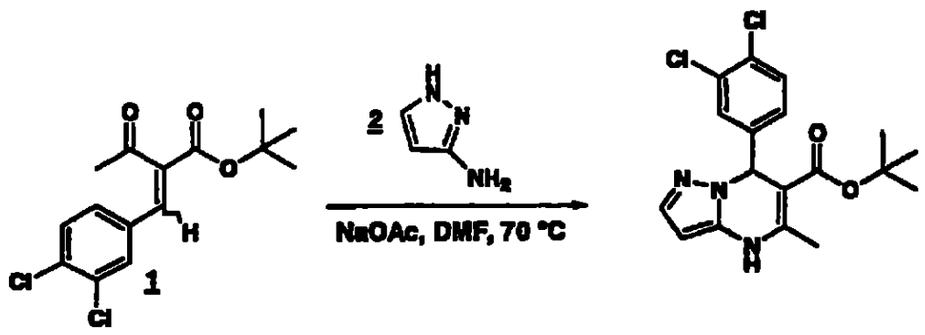
Ejemplo 4

Ester 1,1-dimetiletílico del ácido 7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico



Método 1



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Compuesto 1 El compuesto 1 se preparó por la condensación de t-butoxiacetoacetato y 2,4-diclorobenzaldehido como se describe en el Ejemplo 1 etapa A

Compuesto del Titulo Una mezcla del compuesto 1 (44 4 g, 141 mg, 141 mmol), 3-aminopirazol 2 (17 6 g 212 mmol) y acetato de sodio (46 3 g, 564 mmol) en dimetilformamida (300 mL) se agitó a 70°C durante la noche (17 h) La mezcla se enfrió a temperatura ambiente, se transfirió a un embudo separador, se diluyó con agua y acetato de etilo, se lavó con agua (una pequeña cantidad de metanol se agregó para la dispersión de las emulsiones que se formaron) y salmuera, se secó sobre sulfato de sodio anhidro y se concentró Se formó un precipitado Lo precipitado se colectó y se lavó con acetato de etilo, éter etílico y hexanos y se secaron para dar 8 93 g El licor madre se concentró para dar una segunda cosecha del precipitado 9 32 g El análisis LC/MS indicó que los precipitados no fueron puros Lo precipitado se combinó, se disolvió en diclorometano y se concentró en suficiente gel de sílice, de manera que se

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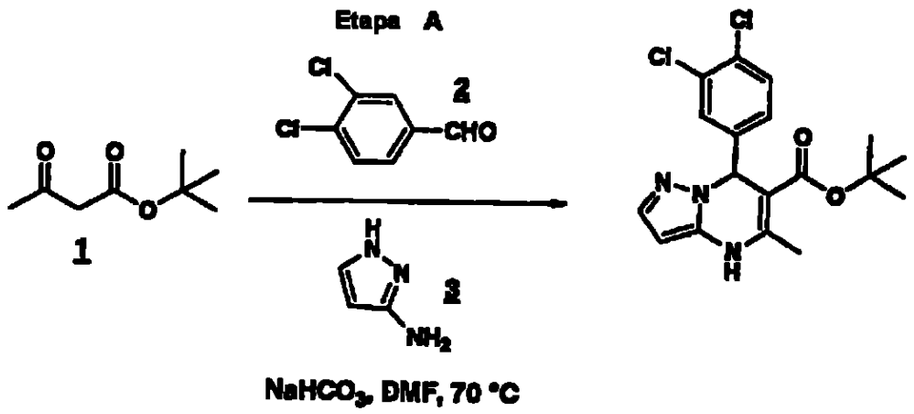
obtuvo un polvo de fluencia suave El polvo resultante se cargó en una columna de cromatografía preempacada con gel de sílice y diclorometano La elución con diclorometano al 100% seguida por metanol/diclorometano al 3% dio 15 1 g (29% rendimiento) del compuesto del título La Columna Balística LC/MS de Fase Inversa YMC S5 ODS 4 6 x 50 mm, detección UV a 220λ, gradiente 4 minutos (MeOH/H_2O al 10% con TFA al 0 1% - MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt= 4 63 min, (97% puro) MS (M+H 380 HNM ($CDCl_3$, 400 MHz), 7 41 (2H, m), 7 33 (1H, d, J=2 Hz), 7 08 (1H, m), 6 21 (1H, s), 5 68 (1H, d, J=2 Hz), 2 43 (3H, s), 1 37 (9H, s)

Método 2



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Una mezcla de t-butoxiacetoacetato 1 (22 6 g, 143 mmol), 3,4-diclorobenzaldehido 2 (25 0 g, 143 mmol), 3-aminopirazol 3 (15 4 g, 185 mmol) y bicarbonato de sodio (36 g, 428 mmol) en dimetilformamida (250 mL) se agitó a 70°C durante la noche (18 h) La mezcla se enfrió a temperatura ambiente, se enfrió rápidamente con acetato de etilo y agua, se transfirió a un embudo separador, se lavó con agua y salmuera, se secó sobre sulfato de sodio, se filtró y se concentró El residuo se recristalizó de acetato de etilo/hexanos para dar 16 8 g (31% rendimiento) del compuesto del titulo como un sólido blanco

Los datos para el compuesto del titulo se dan en el método 1

Ejemplos 5 y 6

Los compuestos de los Ejemplos 5 y 6 mostrados en la tabla proporcionada abajo, se prepararon de una manera similar a aquella

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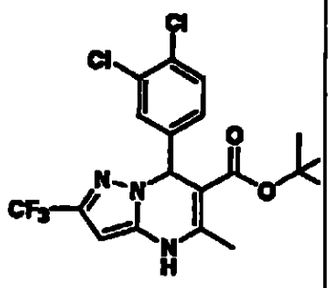
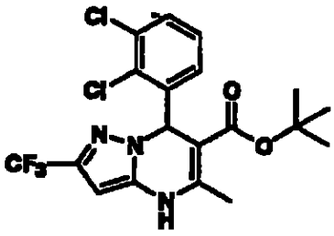
descrita en el Ejemplo 4, Método 1

Ejemplo	Estructura	Nombre	(M+H)
5		Éster 1,1-dimetiletílico del ácido 7-(3,4-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil) pirazolo[1,5-a]pirimidin-6-carboxílico	448
6		Ester 1,1-dimetiletílico del ácido 7-(2,3-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil) pirazolo[1,5-a]pirimidin-6-carboxílico	448

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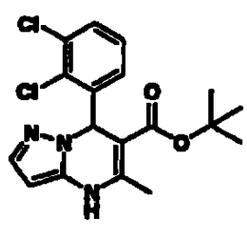
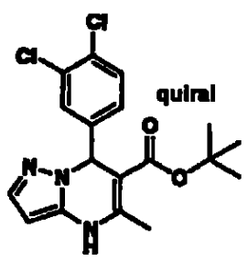
Ejemplos 7-11

Los compuestos de los Ejemplos 7-11, mostrados en la tabla proporcionada abajo, se prepararon en una manera similar a aquella descrita en el Ejemplo 4, Método 2 El compuesto del Ejemplo 4, Método 2 podría resolverse en los correspondiente enantiómeros **A** (Ejemplo 8) y **B** (Ejemplo 9) por HPLC quiral preparativa (Columna Chiracel OD (50 x 500 mm), eluyendo con 7% de isopropanol/hexanos que contienen 0 1% de trietilamina amina a 50 mL/min), detección UV a 254 λ, HPLC analitico (Columna Chiracel OD (4 6 x 250 mm), eluyendo con 10% de isopropanol/hexanos que contienen 0 1% de trietilamina amina a 1 mL/min), detección UV a 254 λ, enantiómero **A** (Rt= 6 98 min, 98% ee), enantiómero **B** (Rt= 9 22 min, 98% ee)

Ejemplo	Estructura	Nombre	(M+H)
7		Ester 1,1-dimetiletílico del ácido 7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico	380
8		Enantiómero A del Ester 1,1-dimetiletílico del ácido 7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico	380

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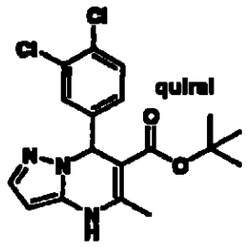
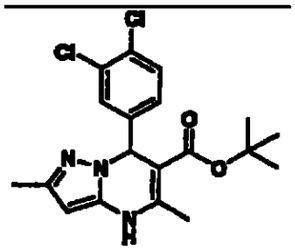
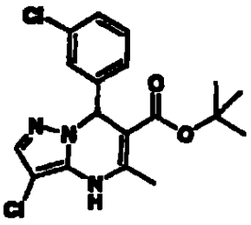
9		Enantiómeor B del Ester 1,1-dimetiletílico del ácido 7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico	380
10		Ester 1,1-dimetiletílico del ácido 7-(3,4-diclorofenil)-4,7-dihidro-2,5-dimetilpirazolo[1,5-a]pirimidin-6-carboxílico	394

11		Ester 1,1-dimetiletílico del ácido 3-cloro-7-(3-clorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico	380

Ejemplo 12

Ester 1,1-dimetiletílico del ácido 7-(2,3-diclorofenil)-4,7-dihidro-4,5-dimetilpirazolo[1,5-a]pirimidin-6-carboxílico

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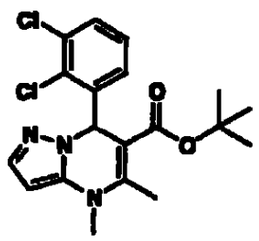
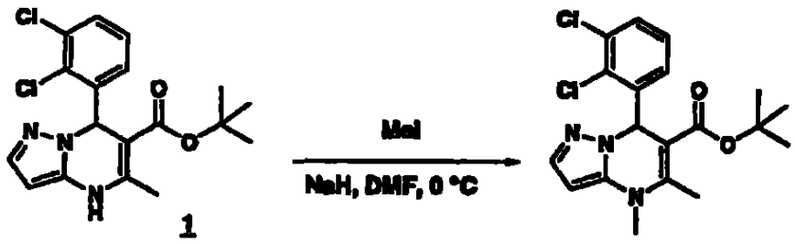


Método



1

Compuesto 1 El compuesto 1 se preparó como se describe en el Ejemplo 4, método 1

Compuesto del titulo Se agregó hidruro de sodio (0 186 g, 7 76 mmol) a una solución a 0°C de 1 (2 27 g, 5 97 mmol) en dimetilformamida (30 mL) Después de 10 minutos, se agregó yoduro de metilo (0 41 mL, 6 57 mmol) Después de un adicional de 85 minutos, la mezcla se enfrió

rápidamente con una solución de cloruro de amonio saturado, se diluyó con acetato de metilo, se transfirió a un embudo separador, se lavó con cloruro de amonio saturado, agua y salmuera, se secó sobre sulfato de sodio anhidro y se concentró con suficiente gel de sílice de manera que se obtuvo un polvo de fluencia suave El polvo resultante se cargó en una columna de cromatografía empacada con diclorometano al 100% La elución con acetato de etilo/diclorometano 0-10% dio 1 16 g (49%) del compuesto del titulo como un sólido ligeramente amarillo Columna Balística LC/MS de Fase Inversa YMC S5 ODS 4 6 x 50 mm, detección UV a 220λ, gradiente 4 minutos, Solvente B/A gradiente 40-100% (Solvente A MeOH/H_2O al 10% con TFA, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt= 3 46 min, (96% puro) MS (M+H 394) HMR (CD_3Cl, 400 MHz) 7 39 (1H, d, J=2 Hz), 7 35 (1H, m), 7 11 (1H, m), 6 91 (1H, s), 5 58 (1H, d, J=2 Hz), 2 38 (3H, s), 2 62 (3H, s), 1 27 (9H, s)

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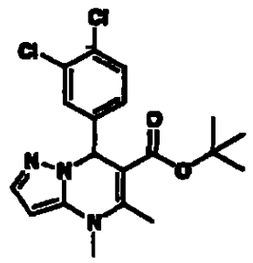
Ejemplo 13

Ester 1,1-dimetiletílico del ácido 7-(3,4-diclorofenil)-4,7-dihidro-4,5-dimetilpirazolo[1,5-a]pirimidin-6-carboxílico



El compuesto del titulo se preparó de una manera similar a aquella proporcionada en el Ejemplo 12, proporcionando un compuesto con (M+H) 394

Ejemplo 14

Ester 1,1-dimetiletílico del ácido 4,7-dihidro-5-metil-7-(1-metiletil)pirazolo[1,5-a]pirimidin-6-carboxílico

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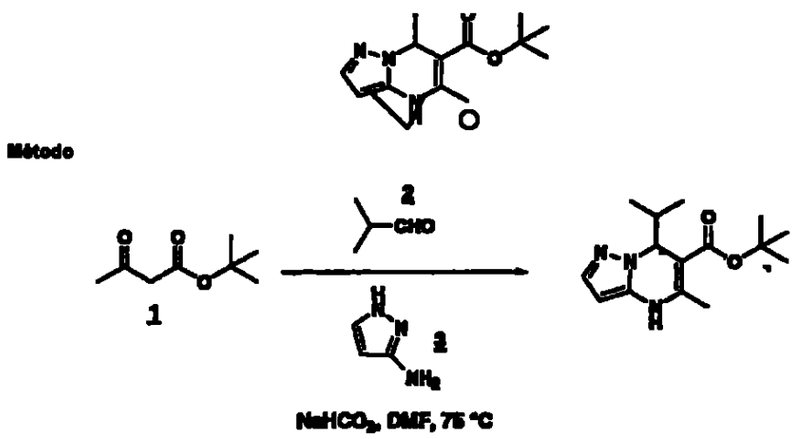

Tubo sellado

Un tubo de presión se secó con un disparo de calor bajo nitrógeno El tubo de presion se cargo en el siguiente orden con isobutiraldehido **2** (0 262 g, 3 63 mmol), dimetilformamida (3 mL), t-butoacetoacetato **1** (0 574 g, 3 63 mmol), 3-aminopirazol **3** (0 362 g, 4 36 mmol) y acetato de sodio (1 22 g, 14 5 mmol) La mezcla se chorreó con nitrógeno El tubo se selló y calentó a 75°C y se agitó durante la noche La mezcla se enfrió a temperatura ambiente, se diluyó con acetato de etilo a un volumen de 20 mL, se lavó con cloruro de litio (2 4 M, 10 mL) y salmuera, se secó

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sobre sulfato de sodio anhidro, se filtró y concentró para dar 1 02 de un aceite amarillo El aceite se purificó por cromatografía instantánea (sílice, acetato de etilo/heptano al 45%) para dar 0 42 g (41% rendimiento) del compuesto del titulo Columna Balística LC/MS de Fase Inversa YMC S5 ODS 4 6 x 50 mm, detección UV a 220λ, gradiente 4 minutos Solvente B/A 0-100% (Solvente A MeOH/H_2O al 10% con PPA al 0 2%, Solvente B MeOH/H_2O al 90% con PPA al 0 2%), 4 mL/min Rt= 3 83 min, (100% puro) Columna Balística LC/MS de Fase Inversa YMC S5 ODS 4 6 x 50 mm, detección UV a 220λ, gradiente 4 minutos, Solvente B/A 0-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt= 3 06 min MS (EM, M+1 278) HMR ($CDCl_3$, 400 MHz) 7 37 (1H, d, J=2 2 Hz), 6 35 (1H, s), 5 55 (1H, d, J=1 8Hz), 5 29 (1H, d, J=2 2 Hz), 2 41 (3H, s), 1 50 (9H, s), 1 28-1 19 (1H, m), 1 07 (3H, d, J=7 0Hz), 0 60 (3H, d, J=7 0 Hz)

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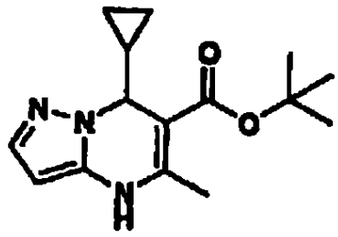
902

Ejemplo 15

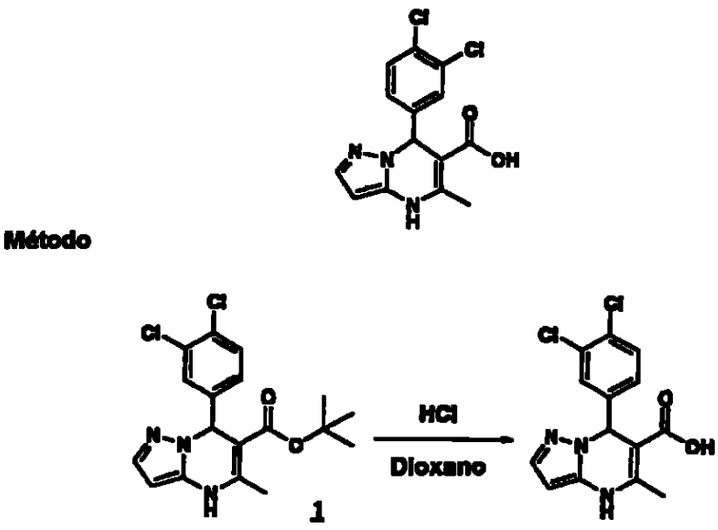
Ester 1,1-dimetiletilico del ácido 7-ciclopropil-4,7-dihidro-5-metilpirazolo-[1,5-a]pirimidin-6-carboxílico



El compuesto del titulo se preparó de una manera similar como aquella proporcionada en el Ejemplo 14, proporcionando un compuesto con (M+H) 275

Ejemplo 16

Acido 7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxilico



Compuesto 1 El compuesto 1 se preparo como se describe en el Ejemplo 4

Compuesto del Titulo Se agregó HCl (4M en dioxano) al compuesto sólido 1 (1 13 g, 2 97 mmol) a temperatura ambiente Se disuelven los sólidos y se forman precipitados La mezcla de reacción espesa resultante se dejó agitar durante la noche y se concentró in vacuo para dar 1 14 g (contiene dioxano al 120%) del compuesto del titulo como un sólido blanco Columna Balistica LC/MS de Fase Inversa YMC S5

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~~904~~

ODS 4 6 x 50 mm, detección UV a 220λ, gradiente 4 minutos, Solvente B/A (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt= 3 54 min, (93% puro) MS (M+H 324) HMR (CD_3OD, 400 MHz), 7 96 (1H, d, J=3Hz), 7 51 (2H, m), 7 21 (1H, m), 6 49(1H, s), 6 11 (1H, d, J=3Hz), 2 51 (3H, s) El compuesto del titulo se usó en las reacciones subsecuentes sin purificación adicional

Ejemplo 17

Acido 7-(3,4-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-carboxílico

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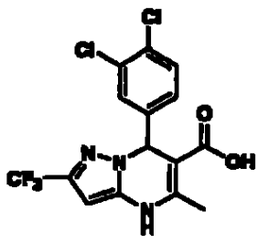
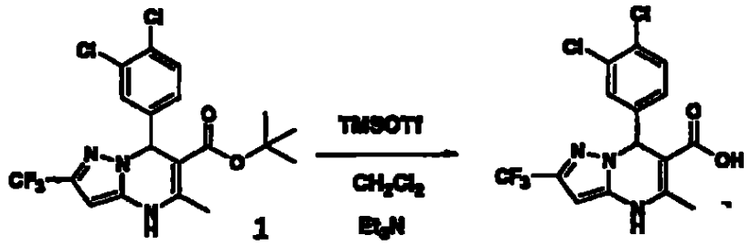
405



Método



1

Compuesto 1 Compuesto 1 (el compuesto del Ejemplo 5) se preparó de una manera similar a aquella que se describe en el Ejemplo 4

Compuesto del Titulo Se agregó trifluorometanosulfonato de trimetilsililo (0 873 mL, 4 82 mmol) a una solución a temperatura ambiente del compuesto 1 (1 08 g, 2 41 mmol) en diclorometano (50 mL) Después de

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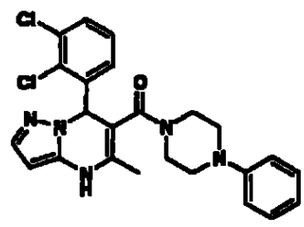
906

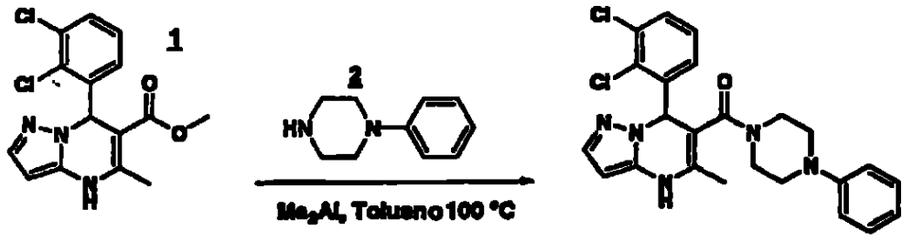
2 horas, se agregó trietilamina (0 672 ml, 4 82 mmol), y la mezcla de reacción se vertió en agua La capa orgánica se separó y se secó sobre Na_2SO_4, se concentró, y purificó por cromatografía instantánea (acetato de etilo/hexano al 50% → acetato de etilo 100%) para dar 0 71 g (75% rendimiento) del compuesto del titulo como un sólido blanco MS (M+H 392)

Ejemplo 18

1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina



Método 1



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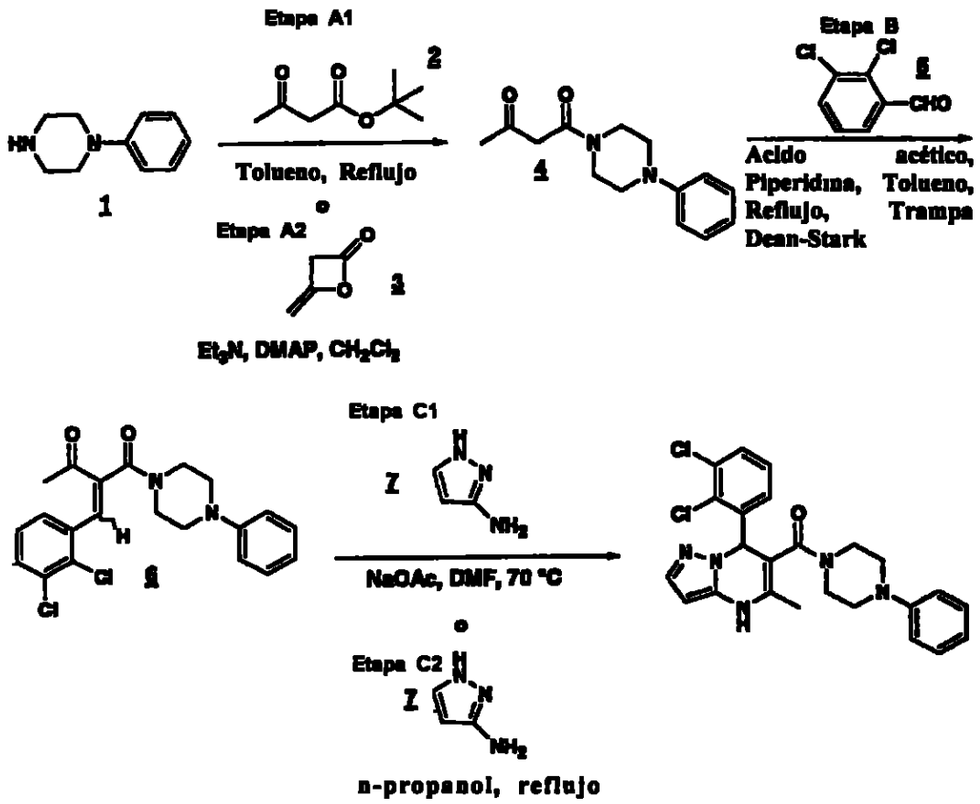
Compuesto 1 El compuesto 1 se preparó como se describe en el Ejemplo 1

Compuesto del Titulo Se agregó trimetilaluminio (1 1 mL, 2 2 mmol, 2M en tolueno) en forma de gotas a una solución a temperatura ambiente de 1-fenilpiperazina 2 (0 4 mL, 2 2 mmol) en tolueno (7 mL) Después de una hora, el compuesto 1 (0 50 g, 1 5 mmol) se agregó y la mezcla resultante se agitó a 100°C por 18 horas La mezcla se enfrió a temperatura ambiente, se enfrió rápidamente con agua, se diluyó con acetato de etilo, se transfirió a un embudo separador, se lavó con HCl acuoso (1M), agua y salmuera, se secó sobre sulfato de sodio anhidro y se concentró in vacuo El residuo se purificó por cromatografia instantánea (gel de sílice, acetato de etilo/hexanos al 50%, seguido por metanol/diclorometano al 5% para proporcionar 0 22 g (32%) de un solido, el cual se purificó además por recristalización de metanol/éter etílico para dar 0 15 g (22%) del compuesto del titulo Columna Balística LC/MS de Fase Inversa YMC S5 ODS 4 6 x 50 mm, detección UV a 220λ, gradiente 4 minutos, Solvente B/A 0-100%

(Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/mın Rt= 3 58 mın, (92% puro) MS (M+H 468) Los datos adıcıonales para el compuesto del tıtulo se reportan en el Método 2, etapa C, varıacıón 1

Método 2



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Etapa A Variación 1 Una mezcla de N-fenilpiperazina 1 (6 7 mL, 41 mmol) y t-butoxiacetoacetato 2 (6 8 mL, 45 mmol) en tolueno (50 mL) se sometió a reflujo durante la noche La mezcla se enfrió a temperatura ambiente, se transfirió a un embudo separador, se diluyó con acetato de etilo y se extrajo (3X) con HCl (1M) acuoso Los extractos HCl se combinaron y se lavaron con éter etílico (2X), se hicieron básicos (pH 9) con NaOH acuoso (p/p al 50%) y se extrajeron con acetato de etilo Los extractos de acetato de etilo se combinaron, se lavaron con agua y salmuera, se secaron sobre sulfato de sodio anhidro, se filtraron y concentraron para dar 9 76 g (97 6%) del compuesto 4 como un aceite ámbar espeso Columna Balística LC/MS de Fase Inversa YMC S5 ODS 4 6 x 50 mm, detección UV a 220λ, gradiente 4 minutos, Solvente B/A 0-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt= 1 65 min, (100% puro) MS (M+H 247) HMR ($CDCl_3$, 400 MHz), 7 28 (2H, m), 6 91 (3H, m), 3 80 (2H, m), 3 78 (2H, m), 3 59 (4H, m), 3 19 (4H, m), 2 30 (3H, s)

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Etapa A Variación 2 Se agregó lentamente Diceteno 3 (5 50 g, 65 5 mmol) durante 15 minutos, a una solución a 0°C de 4-fenilpiperazina 1 (5 31, 32 7 mmol) en diclorometano (50 mL) El TLC después de 4 horas, indicó que el compuesto 1 no se consumió completamente Se agregó diceteno adicional (5 50 g, 65 5 mmol) Después de unas 1 5 horas adicionales, la reaccion se enfrió rápidamente con NaOH 1N, se transfirió a un embudo separador, lavado con NaOH 1H y salmuera, se secó sobre sulfato de sodio, se concentró en suficiente gel de sílice de manera tal que se obtuvo un polvo de flujo suave El polvo resultante se cargo en una columna de cromatografia preempacada con gel de sílice y acetato de etilo/hexanos al 50% La elución con acetato de etilo/hexanos al 50-100% dio 8 2 g (100%) de un compuesto 4 como un aceite amarillo espeso Los datos para el compuesto 4 se dio anteriormente en la Etapa A variación 1

Etapa B Una mezcla del compuesto **4** (9 76 g, 40 mmol), 2,3-diclorobenzaldehído **6** (7 89 g, 45 mmol), piperidina (1 0 ml, 10 mmol), ácido acético (0 59 mL, 10 mmol) en tolueno (100 mL) se sometió a reflujo durante la noche con remoción azeotrópica de agua vía una trampa Dean-Stark La mezcla se enfrió a temperatura ambiente y se concentró in vacuo y se usó típicamente en las reacciones subsecuente sin purificación El compuesto **6** puede ser Purificado por cromatografía en gel de sílice (acetato de etilo/hexanos al 30-40%) Columna Balística LC/MS de Fase Inversa YMC S5 ODS 4 6 x 50 mm, detección UV a 220λ, gradiente 4 minutos, Solvente B/A 0-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt= 3 83 min, (96% puro) MS (M+H 404) HMR ($CDCl_3$ 400 MHz), 7 82 (1H, s), 7 55 (1H, dd, J=1, 8 Hz), 7 48 (1H, dd, J=1, 8 Hz), 7 23 (3H, m), 6 89 (1H, app T, 7 Hz), 6 81 (2H, d, J=8 Hz), 3 78 (2H, m), 3 34 (1H, m), 3 23 (2H, m), 2 96 (1H, m), 2 85 (1H, m), 2 50 (3H, s), 2 42 (1H, M)

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Etapa C Variación 1 Una mezcla del compuesto **6** (16 g, 40 mmol), 3-aminopirazol **7** (5 1 g, 62 mmol) y acetato de sodio (10 1 g, 123 mmol) en dimetilformamida (100 mL) se agitó a 70°C durante la noche (17 h) La mezcla se enfrió a temperatura ambiente, se transfirió a un embudo separador, se diluyó con agua y acetato de etilo, se lavó con agua (una pequeña cantidad de metanol se agregó para dispersar las emulsiones que se formaron), y salmuera, se secó sobre sulfato de sodio anhidro y se concentró El residuo resultante se purificó por cromatografía en gel de sílice La elución con acetato de etilo/hexanos al 50%, seguida por acetato de etilo al 100%, proporcionó 6 2 g (33% rendimiento del compuesto **1**) del compuesto del titulo El compuesto del titulo podrá resolverse en los enantiómeros correspondientes **A** (Ejemplo 28) y **B** (Ejemplo 29) por HPLC quiral preparativo (Columna Chiracel OD (50 X 500 mm), eluyendo con isopropanol/hexanos al 30%, conteniendo 0 1% de trietilamina a 50 mL/min), detección UV a 254 λ, enantiómero **A** Rt= 42 min, enantiómero **B** Rt= 54 min HPLC analítico (Columna Chiracel OD (4 6 x 250 mm), eluyendo con isopropanol/hexanos al 30%

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93

contiene 0 1% de trietilamina a 1 mL/ min), detección UV a 254 λ, enantiómero **A** Rt= 11 7 min, enantiómero **B** Rt= 17 6 min Los datos dados para el enantiómero **A** Columna Balística LC/MS de Fase Inversa YMC S5 ODS 4 6 x 50 mm, detección UV a 220λ, gradiente 4 minutos, Solvente B/A 0-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt= 3 54 min, (91% puro) MS (M+H 468) HMR (Sal de HCl de 8a, $CDCl_3$ 400 MHz), 7 94 (1H, d, J=3 Hz), 7 56 (8H, m), 7 38 (1H, m), 6 05 (1H, d, J= 3Hz), 4 23 (1H, m), 3 57 (7H, m), 2 01 (3H, s)

Etapa C Variación 2 Una mezcla del compuesto 5 (6 0g, 15 mmol), 3-aminopirazol 7 (1 24 g, 15 mmol) en n-propanol (50 mL), se sometió a reflujo durante la noche (19 h) La mezcla se enfrió a temperatura ambiente, se transfirió a un embudo separador, se diluyó con acetato de etilo Un intenso por lavar la solución con cloruro de amonio saturado, resultó en la formación de un precipitado Lo precipitado se disolvió con agua y metanol

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La mezcla resultante se lavó con agua y salmuera, se secó sobre sulfato de sodio anhidro y se concentró El residuo resultante se purificó por cromatografía en gel de sílice La elución con acetato de etilo/hexanos al 70% seguido por acetato de etilo al 100%, proporcionó 2 7 g (39% rendimiento) del compuesto del titulo como un sólido blanco El compuesto podrá resolverse en los enantiómeros **A** y **B** correspondientes como se describen en la Etapa C variación 1

Ejemplos 19-27

Los compuestos de los Ejemplos 19-27, mostrados en la tabla proporcionada abajo, se prepararon de una manera similar a aquella descrita en el Ejemplo 18, Método 1

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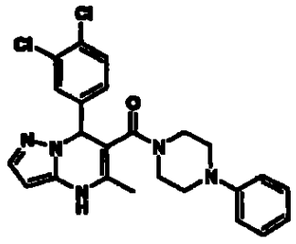
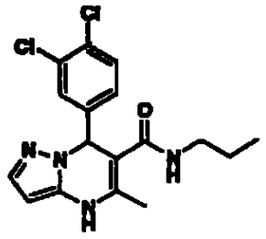
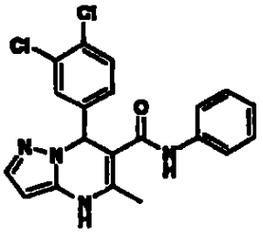
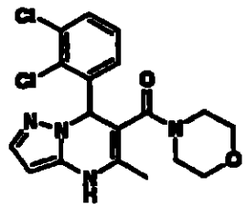
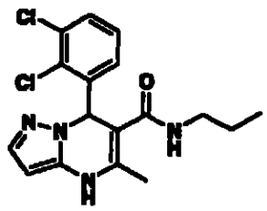
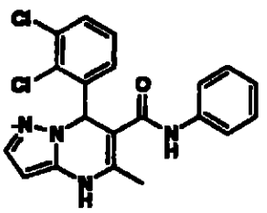
915

Ejemplo	Estructura	Nombre	(M+H)
19		1[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina	468
20		7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-N-propilpirazolo[1,5-a]pirimidin-6-carboxamida	365
21		7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-N-fenil-pirazolo[1,5-a] piramidin-6-carboxamida	399

940
G-16

22		4-[[7-(2,3-Diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]morfolina	393
23		7-(2,3-Diclorofenil)-4,7-dihidro-5-metil-N-propilpirazolo[1,5-a] pirimidin-6-carboxamida	365
24		7-(2,3-Diclorofenil)-4,7-dihidro-5-metil-N-fenilpirazolo[1,5-a]pirimidin-6-carboxamida	399

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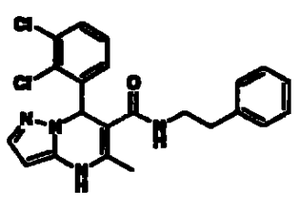
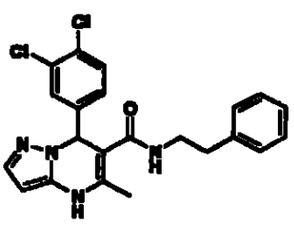
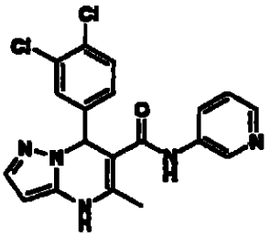
947

25		7-(2,3-Diclorofenil)-4,7-dihidro-5-metil-N-(2-feniletil)pirazolo[1,5-a]pirimidin-6-carboxamida	427
26		7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-N-(2-feniletil) pirazolo[1,5-a]pirimidin-6-carboxamida	427
27		7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-N-3-piridinilpirazolo[1,5-a]pirimidin-6-carboxamida	400

942
948

Ejemplos 28-82

Los compuestos de los Ejemplos 28-82, mostrados en la tabla proporcionada abajo, se prepararon de una manera similar a aquella descrita en el Ejemplo 18, Método 2

La resolución por HPLC del Ejemplo 47, columna Chiracel OD (50 x 500 mm), eluyendo con isopropanol/hexanos al 30% conteniendo trietilamina al 0 1% a 50 mL/min), detección UV a 254λ, proporcionó enantiómeros **A** (Ejemplo 50) y **B** (Ejemplo 51) La columna Chiracel OD (4 6 x 250 mm), eluyendo con isopropanol/hexanos al 30% conteniendo trietilamina al 0 1% a 1 mL/min), detección UV a 254λ, proporcionó enantiómeros **A** Rt= 9 8 min, > 99% ee >99% ee Enantiómero **B** Rt = 14 2 min, >99% ee

La resolución por HPLC del Ejemplo 70, columna Chiralpak AD (50 x 500 mm), eluyendo con etanol/hexanos al 15% conteniendo trietilamina al 0 1% 50 mL/min), detección UV a 254λ, proporcionó enantiómeros **A** (Ejemplo 72) y **B** (Ejemplo 71) Columna Chiralpak AD (4 6 x 250 mm) eluyendo con etanol/hexanos al 15% conteniendo trietilamina al

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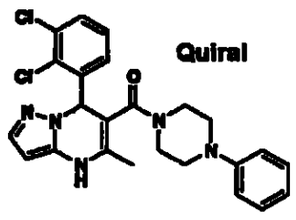
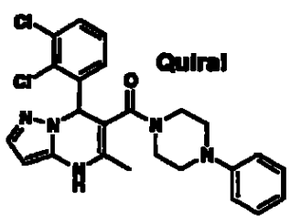
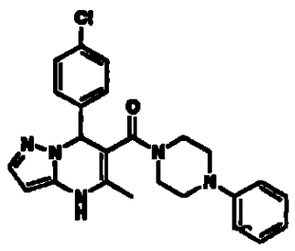
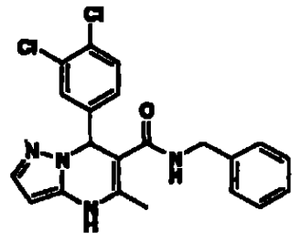
949

0 1% a 1 mL/mın), detección UV a 254λ, enantıómero **A** Rt= 6 9 mın, >99% ee Enantıómero **B** Rt = 13 4 mın, >99% ee

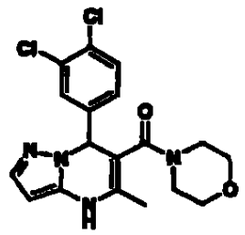
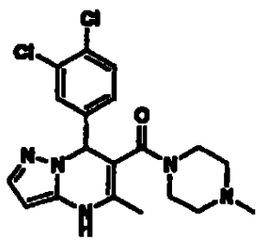
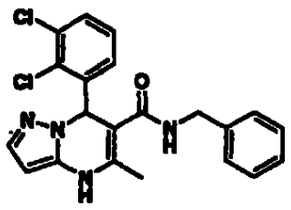
La resolución por HPLC del Ejemplo 80, columna Chıralpak AD (50 x 500 nm), eluyendo con ısopropanol/hexanos al 25% contenıendo trıetılamına al 0 1% a 50 ml/mın), detección UV a 254λ, proporcıonó los enantıómeros **A** (Ejemplo 81) y **B** (Ejemplo 82) Columna Chıralpak AD (4 6 x 250 mm) eluyendo con ısopropanol/hexanos al 30% contenıendo trıetılamına al 0 1% a 1 mL/mın), detección UV a 254λ, enantıómero **A** Rt= 5 3 mın, >99% ee Enantıómero **B** Rt= 7 1 mın, 99% ee

Ejemplo	Estructura	Nombre	(M+H)
28		Enantıomero A 1-[[7-(2,3-Dıclorofenıl)-4,7-dıhıdro-5-metıl-pırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]-4-fenıl-pıperazina	468

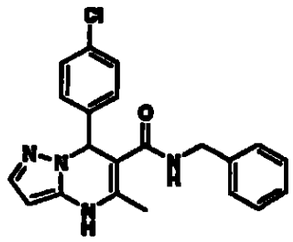
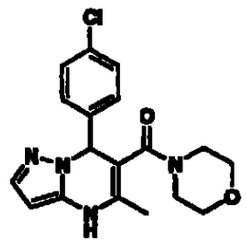
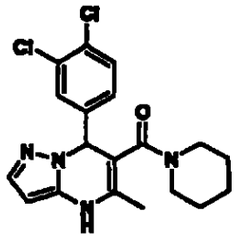
944
940

29		Enantiomero B 1-[[7-(2,3-Diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenil-piperazina	468
30		1-[[7-(4-Clorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina	433
31		1-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-N-(fenilmetil)pirazolo[1,5-a]pirimidin-6-carboxamida	413

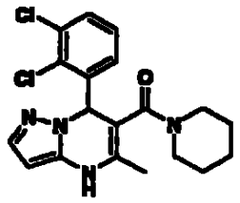
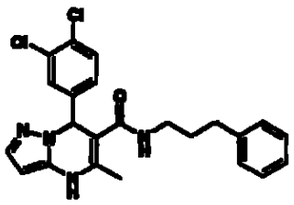
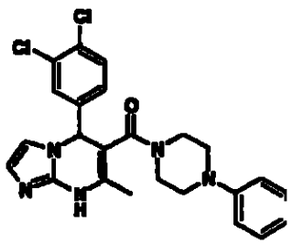
945
9-24

32		4-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]morfolina	393
33		1-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-metil-piperazina	406
34		7-(2,3-Diclorofenil)-4,7-dihidro-5-metil-N-(fenilmetil)pirazolo[1,5-a]pirimidin-6-carboxamida	413

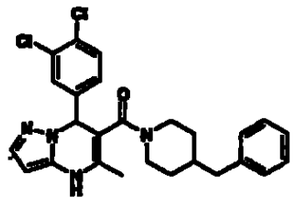
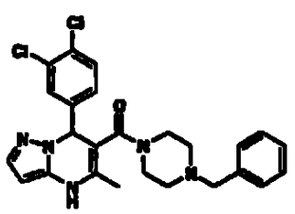
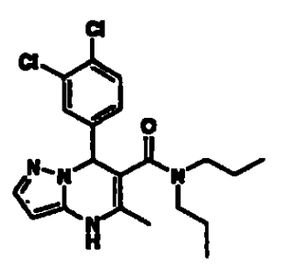
946
922

35		7-(4-Clorofenil)-4,7-dihidro-5-metil-N-(fenilmetil) pirazolo[1,5-a] pirimidin-6-carboxamida	378
36		4-[[7-(4-Clorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]morfolina	358
37		1-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]piramidin-6-il] carbonil] piperidina	391

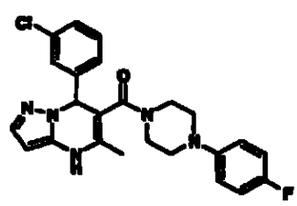
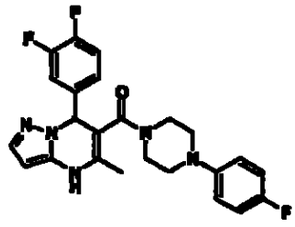
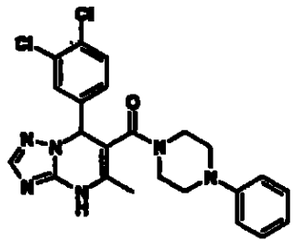
947
923

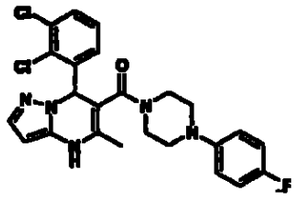
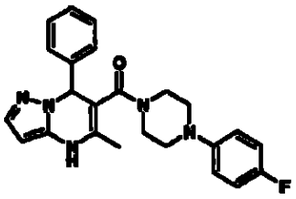
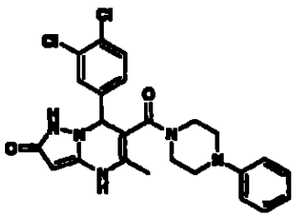
38		1-[[7-(2,3-Diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il] carbonil] piperidina	391
39		7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-N-(3-fenilpropil) pirazolo[1,5-a]pirimidin-6-carboxamida	441
40		1-[[5-(3,4-Diclorofenil)-5,8-dihidro-7-metil-imidazol[1,2-a] pirimidin-6-il] carbonil]-4-fenilpiperazina	468

948
924

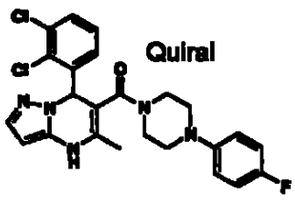
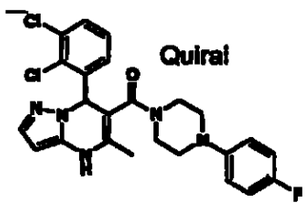
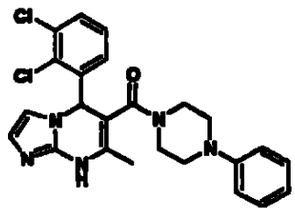
41		1-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(fenil-metil)piperidina	481
42		1-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(fenil-metil)piperazina	482
43		7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-N,N-dipropilpirazolo[1,5-a]pirimidin-6-carboxamida	407

949
925

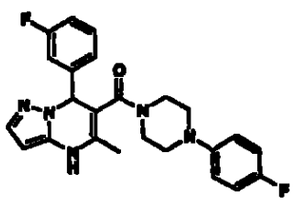
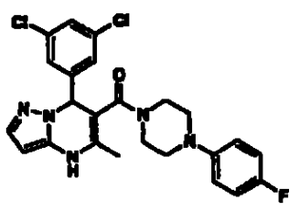
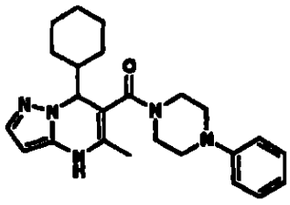
44		1-[[7-(3-Clorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	451
45		1-[[7-(3,4-Difluorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	453
46		1-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metil [1,2,4]triazolo[1,5-a] pirimidin-6-il]carbonil]-4-fenilpiperazina	469

47		1-[[7-(2,3-Diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	486
48		1-(4-Fluorofenil)-4-[(4,7-dihidro-5-metil-7-fenil pirazolo[1,5-a]pirimidin-6-il) carbonil]-piperazina	417
49		1-[[7-(3,4-Diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a] pirimidin-6-il]carbonil]-4-fenilpiperazina	484

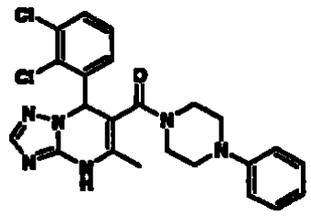
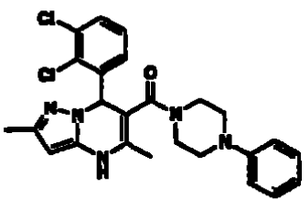
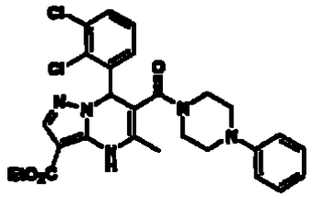
951
927

50		Enantıomero A 1-[[7-(2,3-Dıclorofenıl)-4,7-dıhıdro-5-metıl-pırazolo[1,5-a] pırımıdın-6-ıl] carbonıl]-4-(4-fluorofenıl) pıperazına	486
51		Enantiomero B 1-[[7-(2,3-Dıclorofenıl)-4,7-dıhıdro-5-metıl-pırazolo[1,5-a] pırımıdın-6-ıl] carbonıl]-4-(4-fluoro fenıl)pıperazına	486
52		1-[[5-(2,3-Dıclorofenıl)-5,8-dıhıdro-7-metıl-ımıdazo[1,2-a] pırımıdın-6-ıl] carbonıl]-4-fenıl-pıperazına	468

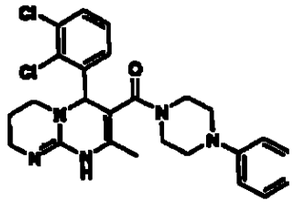
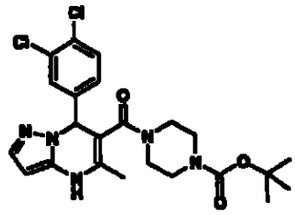
952
928

53		1-(4-Fluorofenil)-4-[[7-(3-fluorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a] pirimidin-6-il] carbonil]-piperazina	435
54		1-[[7-(3,5-Diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(4-fluoro fenil)piperizina	486
55		1-[(7-Ciclohexil-4,7-dihidro-5-metilpirazolo[1,5-a] pirimidin-6-il)carbonil]-4-fenilpiperazina	405

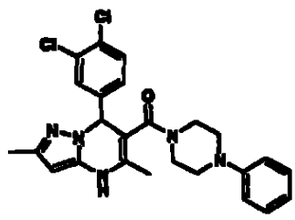
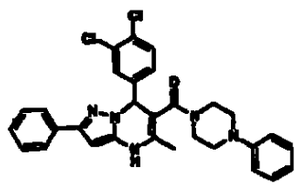
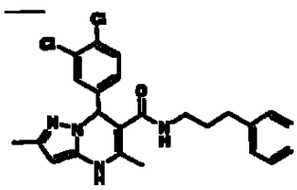
953
959

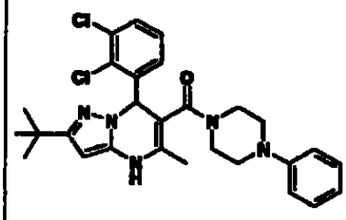
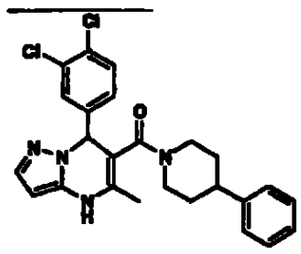
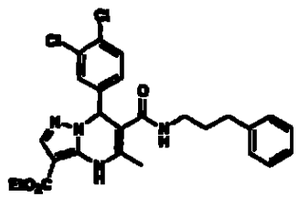
56		1-[[7-(2,3-Diclorofenil)-4,7-dihidro-5-metil-[1,2,4]triazolo[1,5-a]pirimidin-6-il)carbonil]-4-fenil-piperazina	469
57		1-[[7-(2,3-Diclorofenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-4-fenil-piperazina	482
58		Ester etílico del ácido 7-(2,3-Diclorofenil)-4,7-dihidro-5-metil-6-[(4-fenil-1-piperazinil)-carbonil]pirazolo [1,5-a]pirimidin-3-carboxílico	540

954
950

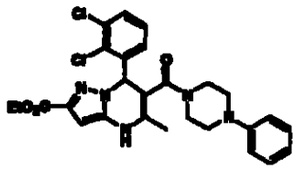
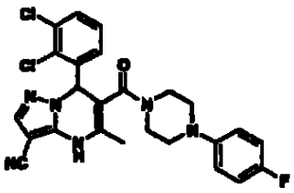
59		1-[[4-(2,3-Diclorofenil)-4,6,7,8-tetrahidro-2-metil-1H-pirimido[1,2-a]pirimidin-3-il]carbonil]-4-fenil-piperazina	484
60		Ester 1,1-dimetil etílico del ácido 4-[[7-(3,4-Dicloro-fenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-1-piperazin-carboxílico	492

937
955

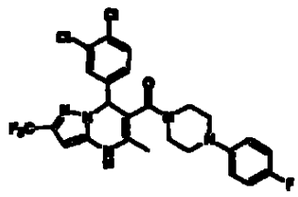
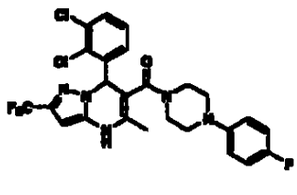
61		1-[[7-(3,4-Diclorofenil)-4,7-dihidro-2,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina	482
62		1-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-2-fenilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina	544
63		7-(3,4-Diclorofenil)-4,7-dihidro-2,5-dimetil-N-(3-fenil-propil)pirazolo[1,5-a]pirimidin-6-carboxamida	455

64		1-[[7-(2,3-Diclorofenil)-2-(1,1-dimetiletil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina	524
65		1-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-4-fenil-piperidina	467
66		Ester etílico del ácido 7-(3,4-Dicloro fenil)-4,7-dihidro-5-metil-6-[[(3-fenil propil)amino]carbonil]pirazolo[1,5-a]pirimidin-3-carboxílico	513

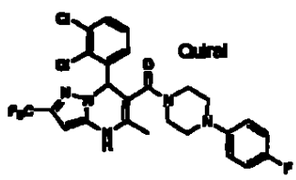
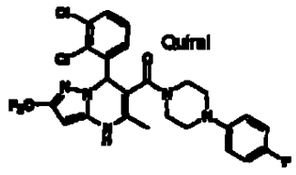
957
933

67		Ester etílico del ácido 7-(2,3-Dicloro fenil)-4,7-dihidro-5-metil-6-[(4-fenil-1-piperazinil)-carbonil]-pirazolo[1,5-a]pirimidin-2-carboxílico	540
68		1-[[3-Ciano-7-(2,3-diclorofenil)-4,7-dihidro-5-metil pirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	511

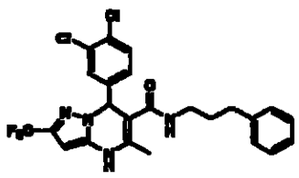
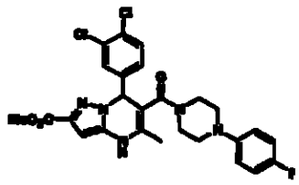
958
9734

69		1-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil) pirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(4-fluoro fenil)piperazina	554
70		1-[[7-(2,3-Diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil) pirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(4-fluoro fenil)piperazina	554

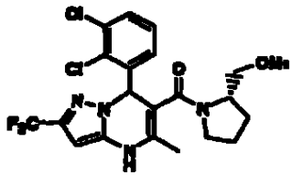
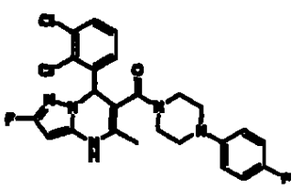
959 935

71		Enantiomero B de 1-[[7-(2,3-Diclorofenil)-4,7-dihidro-5-metil-2-(trifluoro metil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluoro fenil)piperazina	554
72		Enantiomero B de 1-[[7-(2,3-Dicloro fenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(4-fluoro fenil) piperazina	554

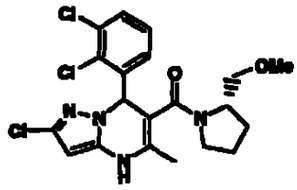
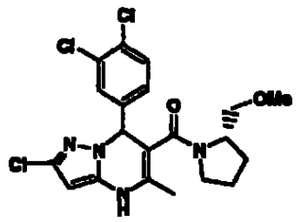
960
936

73		7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-N-(3-fenilpropil)-2-(trifluorometil) pirazolo[1,5-a] pirimidin-6-carboxamida	509
74		Ester metílico del ácido 7-(3,4-dicloro fenil)-6-[[4-(4-fluorofenil)-1-piperazinil] carbonil]-4,7-dihidro-5-metil pirazolo[1,5-a] pirimidin-2-carboxílico	544

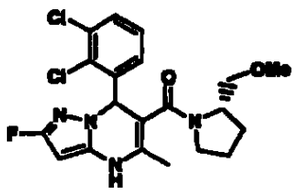
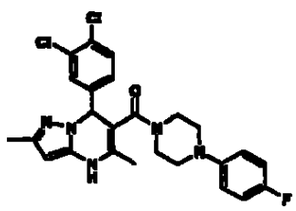
937
961

75		(2S)-1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil) pirrolidina	489
76		1-[[7-(2,3-diclorofenil)-2-fluoro-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	504

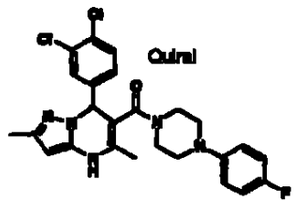
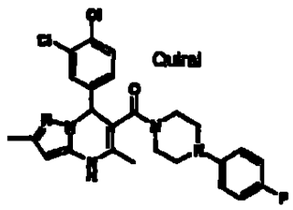
938
962

77		(2S)-1-[[2-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-2-(metoxi metil)pirrolidina	455
78		(2S)-1-[[2-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-2-(metoxi metil)pirrolidina	455

935
963

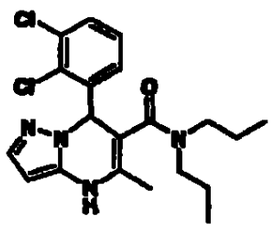
79		(2S)-1-[[7-(2,3-diclorofenil)-2-fluoro-4,7-dihidro-5-metil-pirazolo [1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil) pirrolidina	439
80		1-[[7(-(3,4-diclorofenil)-4,7-dihidro-2,5-dimetil pirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	500

940
964

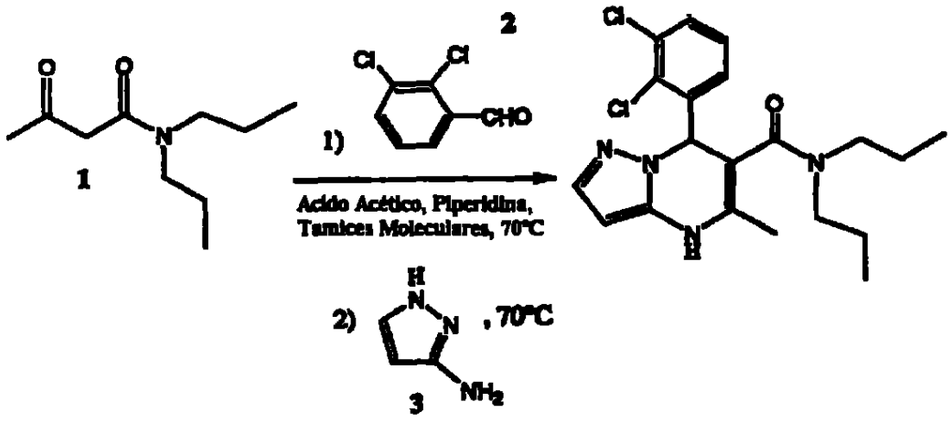
81		Enantiómero A de 1-[[7-(3,4-dicloro fenil)-4,7-dihidro-2,5-dimetilpirazolo [1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	500
82		Enantiómero de 1-[[7-(3,4-dicloro fenil)-4,7-dihidro-2,5-dimetilpirazolo [1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	500

Ejemplo 83

7-(2,3-diclorofenil)-4,7-dihidro-5-metil-N,N-dipropilpirazolo[1,5-a]pirimidin-6-carboxamida



Método



Compuesto 1 El compuesto 1 se preparó como se describe en el Ejemplo 18, Método 2 Etapa A1, a partir de t-butoxiacetoacetato y dipropilamina

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Compuesto del Titulo Una mezcla del compuesto 1 (0 2 g, 1 1 mmol), 2,3-diclorobenzaldehido 2 (0 23 g, 1 3 mmol), piperidina (0 015 ml, 0 27 mmol), ácido acético (0 027 mL, 0 27 mmol) y Tamices Moleculares 4A (punta de espátula) en dimetilformamida (1 mL) se agitó a 70°C durante la noche La mezcla se enfrió a temperatura ambiente Se agregaron 3-aminopirazol 3 (0 13 g, 1 6 mmol) y acetato de sodio (0 28 g, 3 5 mmol), y la mezcla se agitó durante la noche a 70°C La mezcla se enfrió a temperatura ambiente, se transfirió a un embudo separador, se diluyó con agua y acetato de etilo, se lavó con agua (una pequeña cantidad de metanol se agregó para dispersar las emulsiones que se formaron), se secó sobre sulfato de sodio anhidro y se concentró El residuo resultante se purificó por cromatografia en gel de silice (acetato de etilo/hexanos al 50% seguido por acetato de etilo al 100%) para proporcionar 0 10 g (23% rendimiento del compuesto 1) del compuesto del titulo Columna Balistica LC/MS de Fase Inversa YMC S5 ODS 4 6 x 50 mm, detección UV a 220λ, gradiente 4 minutos, Solvente B/A 0-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt= 2 94 min, (96% puro) MS

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(M+H 407)

Ejemplos 84-169

Los compuestos de los Ejemplos 84-169, mostrados en la tabla proporcionada abajo, se prepararon de una manera similar a aquella descrita en el Ejemplo 83

La resolución por HPLC del Ejemplo 84, columna Chiralpak AS (50 x 500 mm), eluyendo con isopropanol/hexanos al 30% conteniendo trietilamina al 0 1% a 50 mL/min), detección UV a 254λ, proporcionó enantiómeros **A** (Ejemplo 166) y **B** (Ejemplo 167) Columna Chiralpak AS (4 6 x 250 mm) eluyendo con isopropanol/hexanos al 40% conteniendo trietilamina al 0 1% a 1 mL/min), detección UV a 254λ, enantiómero **B** Rt= 5 53 min, >99% ee Enantiómero **B** Rt= 12 0 min, 98% ee

Resolución por HPLC del Ejemplo 165, columna Chiralpak AD (50 x 500 mm), eluyendo con isopropanol/hexanos al 20% conteniendo trietilamina al 0 1% a 50 mL/min), deteccion UV a 254λ

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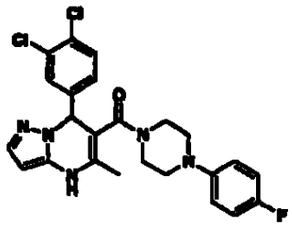
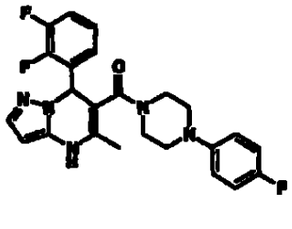
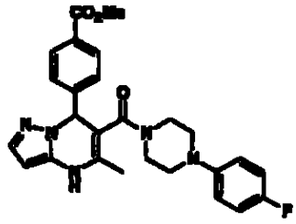
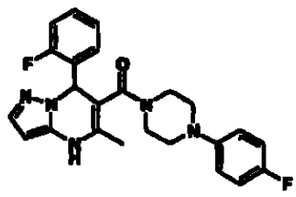
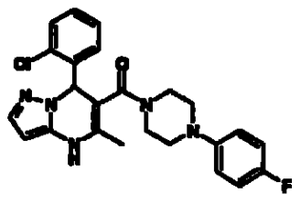
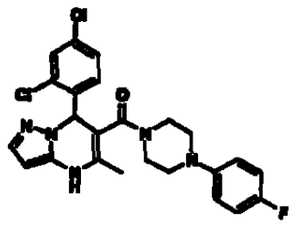
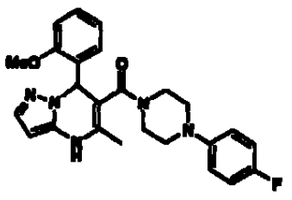
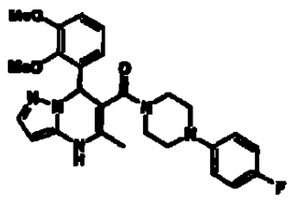
proporcionó enantiómeros **A** (Ejemplo 169) y **B** (Ejemplo 168) Columna Chiralpak AD (4 6 X 250 mm) eluyendo con isopropanol/hexanos al 20% conteniendo trietilamina al 0 1% a 1 mL/min), deteccion UV a 254λ, enantiómero **A** Rt= 8 3 min, >99% ee Enantiómero **B** Rt= 12 8 min, 98% ee

Ejemplo	Estructura	Nombre	(M+H)
84		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	486
85		1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metil pirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	453

969
945

86		Ester metílico del ácido 4-[6-[[4-(4-fluorofenil)-1-pipe-razinil]carbonil]-4,7-dihidro-5-metilpirazolo[1,5-a] pirimidin-7-il] benzoico	475
87		1-(4-fluorofenil)-4-[[7-(2-fluorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a] pirimidin-6-il] carbonil]-piperazina	435
88		1-[[7-(2-cloro fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	451

970
946

89		1-[[7-(2,4-dicloro fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	486
90		1-[[4,7-dihidro-7-(2-metoxifenil)-5-metilpirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	447
91		1-[[7-(2,3-dimetoxi fenil)-4,7-dihidro-5-metil-pirazolo [1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	477

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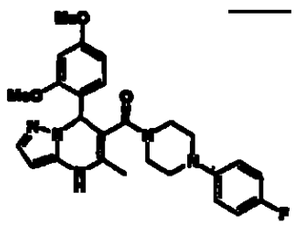
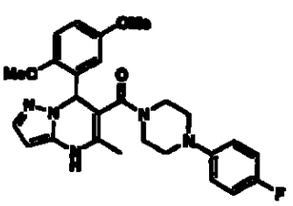
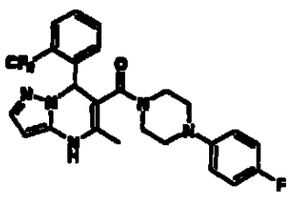
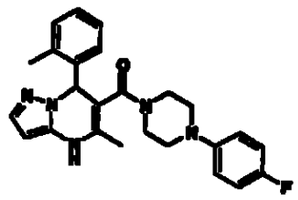
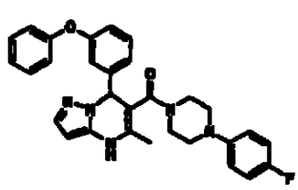
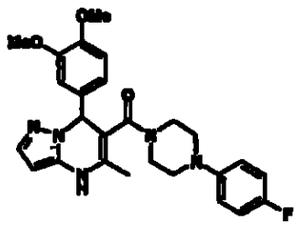
92		1-[[7-(2,4-dimetoxi fenil)-4,7-dihidro-5-metil-pirazolo [1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	477
93		1-[[7-(2,5-dimetoxi fenil)-4,7-dihidro-5-metil-pirazolo [1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	477
94		1-[[4,7-dihidro-5-metil-7-[2-(tri fluorometil)fenil] pirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	485

95		1-[[4,7-dihidro-5-metil-7-(2-metil fenil)pirazolo [1,5-a]pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	431
96		1-[[4,7-dihidro-5-metil-7-(3-fenoxifenil) pirazolo[1,5-a]pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	509
97		1-[[7-(3,4-dimetoxifenil)-4,7-dihidro-5-metil-pirazolo [1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	477

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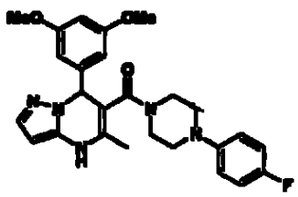
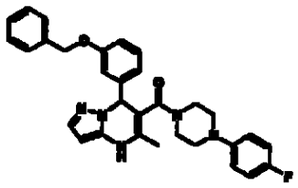
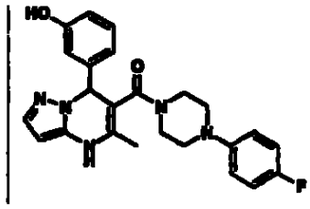
98		1-[[7-(3,5-dımetoxı fenıl)-4,7-dıhıdro-5-metıl-pırazolo [1,5-a]pirimidin-6-ıl]carbonıl]-4-(4-fluorofenıl) pıperazına	477
99		1-[[4,7-dıhıdro-5-metıl-7-[3-(fenılme toxı) fenıl]pırazolo [1,5-a]pırımıdın-6-ıl]carbonıl]-4-(4-fluorofenıl) pıperazına	523
100		1-[[4,7-dıhıdro-7-(3-hıdroxıfenıl)-5-metılpırazolo[1,5-a] pırımıdın-6-ıl] carbonıl]-4-(4-fluorofenıl) pıperazına	433

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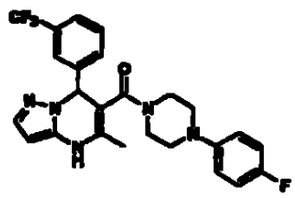
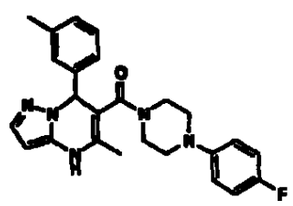
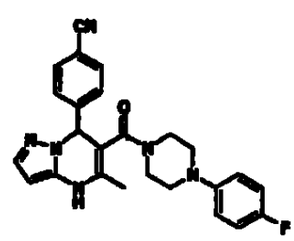
101		1-[[4,7-dihidro-5-metil-7-[3-(trifluorometil)fenil]pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina	485
102		1-[[4,7-dihidro-5-metil-7-(3-metilfenil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina	431
103		1-[[7-(4-ciano fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina	442

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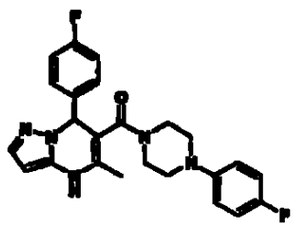
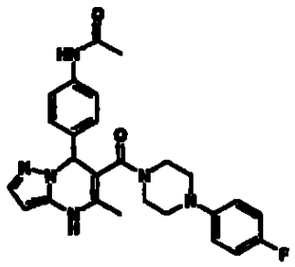
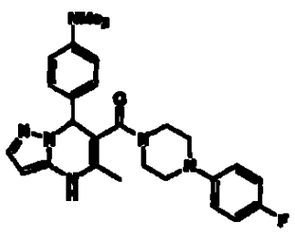
104		1-(4-fluorofenil)-4-[[7-(4-fluorofenil)-4,7-dihidro-5-metil pirazolo[1,5-a] pirimidin-6-il] carbonil]piperazina	435
105		N-[4-[6-[[4-(4-(fluorofenil)-1-piperazinil]carbonil]-4,7-dihidro-5-metilpirazolo[1,5-a] pirimidin-7-il] fenil]acetamida	474
106		1-[[7-[4-(dimetil amino)fenil]-4,7-dihidro-5-metil pirazolo [1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	460

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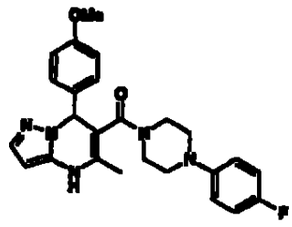
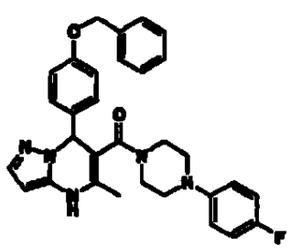
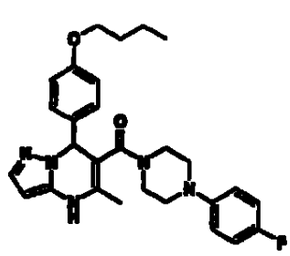
107		1-[[4,7-dihidro-7-(4-metoxifenil)-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	447
108		1-[[4,7-dihidro-5-metil-7-[4-(fenilmetoxi)fenil]pirazolo [1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	523
109		1-[[7-(4-butoxi fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	489

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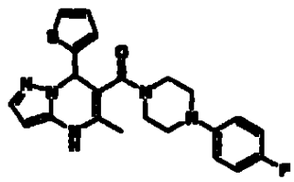
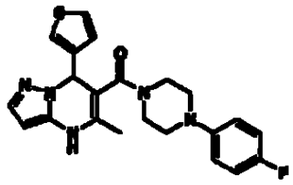
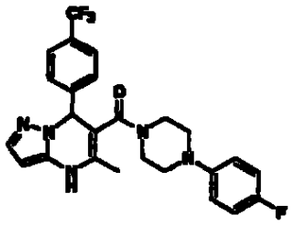
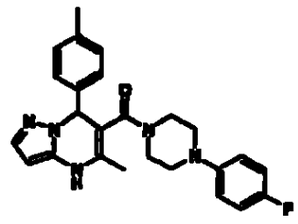
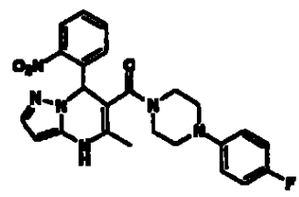
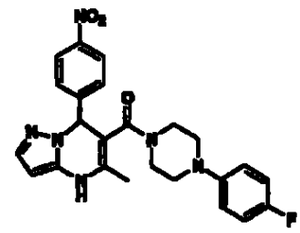
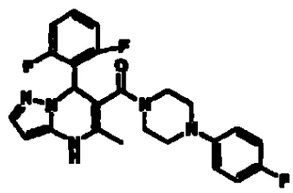
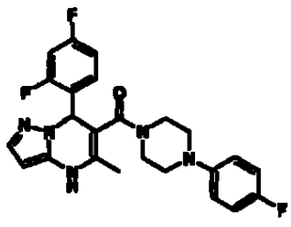
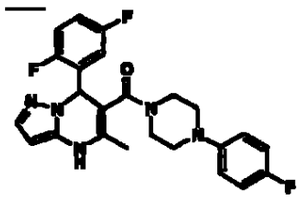
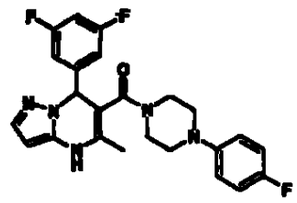
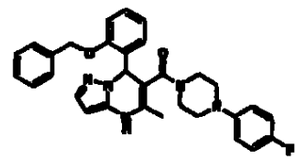
110		1-[[4,7-dihidro-5-metil-7-(2-tienil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina	423
111		1-[[4,7-dihidro-5-metil-7-(3-tienil)pirazolo[1,5-a]pirimidin-6-il)carbonil]-4-(4-fluorofenil)piperazina	423
112		1-[[4,7-dihidro-5-metil-7-[4-(trifluorometil)pirazol[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina	485

113		1-[[4,7-dihidro-5-metil-7-(4-metilfenil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	431
114		1-[[4,7-dihidro-5-metil-7-(2-nitrofenil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	462
115		1-[[4,7-dihidro-5-metil-7-(4-nitro-fenil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	462

116		1-[[7-(2,6-difluoro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	453
117		1-[[7-(2,4-difluorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	453

118		1-[[7-(2,5-difluoro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	453
119		1-[[7-(3,5-difluoro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	453
120		1-[[4,7-dihidro-5-metil-7-[2-(fenilmetoxi)fenil]-pirazolo[1,5-a]piri-midin-6-il]carbo-nil]-4-(4-fluoro-fenil)piperazina	523

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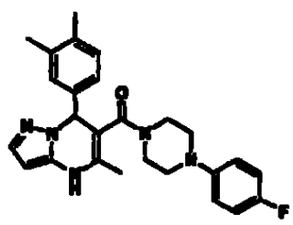
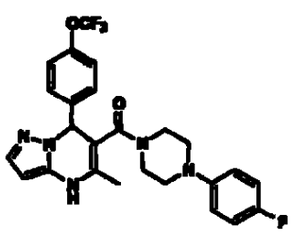
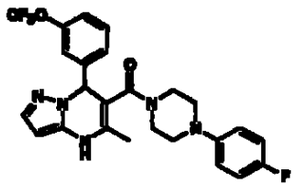
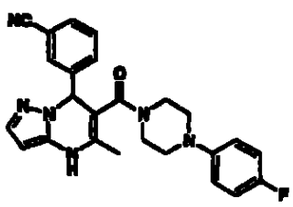
121		1-[[7-(3,4-dimetil-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	445
122		1-[[4,7-dihidro-5-metil-7-[4-(trifluoro-metoxi)-fenil]pirazolo [1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	501

123		1-[[4,7-dihidro-5-metil-7-[3-(trifluoro-metoxi)-fenil]pirazolo [1,5-a] pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	501
124		1-[[7-(3-ciano-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	442

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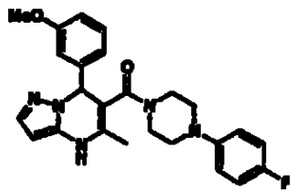
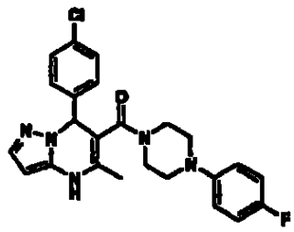
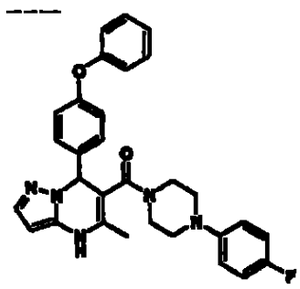
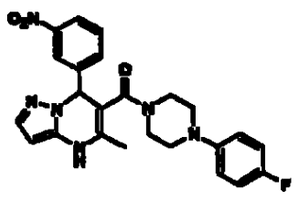
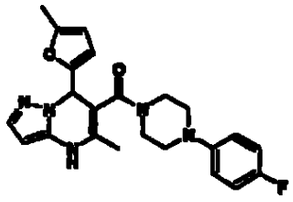
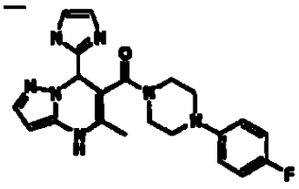
125		1-[[4,7-dihidro-7-(3-metoxifenil)-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	447
126		1-[[7-(4-cloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	451
127		1-[[4,7-dihidro-5-metil-7-(4-fenoxifenil) pirazolo[1,5-a]pirimi-din-6-il]carbonil]-4-(4-fluoro-fenil)piperazina	509

128		1-[[4,7-dihidro-5-metil-7-(3-nitrofenil)pirazolo [1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	462
129		1-[[4,7-dihidro-5-metil-7-(5-metil-2-furanil) pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	421
130		1-[[4,7-dihidro-7-(1H-imidazol-2-il)-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	407

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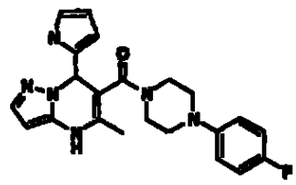
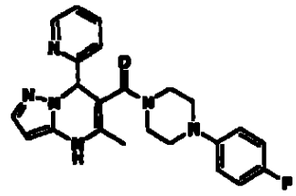
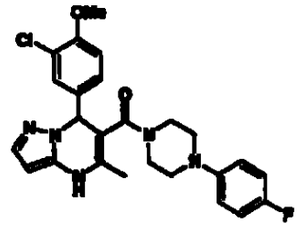
961

131		1-[[4,7-dihidro-5-metil-7-(1H-pirro-2-il)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	406
132		1-[[4,7-dihidro-5-metil-7-(2-piridinil)pirazolo [1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	418
133		1-[[7-(3-cloro-4-metoxifenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	481

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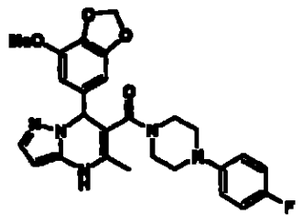
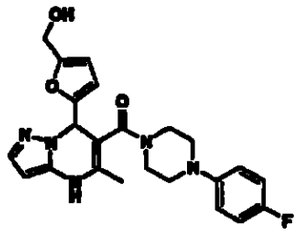
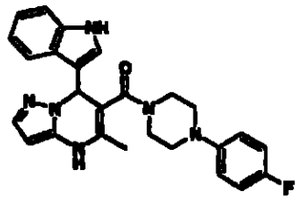
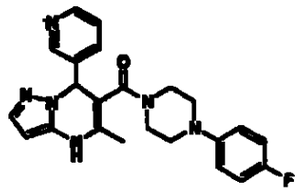
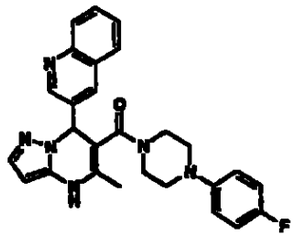
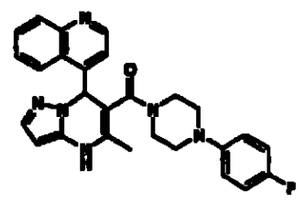
962

134		1-[[4,7-dihidro-7-(4-metoxi-1,3-benzodioxol-6-il)-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	491
135		1-[[4,7-dihidro-7-[5-(hidroximetil)-2-furanil]-5-metil-pirazolo [1,5-a]piri-midin-6-il]carbonil]-4-(4-fluoro-fenil)piperazina	437
136		1-[[4,7-dihidro-7-(1H-indol-3-il)-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	456

137		1-[[4,7-dihidro-5-metil-7-(3-piridinil)pirazolo [1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	418
138		1-[[4,7-dihidro-5-metil-7-(3-quinolinil)pirazolo [1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	468
139		1-[[4,7-dihidro-5-metil-7-(4-quinolinil)pirazolo [1,5-a] pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	468

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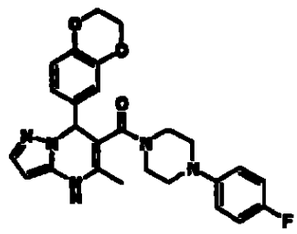
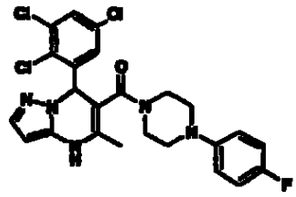
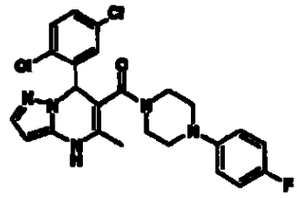
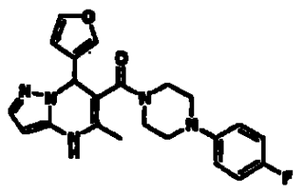
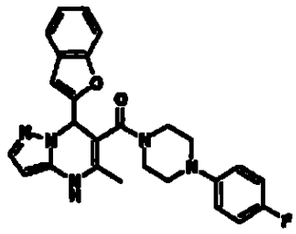
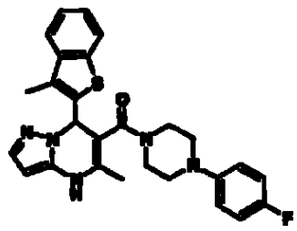
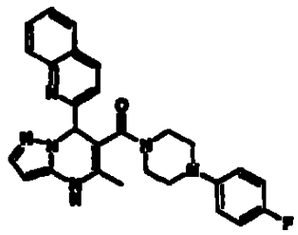
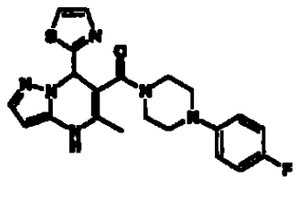
964

140		1-[[7-(2,3-dihidro-1,4-benzodioxol-6-il)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	475
141		1-[[4,7-dihidro-5-metil-7-(2,3,5-tri-clorofenil) pirazolo-[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	520
142		1-[[7-(2,5-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	486

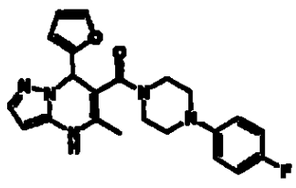
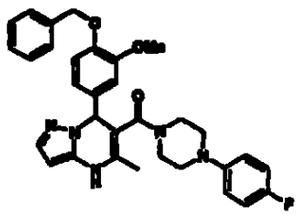
989
965

143		1-(4-fluorofenil)-4-[[7-(3-furanil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-piperazina	407
144		1-[[7-(2-benzo-furanil)-4,7-dihidro-5-metilpira-zolo[1,5-a]piri-midin-6-il] carbonil]-4-(fluoro-fenil) piperazina	457

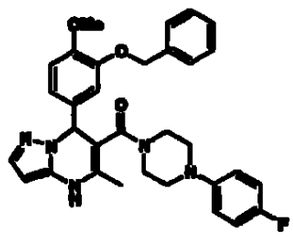
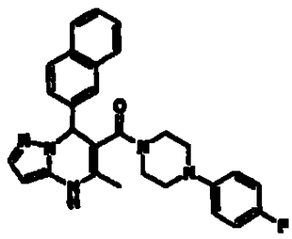
990
966

145		1-[[4,7-dihidro-5-metil-7-(3-metil-benzo[b]tiofen-2-il) pirazolo [1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	487
146		1-[[4,7-dihidro-5-metil-7-(2-quinolinil)pirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	468
147		1-[[4,7-dihidro-5-metil-7-(2-tiazolil)pirazolo [1,5-a] pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	424

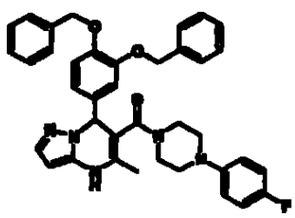
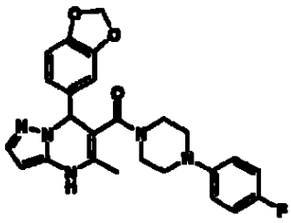
991
997

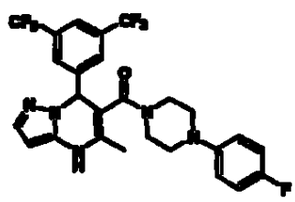
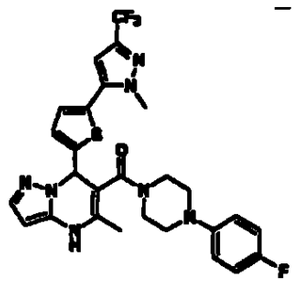
148		1-(4-fluorofenil)-4-[[7-(2-furanil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil] piperazina	407
149		1-[[4,7-dihidro-7-(3-metoxi-4-(fenilmetoxi) fenil]-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	553

992
968

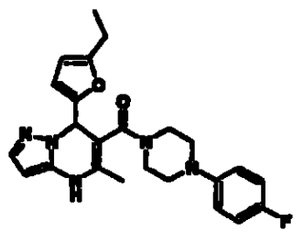
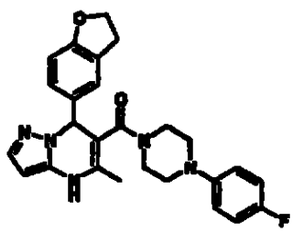
150		1-[[4,7-dihidro-7-[4-metoxi-3-(fenilmetoxi) fenil]-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	553
151		1-[[4,7-dihidro-5-metil-7-(2-naftalenil) pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	467

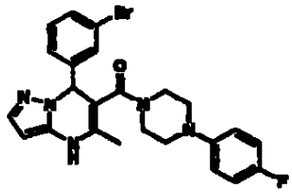
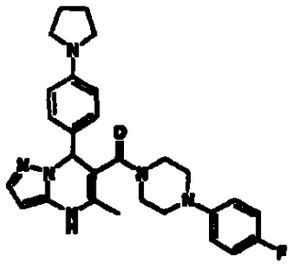
993
969

152		1-[[7-[3,4-bis-(fenilmetoxi) fenil] -4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	629
153		1-[[7-(1,3-benzodioxol-5-il)-4,7-dihidro-5-metil-pirazolo [1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	461

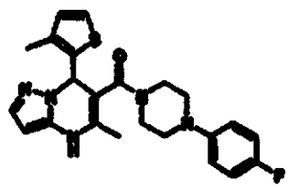
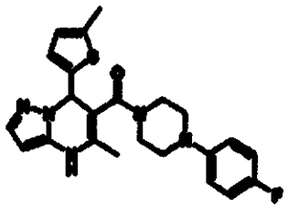
154		1-[[7-[3,5-bis-(trifluorometil)fenil]-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluoro-fenilpiperazina	553
155		1-[[4,7-dihidro-5-metil-7-[5-[1-metil-3-(trifluorometil)-1H-pirazol-5-il]-2-tienil]pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina	571

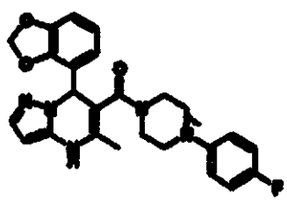
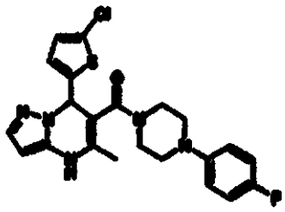
995

156		1-[[7-(5-etil-2-furanil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il])carbonil]-4-(4-fluoro-fenil)piperazina	435
157		1-[[7-(2,3-dihidro-5-benzofuranil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	459

158		1-[[7-(3-bromo-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina	496
159		1-[[4,7-dihidro-5-metil-7-[4-(1-pirrolidinil)-fenil]pirazolo [1,5-a] pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	486

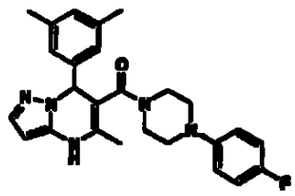
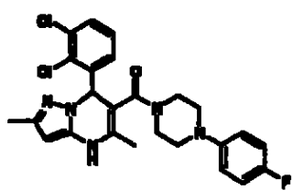
997
973

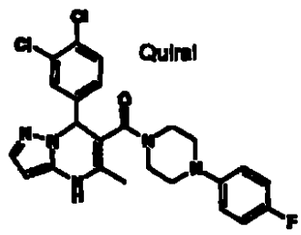
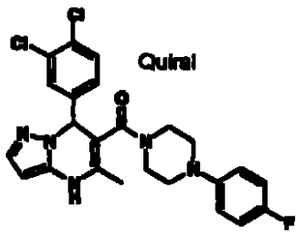
160		1-[[4,7-dihidro-5-metil-7-(3-metil-2-tienil) pirazolo[1,5-a] pirimidin-6-il]-(4-fluorofenil) piperazina	437
161		1-[[1-(4,7-dihidro-5-metil-7-(5-metil-2-tienil)pirazolo [1,5-a]pirimidin-6-il]carbonil]-4-(fluorofenil) piperazina	437

162		1-[[7-(1,3-benzodioxol-4-il)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	461
163		1-[[7-(5-cloro-2-tienil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	457

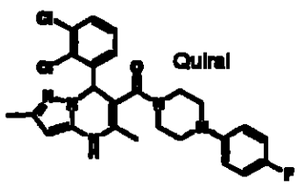
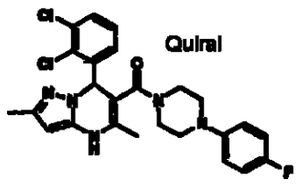
999

975

164		1-[[7-3,5-dimetilfenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	445
165		1-[[7-(2,3-diclorofenil)-4,7-dihidro-2,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	500

166		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina, enantiómero A	486
167		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina, enantiómero B	486

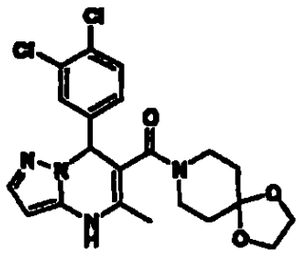
1001

168		1-[[7-(2,3-diclorofenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a]pirimidin-6-il] carbonil]-4-(4-fluorofenil) piperazina, enantiómero B	500
169		1-[[7-(2,3-diclorofenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina, enantiómero A	500

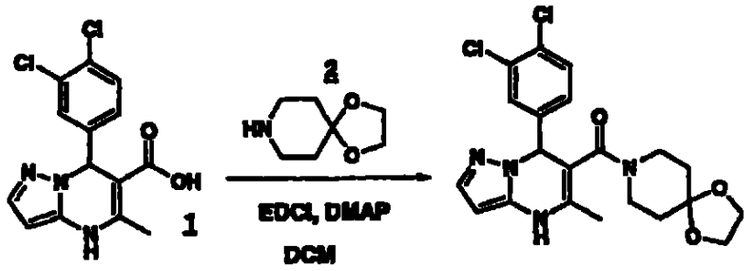
1002
978

Ejemplo 170

8-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,4-dioxa-8-azaspiro[4 5]decano



Método



Compuesto 1 El compuesto 1 se preparó como se describe en el Ejemplo 16

Compuesto del Titulo Se agregó el compuesto 2 (0 68 g, 0 47 mmol)a una suspension del

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compuesto 1 (0 10 g, 0 32 mmol), EDCI (0 09 g, 0 47 mmol), DMAP (0 004 g, 0 03 mmol) en diclormetano (1 mL) Cuando el LC/MS indicó que la reacción se completo la mezcla se cargo directamente en un CARTUCHO CLEAN-UP Worldwide Monitoring (gel de silice, CUSIL12M6) el cual ha sido equilibrado con hexano al 100% Elución con hexanos al 100% (40 mL), seguido por acetato de etilo/hexanos al 50% (40 mL) y acetato de etilo al 100% (70 mL) Las fracciones más puras (análisis TLC) se combinaron para dar 0 043 g (rendimiento al 30%) del compuesto del titulo como un sólido blanco LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección UV a 220 λ, gradiente 4 min Solvente B/A (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt = 2 12 min, (97% puro) MS (M+H) 449) HMR (DMSO-d_6, 400 MHz, 100°C) 9 02 (1H, bs), 7 49 (1H, d, J = 8Hz), 7 26 (1H, d, J = 2 Hz), 7 14 (1H, d, J = 2 Hz), 6 95 (1H, d, J = 8 Hz), 6 08 (1H, s), 5 55 (1H, d, J =2 Hz), 3 84 (4H, m), 3 55 (2H, m), 3 20 (2H, m), 1 86 (3H, s), 1 37 (2H, m), 1 26 (2H, m)

1004
980

Ejemplos 171-377

Los compuestos de las Ejemplos 171-377, mostrados en la tabla proporcionada abajo, se prepararon en una manera similar a aquella descrita en el Ejemplo 170

La resolución HPLC del Ejemplo 194, columna AD Chiralpak (50 x 500 mm), elución con isopropanol/hexanos al 30% conteniendo trietilamina al 0 1% a 50 mL/min), detección UV a 254 λ, proporciona enatiómeros A (Ejemplo 250) y B (Ejemplo 251) Columna AD Chiralpak (4 6 x 250 mm) elución con isopropanol/hexanos al 30% conteniendo trietilamina al 0 1% a 1 mL/min), detección UV a 254 λ, enatiómero A Rt = 5 32 min, 99% ee Enantiómero B Rt = 8 59 min, 98% ee

La resolución HPLC del Ejemplo 221, columna AS Chiralpak (50 x 500 mm), elución con isopropanol/hexanos al 50% conteniendo trietilamina al 0 1% a 42 mL/min), deteccion UV a 254 λ proporcionando anatiómeros A (Ejemplo 328) y B (Ejemplo 329) Columna AS Chiralpak (4 6 x 250 mm), elución con isopropanol/hexanos al 30% conteniendo amina de trietilamina al 0 1% a 1 mL/min), detección UV a 254 λ, enantiómero A

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Rt = 5 12 mın, >99% ee Enantıómero B Rt = 8 70 mın, > 99% ee

La resolución HPLC del Ejemplo 288, columna AD Chıralpak (50 x 500 mm), elución con ısopropanol/hexanos al 30% conteniendo trıetılamına al 0 1% a 50 mL/mın), deteccion UV a 254 λ proporcıonando enantıómeros A (Ejemplo 376) y B (Ejemplo 377) Columna AD Chıralpak (4 6 x 250 mm), elución con ısopropanol/hexanos al 30% conteniendo trıetılamına al 0 1% a 1 mL/mın), detección UV a 254 λ, enantıómero A Rt = 3 8 mın, > 99% ee Enantıomero B Rt = 5 6 mın, > 99% ee

La resolución HPLC del Ejemplo 333, columna AD Chıralpak (50 x 500 mm), elución con ısopropanol/hexanos al 40% conteniendo trıetılamına al 0 1% a 50 mL/mın), detección UV a 254 λ, proporcıonando enantıómeros A (Ejemplo 364) y B (Ejemplo 365) Columna AD Chıralpak (4 6 x 250 mm), elución con ısopropanol/hexanos al 40%, conteniendo trıetılamına al 40% a 1 mL/mın), deteccion UV a 254 λ, enantıómero A Rt = 4 92 mın, > 99% ee Enantıomero B Rt = 8 0 mın, > 97% ee

El compuesto del Ejemplo 360 se separó

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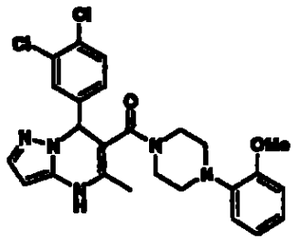
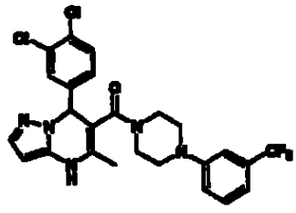
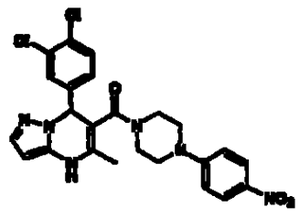
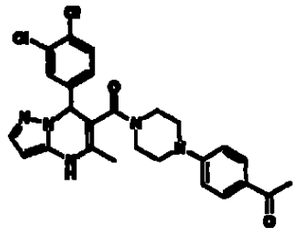
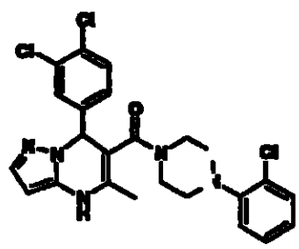
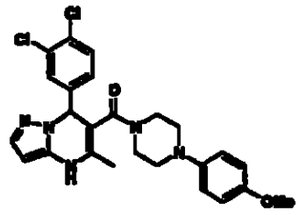
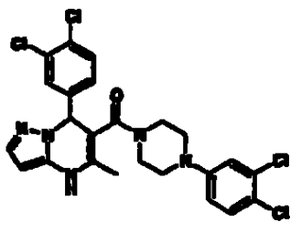
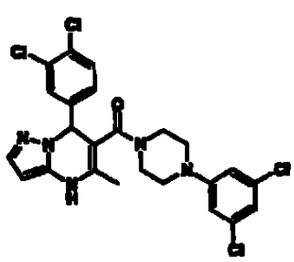
en diastereoisómeros puros por cromatografía en columna (gel de sílice eluído con acetato de etilo al 75%, hexanos) El isómero que eluye más rápido es el diastereómero 1, el isómero que eluye más lento es el diastereómero 2 Cuando se separa por TLC (acetona al 20%, diclorometano), el diastereómero 1 tiene un R_f de 0 26 y el diastereómero 2 tiene un R_f de 0 17 El diastereómero 2 fue además, separado en la forma quiral pura vía el HPLC preparativo (columna Chiralpak AD 5 cm x 50 cm, eluida con etanol al 13% en hexanos con TEA al 0 1% a 50 mL/min con detección UV a 254 nM) El isómero que eluye más rápido es el enantiómero A (tiempo de retención 8 1 min por HPLC, columna Chiralpak AD 4 6 x 250 mm, eluida con etanol al 10%, hexano con trietilamina al 0 1% a 2 mL/min, con detección UV a 254 nm) y el isómero que eluye más lento es el enantiómero B (tiempo de retención por HPLC 10 6 minutos, columna Chiralpak AD 4 6 x 250 mm, eluida con etanol al 10%, hexano con 0 1% de trietilamina a 2 mL/min con deteccion UV a 254 mm) El diasteromero 1 puede también ser separado en forma quiral pura por metodología similar como aquella descrita para el

diastereómero 2 anterior, para proporcionar los enantiómeros C y D

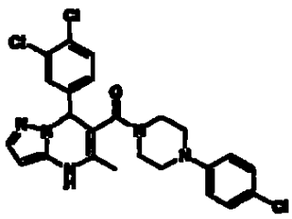
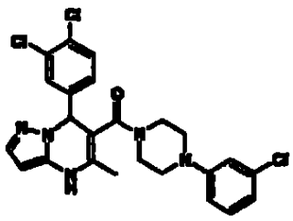
Ejemplo	Estructura	Nombre	(M+H)
171		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(2-metoxifenil) piperazina	498
172		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-[3-(trifluoro-metil)-fenil] piperazina	536

173		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-nitrofenil) piperazina	513
174		1-(4-acetilfenil)-4-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil] piperazina	510

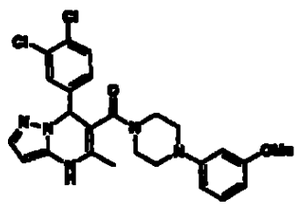
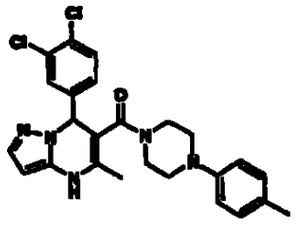
175		1-(2-Clorofenil)-4-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil] piperazina	502
176		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-metoxifenil) piperazina	498

177		1-(3,4-Dicloro-fenil)-4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil] piperazina	537
178		1-(3,5-Dicloro-fenil)-4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo [1,5-a] pirimidin-6-il]carbonil] piperazina	537

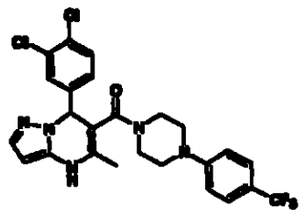
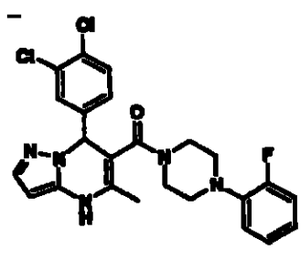
1011
937

179		1-(4-Clorofenil)-4-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil] piperazina	502
180		1-(3-clorofenil)-4-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil] piperazina	502

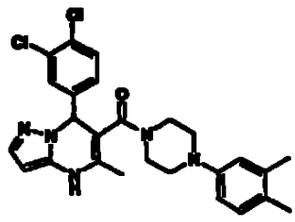
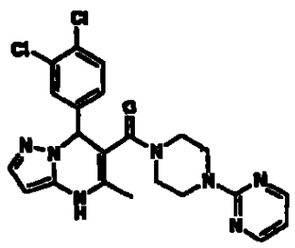
1012
498

181		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(3-metoxifenil) piperazina	498
182		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-metilfenil) piperazina	482

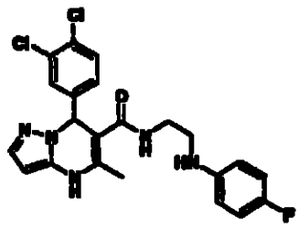
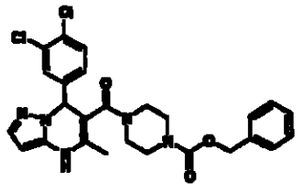
1013

183		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-[4-(trifluoro-metil)-fenil]piperazina	536
184		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(2-fluorofenil) piperazina	486

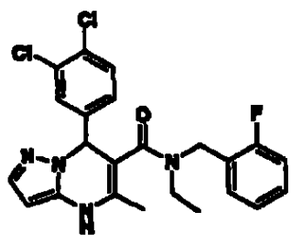
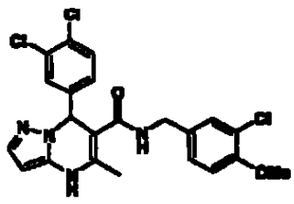
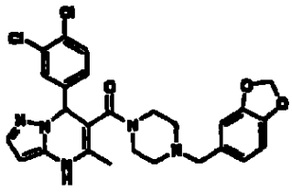
1014
990

185		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(3,4-dimetilfenil) piperazina	496
186		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil pirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(2-pirimidin-piperazina	470

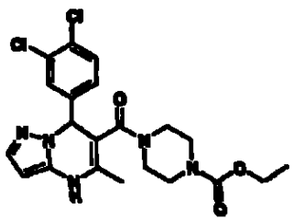
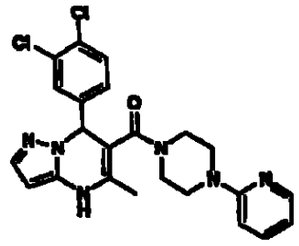
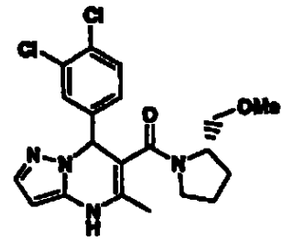
1015
994

187		7-(3,4-diclorofenil)-N-[2-[(4-fluorofenil)amino]etil]-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-carboxamida	460
188		Ester fenilmetílico del ácido 4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1-perazincarboxílico	526

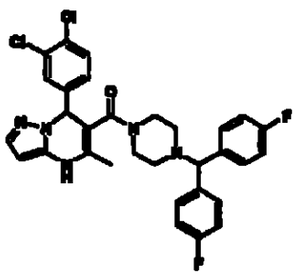
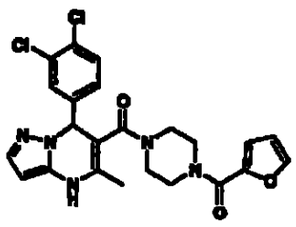
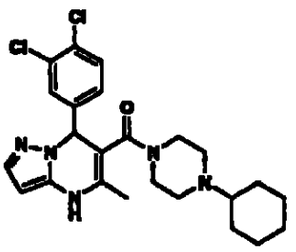
1016
972

189		7-(3,4-diclorofenil)N-etil-N-[(2-fluorofenil)metil)]-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida	459
190		N-[(3-cloro-4-metoxifenil)metil]-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-carboxamida	477
191		1-(1,3-benzodioxol-5-ilmetil)-4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil] piperazina	526

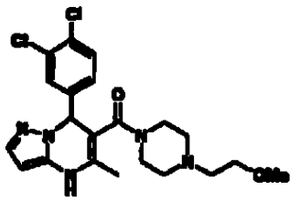
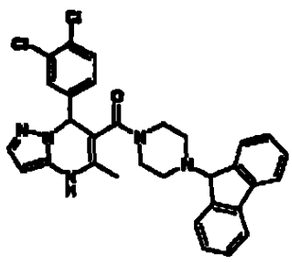
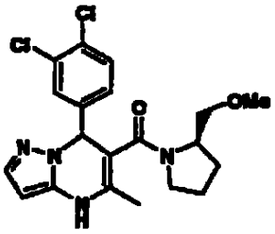
1017
993

192		Ester etílico del ácido 4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1-piperazincarboxílico	464
193		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(2-piridinil)piperazina	469
194		(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina	421

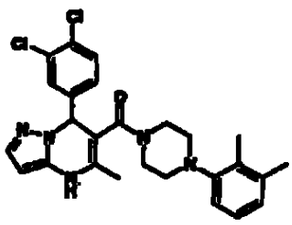
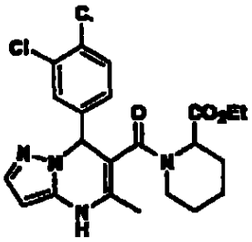
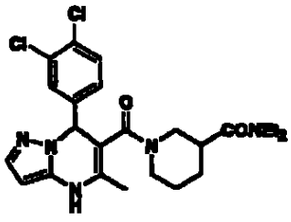
1018
994

195		1-[bis(4-fluoro-fenil)-metil]-4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil pirazolo[1,5-a] pirimidin-6-il] carbonil]piperazina	594
196		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(2-furanil-carbonil)piperazina	486
197		1-ciclohexil-4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil pirazolo[1,5-a] pirimidin-6-il] carbonil]piperazina	474

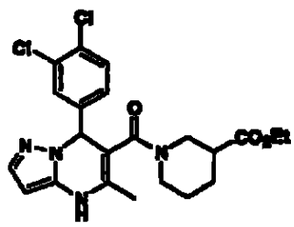
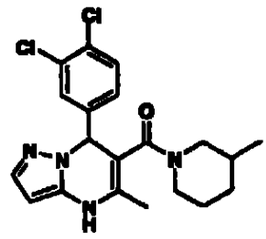
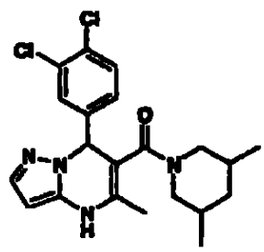
1019
995

198		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil pirazolo[1,5-a] pirimidin-6-il] carbonil]-4-(2-metoxietil) piperazina	450
199		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(9H-fluoren-9-il)piperazina	556
200		2(R)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil pirazolo[1,5-a] pirimidin-6-il] carbonil]-2-(metoximetil) pirrolidina	421

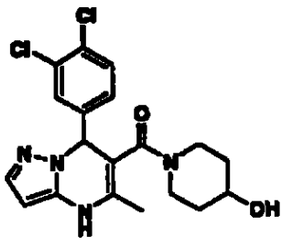
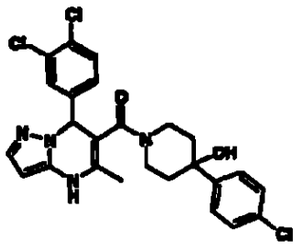
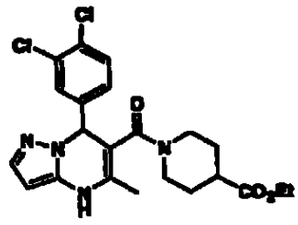
1020
996

201		1-[[7(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(2,3-dimetilfenil) piperazina	496
202		Ester etílico del ácido 1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil pirazolo[1,5-a] pirimidin-6-il] carbonil]-2-pipe-ridin-carboxílico	463
203		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-N,N-dietil-3-piperidincarboxamida	490

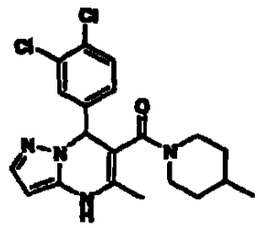
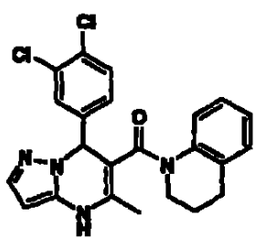
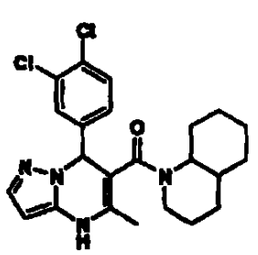
1021
947

204		Ester etílico del ácido 1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3-piperidin-carboxílico	463
205		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3-metil-piperidina	405
206		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3,5-dimetil-piperidina	419

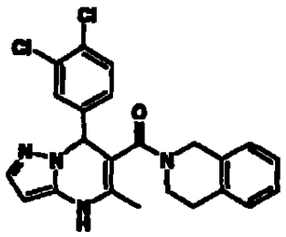
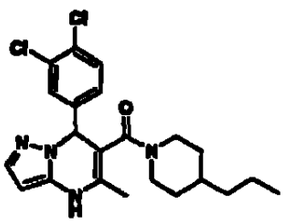
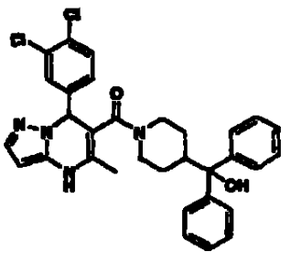
1022
998

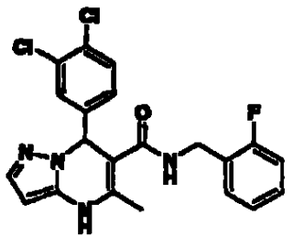
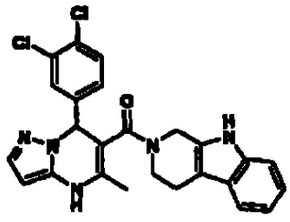
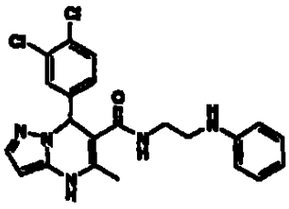
207		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-hidroxi-piperidina	407
208		4-(4-clorofenil)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-hidroxipiperidina	517
209		Ester etílico del ácido 1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-piperidin-carboxílico	463

1023
999

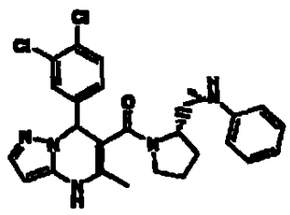
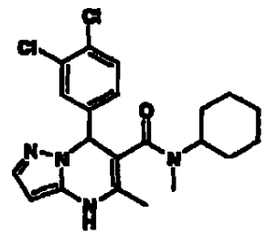
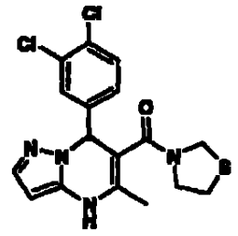
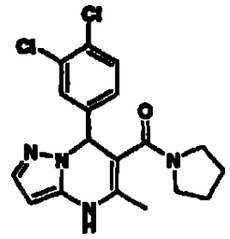
210		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-metilpiperidina	405
211		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,4-tetrahidroquinolina	439
212		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-decahidroquinolina	445

1024

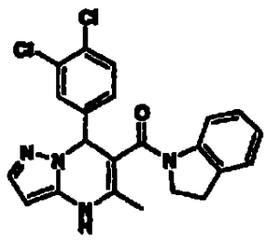
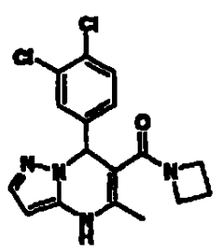
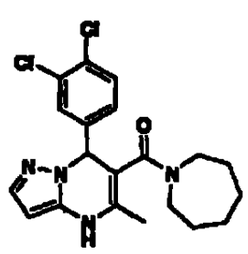
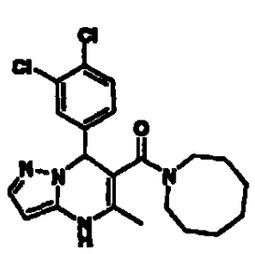
213		2-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-1,2,3,4-tetra-hidroisoquinolina	439
214		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-propilpiperidina	433
215		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(hidroxidifenil-metil)piperidina	573

216		7-(3,4-diclorofenil)-N-[(2-fluorofenil)metil]-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida	431
217		2-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2,3,4,9-tetrahidro-1H-pirido[3,4-b]indol	478
218		7-(3,4-dicloro-fenil)-4,7-dihidro-5-metil-N-[2-(fenilamino)-etil]pirazolo[1,5-a]pirimidin-6-carboxamida	442

1002 1026

219		(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-[(fenilamino) metil]pirrolidina	482
220		N-ciclohexil-7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-pirazolo[1,5-a]pirimidin-6-carboxamida	419
221		3-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]tiazolo	395
222		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-pirrolidina	377

1003
1027

223		1-[[7-(3,4-dıcloro-fenıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]-3,4-dıhıdro-1H-ındol	425
224		1-[[7-(3,4-dıcloro-fenıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]-azetıdina	363
225		1-[[7-(3,4-dıcloro-fenıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]-hexahıdro-1H-azepına	405
226		1-[[7-(3,4-dıcloro-fenıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]-octahıdroazocına	419

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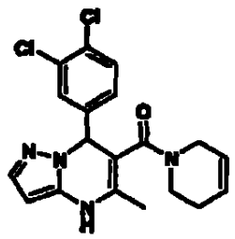
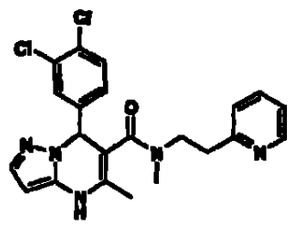
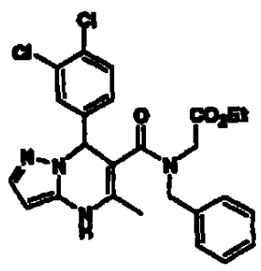
1508

227		1-[[7-(3,4-dıcloro-fenıl)-4,7-dıhidro-5-metılpırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]-1,2,3,6-tetrahıdropırıdına	389
228		7-(3,4-dıcloro-fenıl)-4,7-dıhıdro-N,5-dımetil-N-[2-(2-pırıdınıl)-etıl]pirazolo[1,5-a]pırımıdin-6-carboxamıda	442
229		Ester etílico de N-[[7-(3,4-dıcloro-fenıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]-N-(fenılmetıl)glıcına	499

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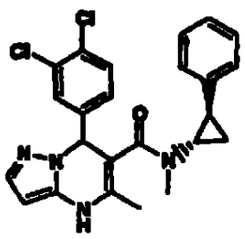
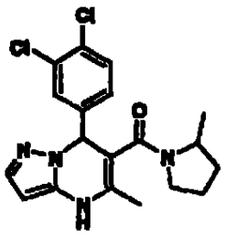
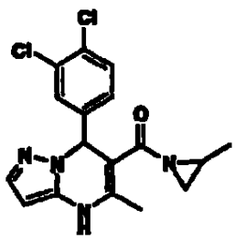
1029

230		Trans-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-(2-fenilciclo propil)pirazolo[1,5-a]pirimidin-6-carboxamida	439
231		1-[[7(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-2-metilpirrolidina	391
232		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-2-metilaziridina	363

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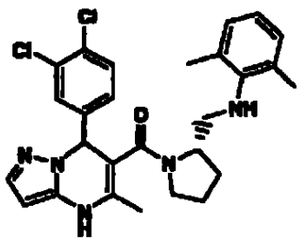
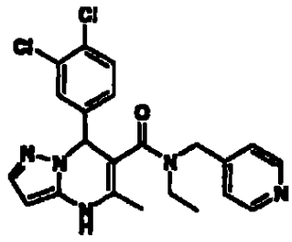
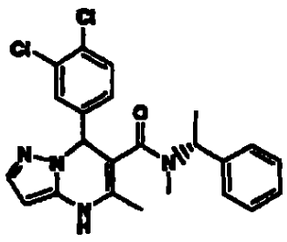
233		(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-[[(2,6-dimetil fenil)amino]metil] pirrolidina	510
234		7-(3,4-dicloro fenil)-N-etil-4,7-dihidro-5-metil-N-(4-piridinil metil)pirazolo[1,5-a]pirimidin-6-carboxamida	442
235		7-(3,4-dicloro fenil)-4,7-dihidro-N,5-dimetil-N-[(1R)-1-feniletil]pirazolo [1,5-a]pirimidin-6-carboxamida	441

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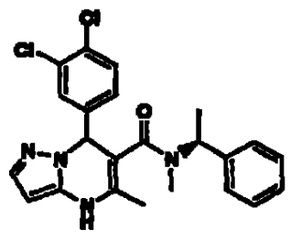
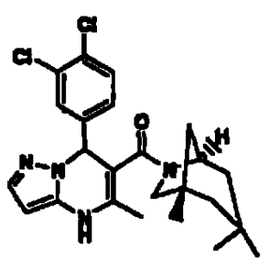
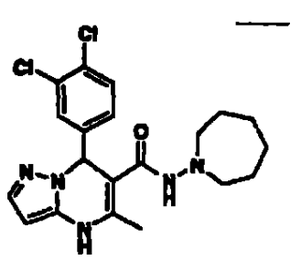
1031

236		7-(3,4-dıcloro-fenıl)-4,7-dıhıdro-N,5-dımetil-N-[(1S)-1-fenıletıl]pırazolo[1,5-a]pırımıdın-6-carboxamıda	441
237		6-[[7-(3,4-dıcloro fenıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdın-6-ıl] carbonıl]-1,3,3-trımetıl-6-azabıcıclo[3 2 1] octano	459
238		7-(3,4-dıcloro-fenıl)-N-(hexahıdro-1H-azepın-1-ıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdın-6-carboxamıda	420

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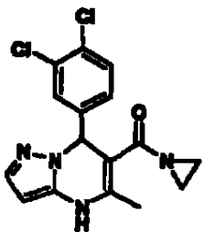
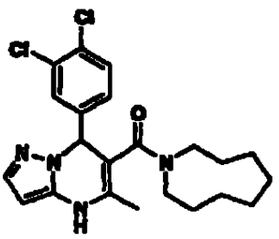
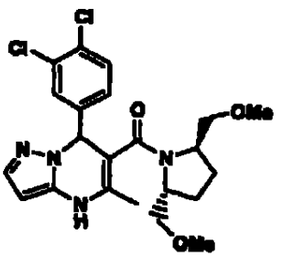
1032

239		1-[[7-(3,4-dıcloro-fenıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]-azırıdına	349
240		1-[[7-(3,4-dıcloro fenıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdın-6-ıl] carbonıl]octahıdro-1H-azonına	433
241		(2R-trans)-1-[[7-(3,4-dıclorofenıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdın-6-ıl] carbonıl]-2,5-bıs(metoxımetıl)-pırrolıdına	465

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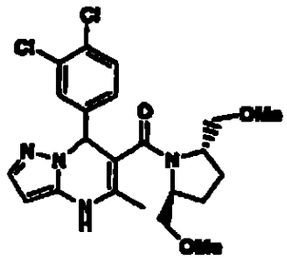
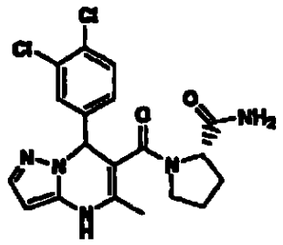
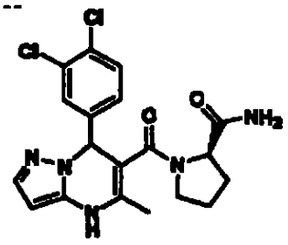
242		(2S-trans)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-2,5-bis-(metoximetil) pirrolidina	465
243		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-L-prolinamida	420
244		1-[[7-(3,4-dicloro fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-D-prolinamida	420

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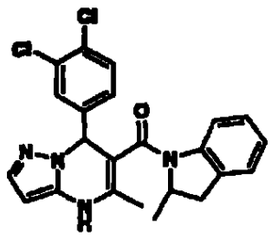
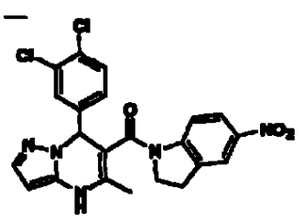
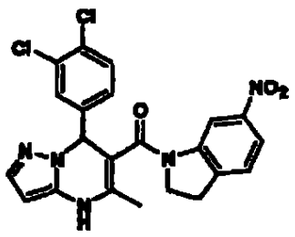
p34

245		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2,3-dihidro-2-metil-1H-indol	439
246		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil pirazolo[1,5-a] pirimidin-6-il] carbonil]-2,3-dihidro-5-nitro-1H-indol	470
247		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2,3-dihidro-6-nitro-1H-indol	470

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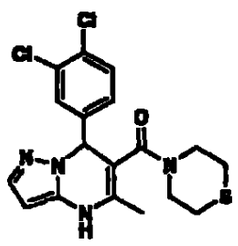
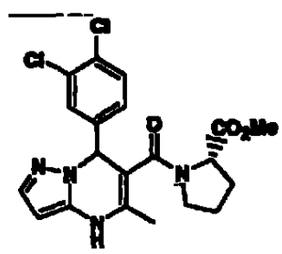
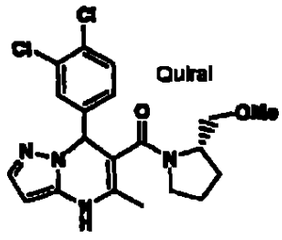
248		4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-tiomorfolina	409
249		Ester metílico de 1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-L-prolina	435
250		Enantiómero A de (2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-2-(metoxi-metil)pirrolidina	421

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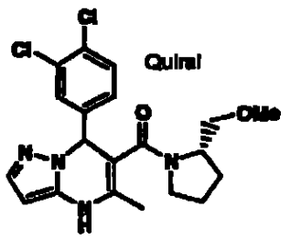
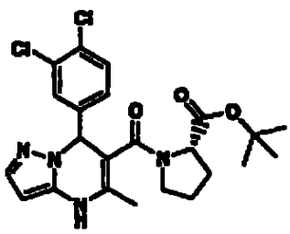
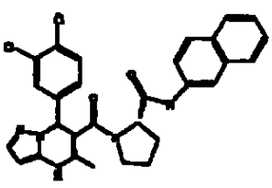
1036

251		Enantiómero B de (2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoxi-metil)pirrolidinina	421
252		Ester 1,1-dimetiletílico de 1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-L-prolina	477
253		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-N-(2-naftalenil)-L-prolinamida	560

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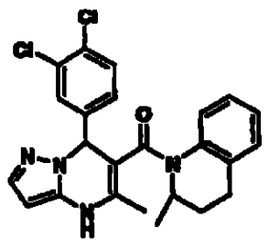
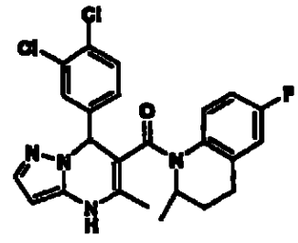
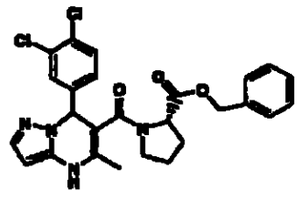
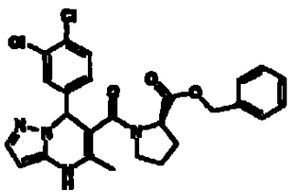
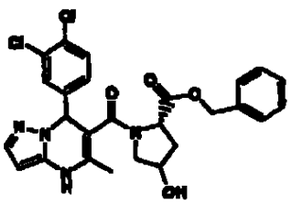
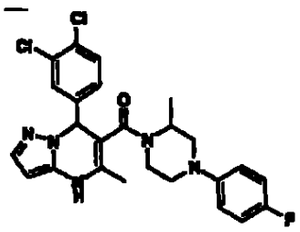
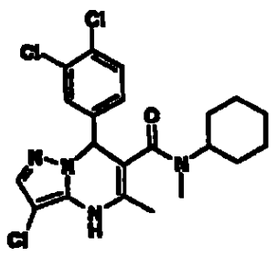
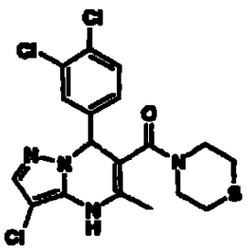
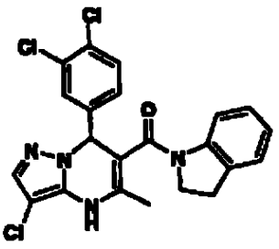
254		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,4-tetrahidro-2-metilquinolina	453
255		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-6-fluoro-1,2,3,4-tetrahidro-2-metilquinolina	471
256		Ester fenilmetílico de 1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-L-prolina	511

1038

257		Ester fenilmetílico 1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-D-prolina	511
258		Ester fenilmetílico de 1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-hidroxi-L-prolina	527
259		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)-2-metilpiperazina	500

260		3-cloro-N-ciclohexil-7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil pirazolo[1,5-a] pirimidin-6-carboxamida	453
261		4-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-tiomorfolina	443
262		1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2,3-dihidro-1H-indol	459

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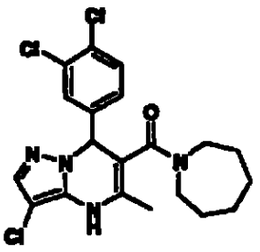
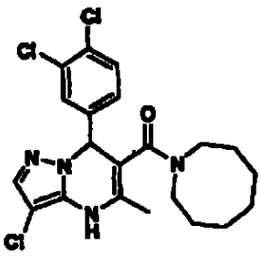
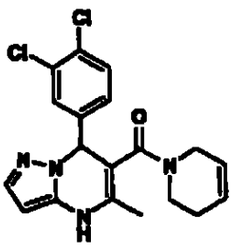
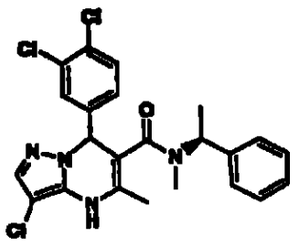
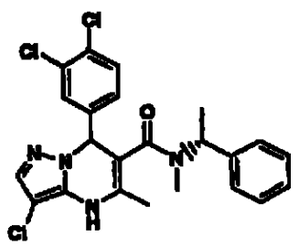
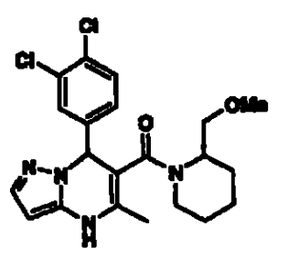
1040

263		1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]hexahidro-1H-azepina	439
264		1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-octahidroazocina	453
265		1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,6-tetrahidropiridina	423

266		3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-N-[(1S)-1-feniletil]-pirazolo[1,5-a]pirimidin-6-carboxamida	475
267		3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-N-[(1R)-1-feniletil]-pirazolo[1,5-a]pirimidin-6-carboxamida	475
268		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoxi-metil)piperidina	435

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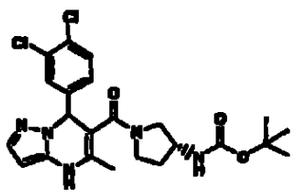
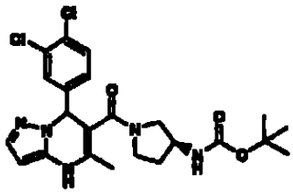
269		Ester 1,1-dimetiletílico del ácido [(3R)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-3-pirro-lidinil]carbámico	492
270		Ester 1,1-dimetiletílico del ácido [(3S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-3-pirrolidinil] carbámico	492

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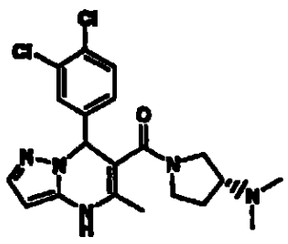
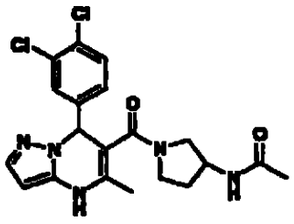
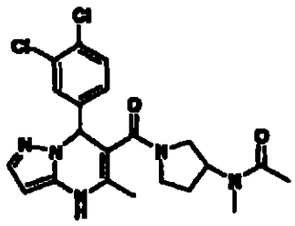
271		(3R)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-3-(dimetilamino)pirrolidina	420
272		N-[1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3-pirrolidinil]acetamida	434
273		N-[1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3-pirrolidinil]-N-metilacetamida	448

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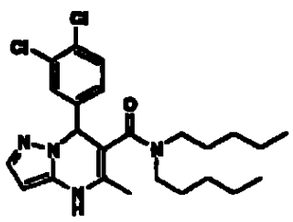
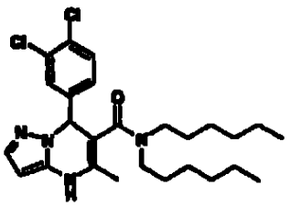
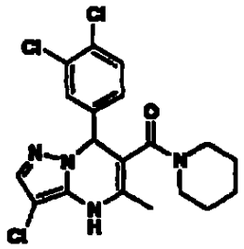
274		7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N,N-dipentil-pirazolo[1,5-a]pirimidin-6-carboxamida	463
275		7-(3,4-diclorofenil)-N,N-dihexil-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida	491
276		1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]piperidina	425

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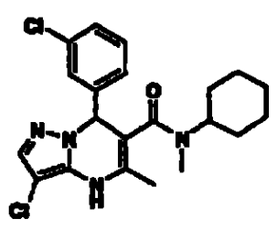
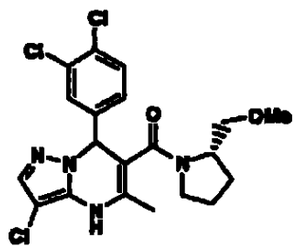
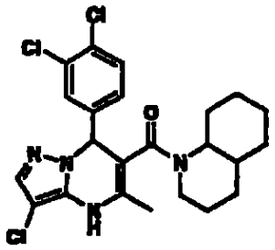
277		3-cloro-7-(3-clorofenil)-N-ciclohexil-4,7-dihidro-N,5-dimetil-pirazolo[1,5-a]pirimidin-6-carboxamida	419
278		(2S)-1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoxi-metil)pirrolidina	455
279		1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-decahidroquinolina	479

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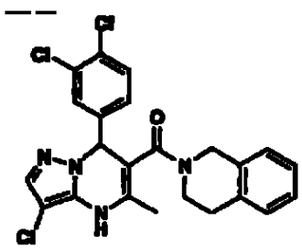
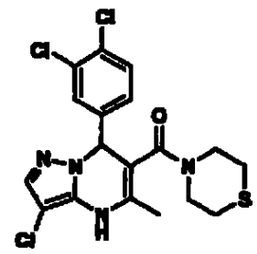
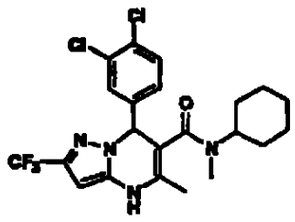
280		2-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-1,2,3,4-tetrahidro-isoquinolina	473
281		4-[[3-cloro-7-(3-clorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-tiomorfolina	409
282		N-ciclohexil-7-(3,4-diclorofenil)-4,7-dihidro-N,5-metil-2-(trifluorometil) pirazolo[1,5-a] pirimidin-6-carboxamida	487

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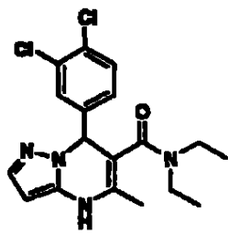
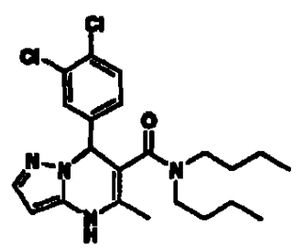
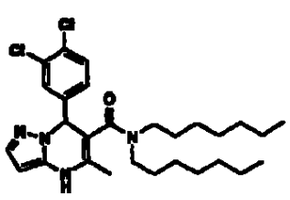
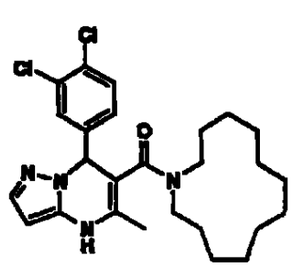
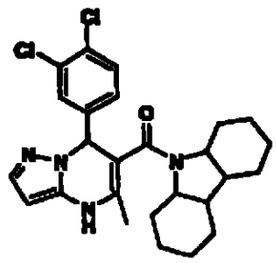
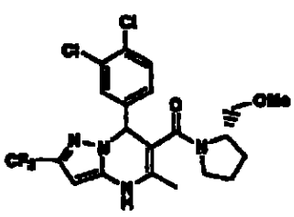
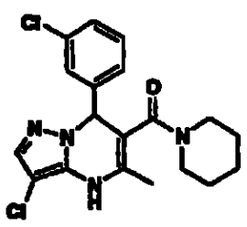
283		7-(3,4-diclorofenil)-N,N-dietil-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida	379
284		N,N-dibutil-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida	435
285		7-(3,4-dicloro fenil)-N,N-diheptil-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-carboxamida	519
286		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-azaciclotridecano	489

287		9-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-dodecahidro-1H-fluoreno	485
288		(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil) pirrolidina	489
289		1-[[3-cloro-7-(3-clorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]piperidina	391

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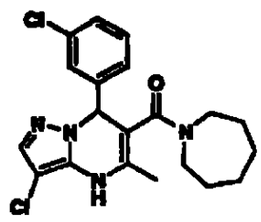
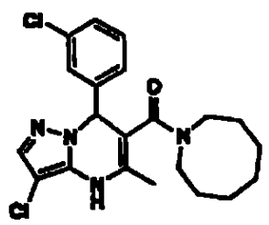
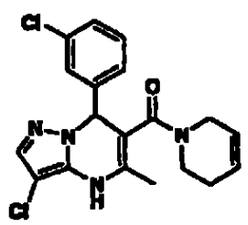
290		1-[[3-cloro-7-(3-clorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]hexahidro-1H-azepina	405
291		1-[[3-cloro-7-(3-clorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-octahidroazocina	419
292		1-[[3-cloro-7-(3-clorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,6-tetrahidropiridina	389

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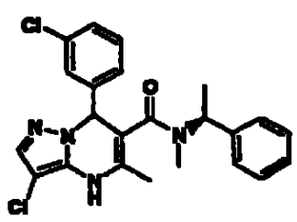
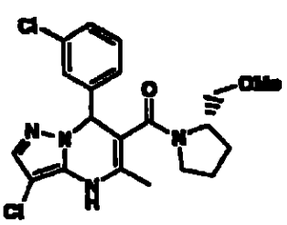
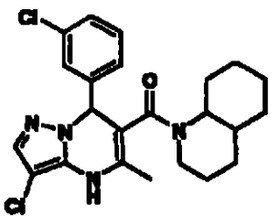
293		3-cloro-7-(3-clorofenil)-4,7-dihidro-N,5-dimetil-N-[(1S)-1-fenil-etil]pirazolo[1,5-a]pirimidin-6-carboxamida	441
294		(2S)-1-[[3-cloro-7-(3-clorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-2-(metoxi-metil)pirrolidina	421
295		1-[[3-cloro-7-(3-clorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-decahidroquinolina	445

1051
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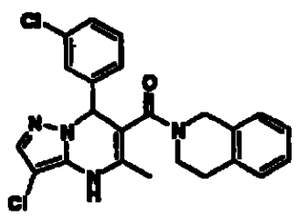
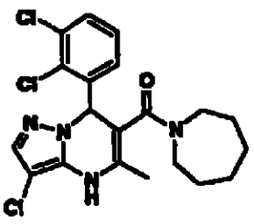
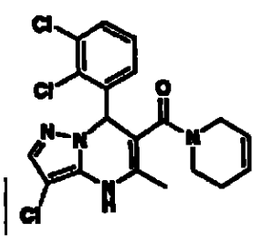
296		2-[[3-cloro-7-(3-clorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,4-tetrahidroisoquinolina	439
297		1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]hexahidro-1H-azepina	439
298		1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,6-tetrahidropiridina	423

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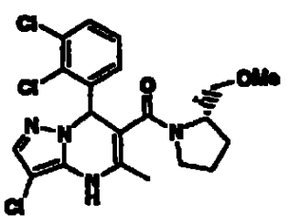
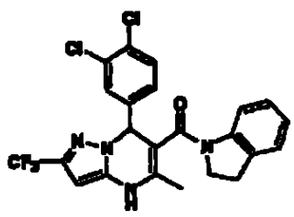
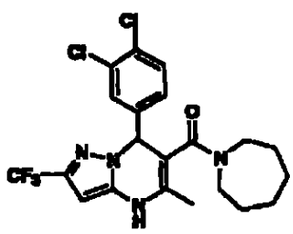
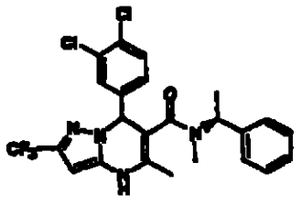
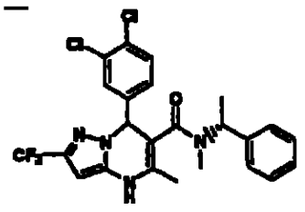
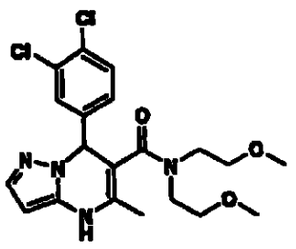
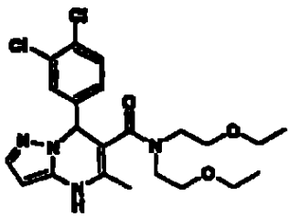
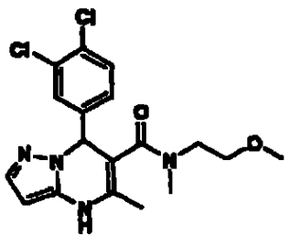
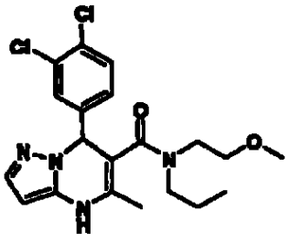
299		(2S)-1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-2-(metoxi-metil)pirrolidina	455
300		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a] pirimidin-6-il] carbonil]-2,3-dihidro-1H-indol	493
301		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metil-2-(trifluoro-metil)pirazolo[1,5-a]pirimidin-6-il] carbonil]hexahidro-1H-azepina	473

1029 1053

302		7-(3,4-dıcloro-fenıl)-4,7-dıhıdro-N,5-dımetıl-N-[(1S)-1-fenıletıl]-2-(trıfluoro-metıl)pırazolo[1,5-a]pırımıdın-6-carboxamıda	509
303		7-(3,4-diclorofenil)-4,7-dıhıdro-N,5-dımetıl-N-[(1R)-1-fenıl-etıl]-2-(trıfluoro-metıl)pırazolo[1,5-a]pırımıdın-6-carboxamıda	509
304		7-(3,4-dıclorofenıl)-4,7-dıhıdro-N,N-bıs(2-metoxıetıl)-5-metılpırazolo[1,5-a]pırımıdın-6-carboxamıda	439

305		7-(3,4-diclorofenil)-N,N-bis(2-etoxietil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida	467
306		7-(3,4-diclorofenil)-4,7-dihidro-N-(2-metoxietil)-N,5-dimetilpirazolo[1,5-a]pirimidin-6-carboxamida	395
307		7-(3,4-diclorofenil)-4,7-dihidro-N-(2-metoxietil)-5-metil-N-propilpirazolo [1,5-a]pirimidin-6-carboxamida	423

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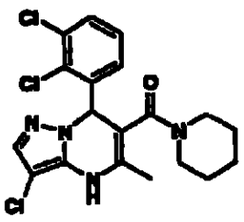
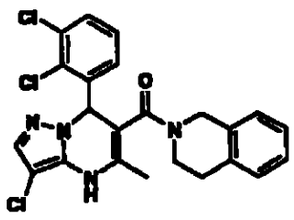
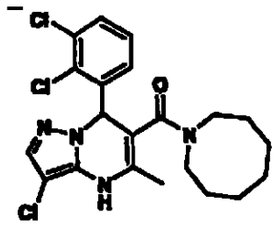
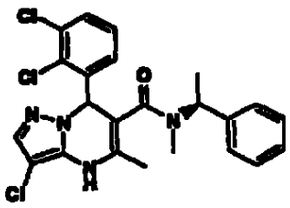
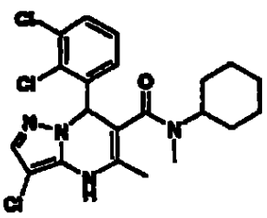
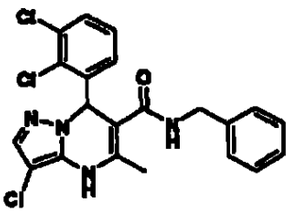
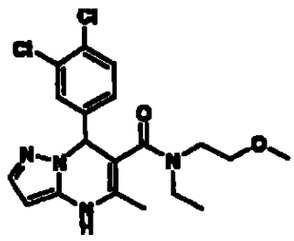
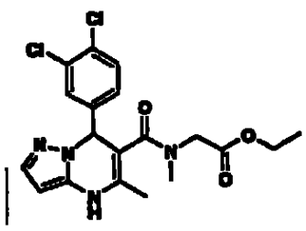
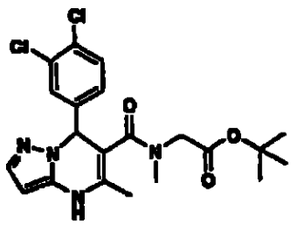
308		1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]piperidina	425
309		2-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a] pirimidin-6-il] carbonil]-1,2,3,4-tetra-hidroisoquinolina	473
310		1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-octahidroazocina	453

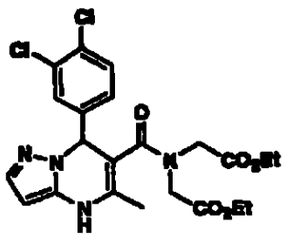
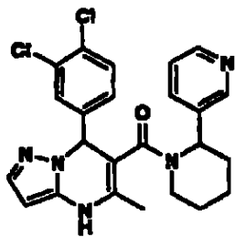
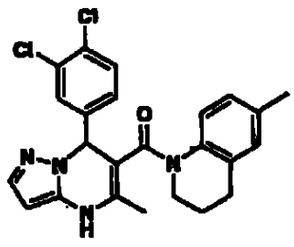
1032 p56

311		3-cloro-7-(2,3-diclofenil)-4,7-dihidro-N,5-dimetil-N-[(1S)-1-feniletil]-pirazolo[1,5-a]pirimidin-6-carboxamida	475
312		3-cloro-N-ciclohexil-7-(2,3-diclorofenil)-4,7-dihidro-N,5-dimetil-pirazolo[1,5-a]pirimidin-6-carboxamida	453
313		3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-N-(fenilmetil)pirazolo[1,5-a]pirimidin-6-carboxamida	447

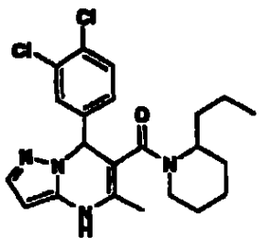
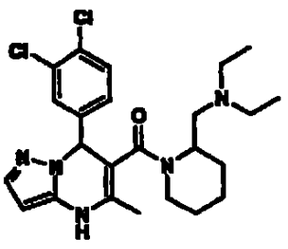
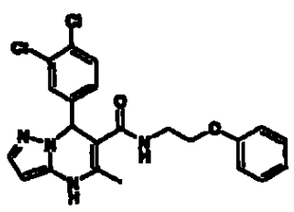
1033 1057

314		7-(3,4-diclorofenil)-N-etil-4,7-dihidro-N-(2-metoxietil)-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida	409
315		Ester etílico de N-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-N-metilglicina	423
316		Ester 1,1-dimetiletílico de N-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-N-metilglicina	451

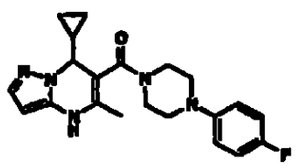
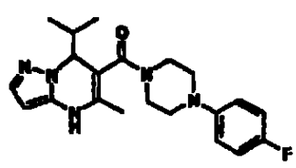
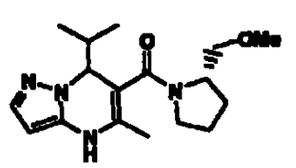
1034 1058

317		Ester etílico de N-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-N-(2-etoxi-2-oxoetil) glicina	495
318		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(3-piridinil)piperidina	468
319		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,4-tetrahidro-6-metilquinolina	453

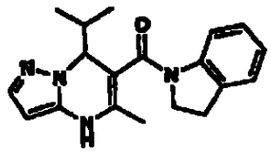
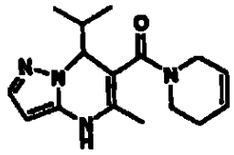
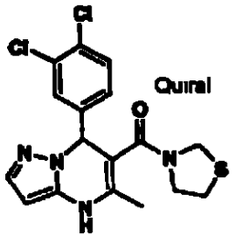
1035 1059

320		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-propilpiperidina	433
321		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-[(dietilamino)metil] piperidina	476
322		7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-(2-fenoxietil)-pirazolo[1,5-a]pirimidin-6-carboxamida	443

1030 1060

323		1-[(7-ciclopropil-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il) carbonil]-4-(4-fluorofenil) piperazina	381
324		1-[[4,7-dihidro-5-metil-7-(1-metil-etil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	383
325		(2S)-1-[[4,7-dihidro-5-metil-7-(1-metil-etil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil) pirrolidina	318

1037 1061

326		1-[[4,7-dihidro-5-metil-7-(1-metil-etil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-2,3-dihidro-1H-indol	322
327		1-[[4,7-dihidro-5-metil-7-(1-metil-etil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,6-tetrahidropiridina	286
328		Enantiómero A de 3-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-tiazolidina	395

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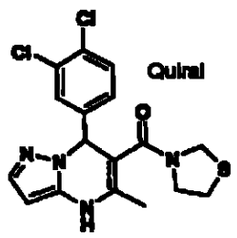
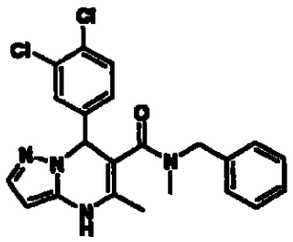
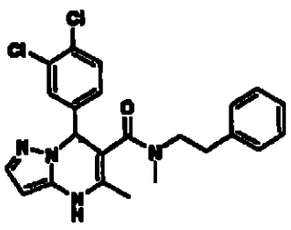
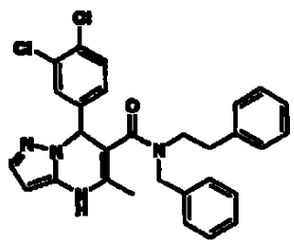
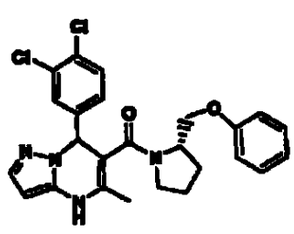
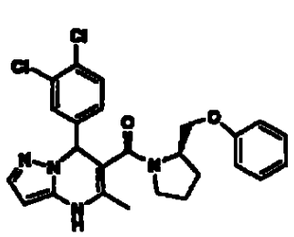
329		Enantiómero B de 3-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-tiazolidina	395
330		7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-N-(fenilmetil) pirazolo[1,5-a] pirimidin-6-carboxamida	427
331		7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-N-(2-feniletil) pirazolo[1,5-a] pirimidin-6-carboxamida	441

1039, 1063

332		7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-(2-feniletil)-N-(fenilmetil)pirazolo[1,5-a]pirimidin-6-carboxamida	517
333		(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(fenoxi-metil)pirrolidina	483
334		(2R)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(fenoxi-metil)pirrolidina	483

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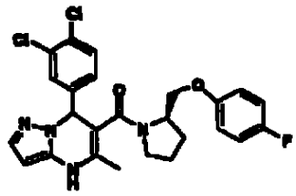
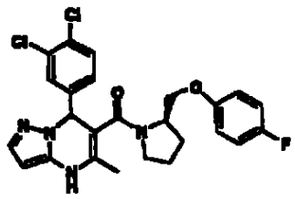
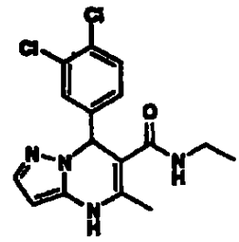
335		(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-[(4-fluorofenoxi)metil]-pirrolidina	501
336		(2R)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-[(4-fluorofenoxi)metil]-pirrolidina	501
337		7-(3,4-diclorofenil)-N-etil-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida	351

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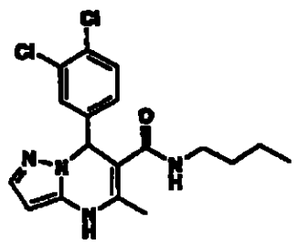
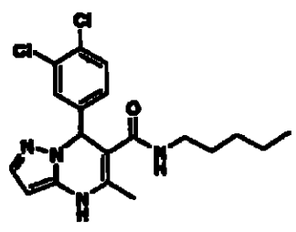
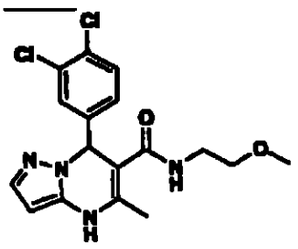
338		N-butil-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida	379
339		7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-pentilpirazolo[1,5-a]pirimidin-6-carboxamida	393
340		7-(3,4-diclorofenil)-4,7-dihidro-N-(2-metoxietil)-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida	381

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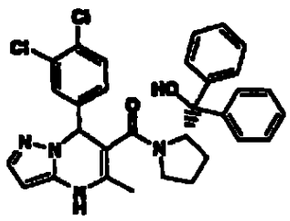
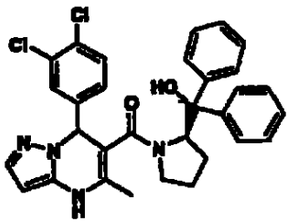
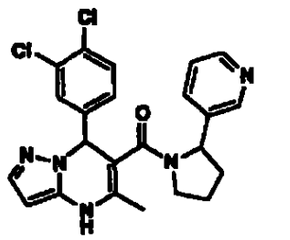
341		(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-2-(hidroxidifenil-metil)pirrolidina	559
342		(2R)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(hidroxidifenil-metil)pirrolidina	559
343		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-2-(3-piridinil) pirrolidina	454

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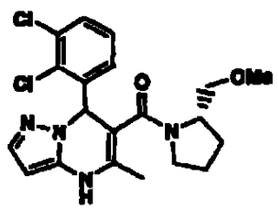
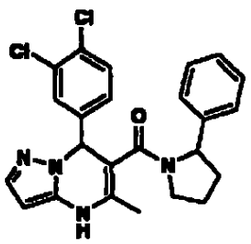
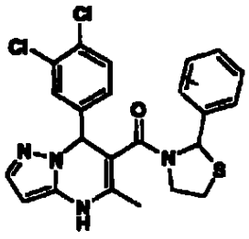
344		(2S)-1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil) pirrolidina	421
345		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-fenilpirrolidina	453
346		3-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-feniltiazolidina	471

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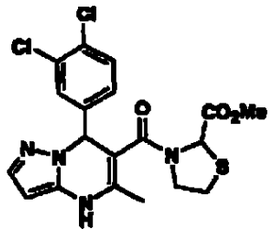
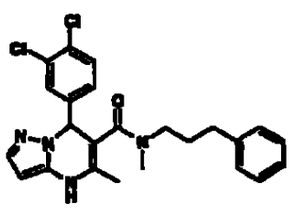
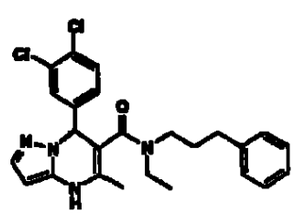
347		Ester metílico del ácido 3-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a] pirimidin-6-il] carbonil]-2-tiazo-lidinocarboxílico	453
348		7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-N-(3-fenilpropil) pirazolo[1,5-a]pirimidin-6-carboxamida	455
349		7-(3,4-diclorofenil)-N-etil-4,7-dihidro-5-metil-N-(3-fenil-propil)pirazolo[1,5-a]pirimidin-6-carboxamida	469

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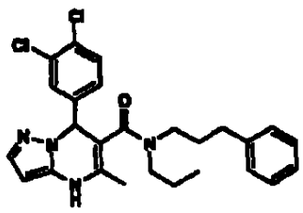
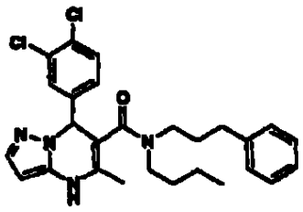
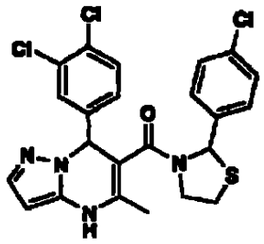
350		7-(3,4-Dıcloro-fenıl)-4,7-dıhıdro-5-metıl-N-(3-fenılpropıl)-N-propılpırazolo[1,5-a]pırımıdın-6-carboxamıda	483
351		N-Butıl-7-(3,4-dıclorofenıl)-4,7-dıhıdro-5-metıl-N-(3-fenılpropıl) pırazolo[1,5-a]pirımıdına-6-carboxamıda	497
352		2-(4-clorofenıl)-3-[[7-(3,4-dıcloro-fenıl)-4,7-dıhıdro-5-metıl-pırazolo[1,5-a]pırımıdın-6-ıl] carbonıl]tıazolıdına	505

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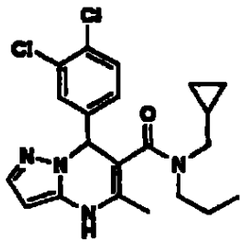
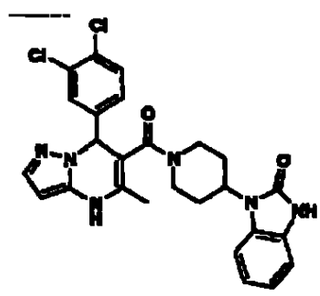
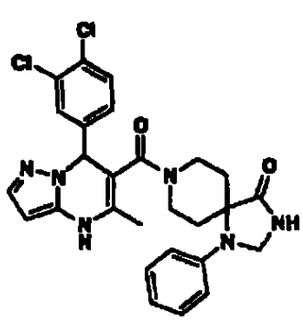
1070

353		N-(ciclopropil-metil)-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-propilpirazolo[1,5-a]pirimidin-6-carboxamida	419
354		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il] carbonil]-4-(2,3-dihidro-2-oxo-1H-bencimidazol-1-il)piperidina	523
355		8-[[7-(2,3-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1-fenil-1,3,8-triazaspiro[4 5] decan-4-ona	537

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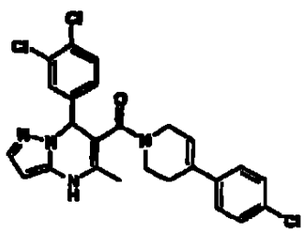
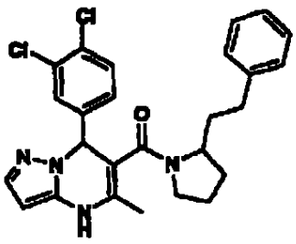
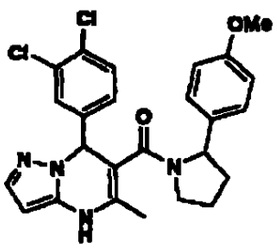
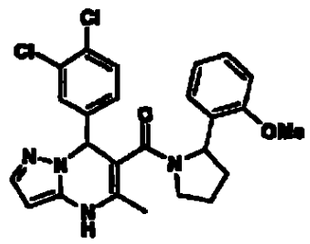
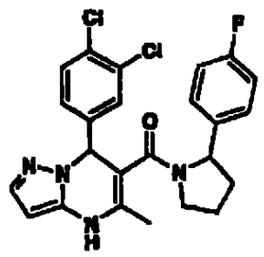
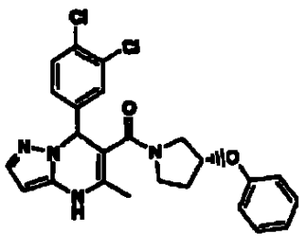
356		4-(4-clorofenil)-1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-1,2,3,6-tetrahidropiridina	499
357		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(2-feniletil) pirrolidina	481
358		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(4-metoxifenil) pirrolidina	483

359		1-[[7-(3,4-Dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(2-metoxifenil) pirrolidona	483
360		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazol[1,5-a]pirimidin-6-il]carbonil]-2-(4-fluorofenil) pirrolidina	471
361		(3R)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-3-fenoxipirrolidina	469

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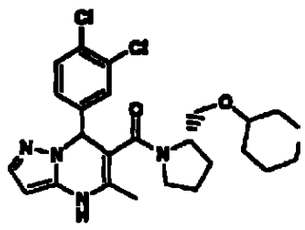
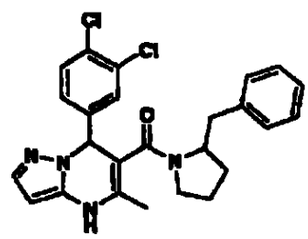
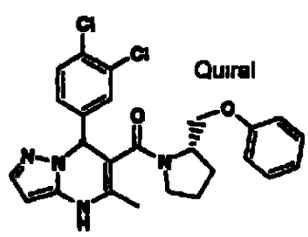
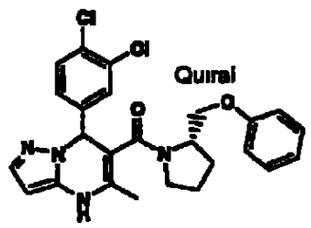
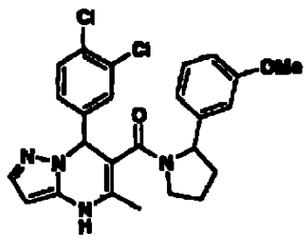
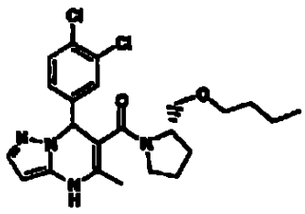
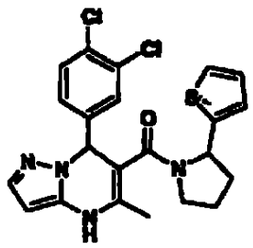
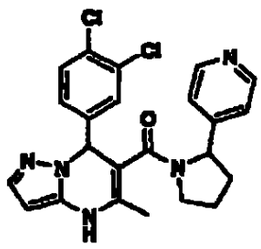
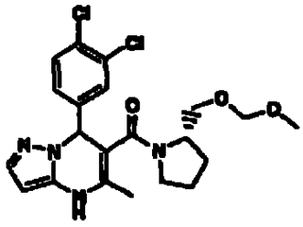
1073

362		(2S)-2-[(ciclo-hexiloxi)metil]-1-[[7-(3,4-Dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]pirrolidina	489
363		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il] carbonil]-2-(fenil-metil)pirrolidina	467
364		(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il] carbonil]-2-(fenoxi-metil)pirrolidina, diastereómero A	483

365		(2S)-1-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il] carbonil]-2-(fenoxi-metil)pirrolidina, Diastereómero B	483
366		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(3-metoxifenil) pirrolidina	483
367		(2S)-2-(butoxi-metil-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]pirro-lidina	463

368		1-[[7-(3,4-Dıcloro-fenıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]-2-(2-tıenıl)pırrolıdına	459
369		1-[[7-(3,4-dıcloro-fenıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdın-6-ıl] carbonıl]-2-(4-pırıdınıl) pırrolıdına	454
370		(2S)-1-[[7-(3,4-dıclorofenıl)-4,7-dıhıdro-5-metıl-pırazolo[1,5-a] pırımıdın-6-ıl] carbonıl]-2-[(metoxımetoxı)-metıl]pırrolıdına	451

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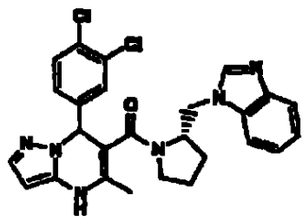
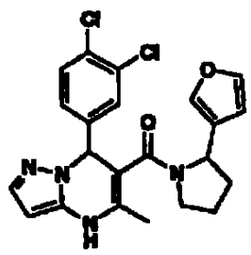
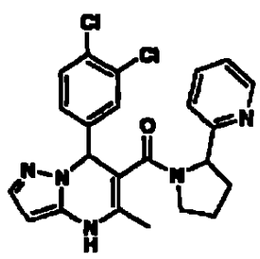
371		(2S)-2-[(1H-Bencımıdazol-1-ılmetıl)-[[7-(3,4-Dıclorofenıl)-4,7-dıhıdro-5-metıl-pırazolo[1,5-a] pırımıdın-6-ıl] carbonıl]pırrolıdına	507
372		1-[[7-(3,4-dıcloro-fenil)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]-2-(3-furanıl)pırrolıdına	443
373		1-[[7-(3,4-dıcloro-fenıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]-2-(2-pırıdınıl) pırrolıdına	454

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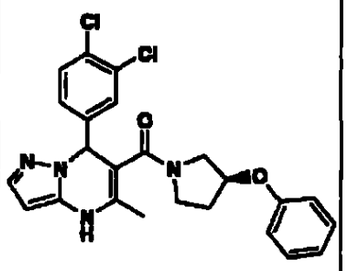
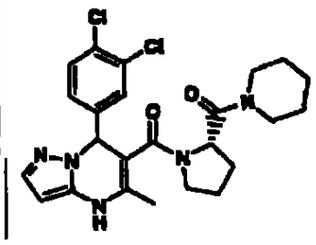
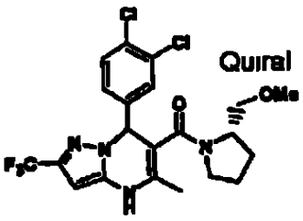
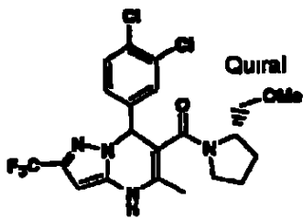
1077

374		(3S)-1-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-3-fenoxipirrolidina	469
375		(3S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-3-fenoxipirrolidina	488
376		(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil) pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoxi-metil)pirrolidina, enantiómero A	489

377		(2S)-1-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)-pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina enatiómero B	489

Ejemplo 378

1-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-L-prolina

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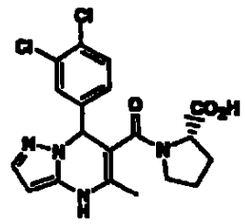
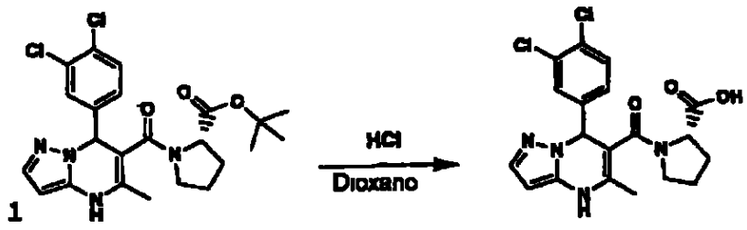


Método



1

Compuesto 1 El compuesto 1 (el compuesto del ejemplo 252) se preparó en una manera similar a aquella descrita en el ejemplo 170

Compuesto del titulo Se agregó ácido clorhídrico (5 mL, 4M en Dioxano) al compuesto 1 (0 05 g, 0 1 mmol) La mezcla resultante se agitó a temperatura ambiente Después de 3 horas la mezcla se concentro in vacuo El análisis LC/MS del residuo indicó que permaneció el material iniciador Se agregó acido clorhídrico adicional (5 mL, 4M en dioxano) La mezcla resultante

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se agitó a temperatura ambiente por 7 horas El análisis TLC indicó que el compuesto 1 se consumió La mezcla se concentró in vacuo El residuo se purificó por HPLC preparativa en fase inversa para dar el compuesto del titulo como una mezcla de diastereómeros El LC/MS indicó que el compuesto es todavía impuro (50% puro) LC/MS de fase inversa YMC S5 ODS 4 6 x 50 mm balistica, detección de UV a 220 λ, gradiente 4 min , Solvente B/A al 0-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con con TFA al 0 1%), 4 mL/min Diastereómero A Rt = 3 34, Diastereómero B Rt = 3 49 min MS (M+H 421) El producto se trituro con diclorometano para dar 0 014 g (rendimiento al 32%) del compuesto del titulo (85% puro por HPLC) LC/MS de fase inversa YMC S5 4 6 x 50 mm combiscreen, detección de UV a 220 λ, gradiente 4 min, Solvente B/A al 0-100% (Solvente A MeOH/H_2O al 10% con H_3PO_4 al 0 2%, Solvente B MeOH/H_2O al 90% con H_3PO_4 al 0 2%) 4 mL/min Diastereómero A Rt = 2 82, Diastereómero B Rt = 2 97 min

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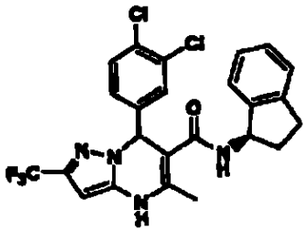
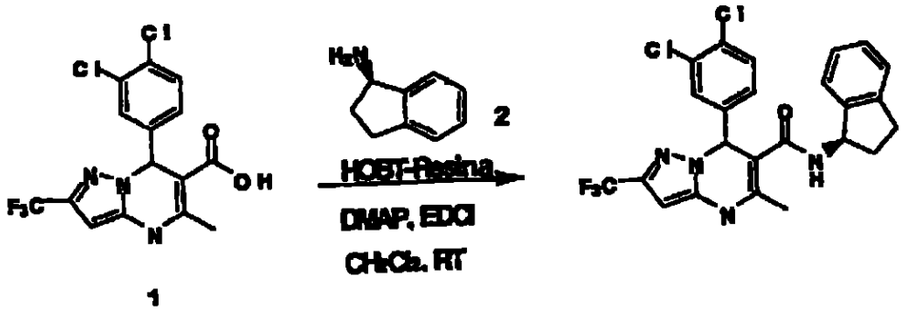
Ejemplo 379

7-(3,4-Diclorofenil)-4,7-dihidro-N-[(1R)-2,3-dihidro-1H-inden-1-il]-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-carboxamida



Método



1

Compuesto 1 El compuesto 1 se preparó como se describe en el Ejemplo 17

Compuesto del título A una suspensión de resina HOBt soportada con poliestireno (NovaBiochem, > 1 2 mmol/g, 50 mg, 1 0 eq) en CH_2Cl_2 anhidro (1 0 mL) se agregó el compuesto 1 (47 mg, 2 0 eq), EDCI (23 mg, 2 0 eq) y DMPA (0 7 mg, 0 1 eq) La suspensión se sacudio vigorosamente usando un VORTEX-GENIE2 por 1

hora El solvente entonces se drenó y la resina se lavó secuencialmente con DMF (3x2 mL), THF (3x2 mL) y CH_2Cl_2 (3x2 mL) con agitación vigorosa La resina se resuspendió en CH_2Cl_2 (1 mL) y a la cuál se agregó (R)-(-)-Aminoidano 2 (0 006 mL, 0 8 eq) La mezcla se sacudió por 2 horas El solvente se drenó y la resina se lavó con CH_2Cl_2 (3x1 mL) con agitación vigorosa Todas las soluciones lavadas se combinaron y el solvente se removió bajo presión reducida El residuo se purificó a través de un cartucho del gel de sílice eluido con EtOAc al 100% para dar el compuesto del titulo como un sólido blanco LC/MS de fase inversa Columna Ballistica YMC S5 ODS 4 6 x 50 mm, detección de UV a 220 λ, gradiente 4 min , Solvente B/A al 0-100% (Solvente A MeOH/H_2O al 10% con H_3PO_4 al 0 2%, Solvente B MeOH/H_2O al 90% con H_3PO_4 al 0 2%), 4 mL/min Rt = 2 96 min, (Diastereómero, puro al 96%) MS (M+H) 507)

Ejemplos 380-391

Los compuestos de los ejemplos 380-391, mostrados en la tabla proporcionada abajo, se prepararon de una manera similar a aquella descrita en el ejemplo 379

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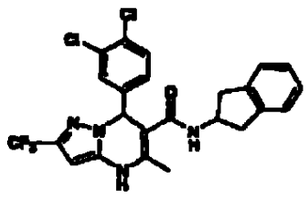
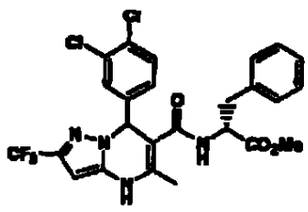
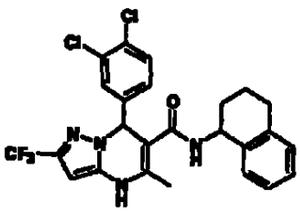
Ejemplo	Estructura	Nombre	(M+H)
380		7-(3,4-Diclorofenil)-N-(2,3-dihidro-1H-inden-2-il)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-carboxamida	507
381		Ester metílico N-[[7-(3,4-Dicloro-fenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-D-fenilalanina	553
382		7-(3,4-Dicloro-fenil)-4,7-dihidro-5-metil-N-(1,2,3,4-tetrahidro-1-naftalenil)-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-carboxamida	521

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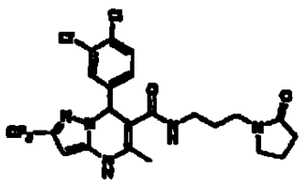
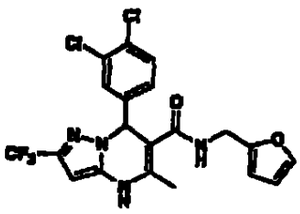
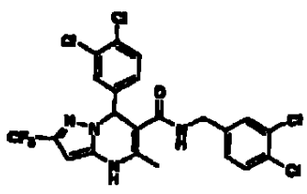
p84

383		7-(3,4-Dıcloro-fenıl)-4,7-dihıdro-5-metıl-N-[3-(2-oxo-1-pırrolıdınıl)-propıl]-2-(trı-fluorometıl)pırazolo [1,5-a]pırımıdın-6-carboxamıda	516
384		7-(3,4-Dıcloro-fenıl)-N-(2-furanılmetıl-4,7-dıhıdro-5-metıl-2-(trıfluorometıl) pırazolo[1,5-a] pırımıdın-6-carboxamıda	471
385		7-(3,4-Dıcloro-fenıl)-N-[(3,4-dıclorofenıl)metıl]-4,7-dıhıdro-5-metıl-2-(trıfluorometıl)-pırazolo[1,5-a]pırı-mıdın-6-carboxamıda	550

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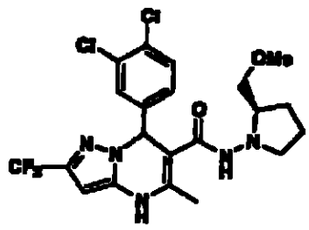
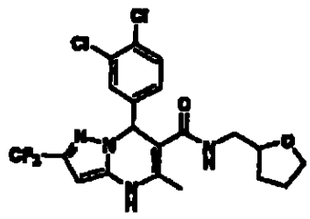
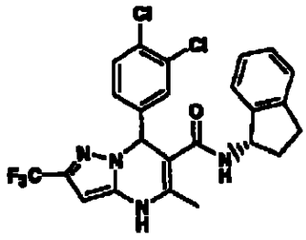
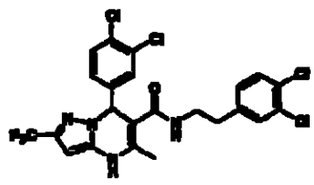
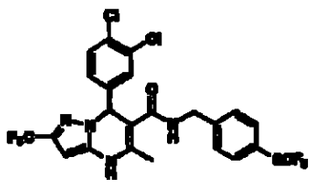
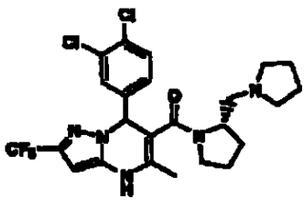
1061

386		7-(3,4-Dıcloro-fenıl)-4,7-dıhıdro-N-[(2R)-2-(metoxı-metıl)-1-pırrolı-dın]-5-metıl-2-(trı-fluorometıl)-pırazolo[1,5-a] pırımıdın-6-carboxamıda	504
387		7-(3,4-Dıcloro-fenıl)-4,7-dıhıdro-5-metıl-N-[(tetra-hıdro-2-furanıl)-metıl]-2-(trıfluoro-metıl)pırazolo[1,5-a]pırımıdın-6-carboxamıda	475
388		7-(3,4-Dıcloro-fenıl)-4,7-dıhıdro-N-[(1S)-2,3-dıhıdro-1H-ınden-1-ıl]-5-metıl-2-(trıfluoro-metıl)pırazolo[1,5-a]pırımıdın-6-carboxamıda	507

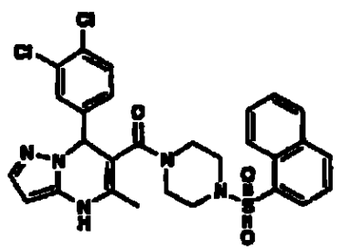
389		7-(3,4-Dıcloro-fenıl)-N-[2-(3,4-dıclorofenıl)etıl]-4,7-dıhıdro-5-metıl-2-(trıfluorometıl) pırazolo[1,5-a] pırımıdın-6-carboxamıda	564
390		7-(3,4-Dıcloro-fenıl)-4,7-dıhıdro-5-metıl-2-(trıfluoro metıl)-N-[[4-[(trıfluorometıl)-tıo]fenıl]metıl] pırazolo[1,5-a] pırımıdın-6-carboxamıda	581

1063 p887

391		(2S)-1-[[7-(3,4-Diclorofenil)-4,7dihidro-5-metil-2-(trifluorometil) pirazolo[1,5-a] pirimidin-6-il] carbonil]-2-(1-pirrolidinilmetil)-pirrolidina	666

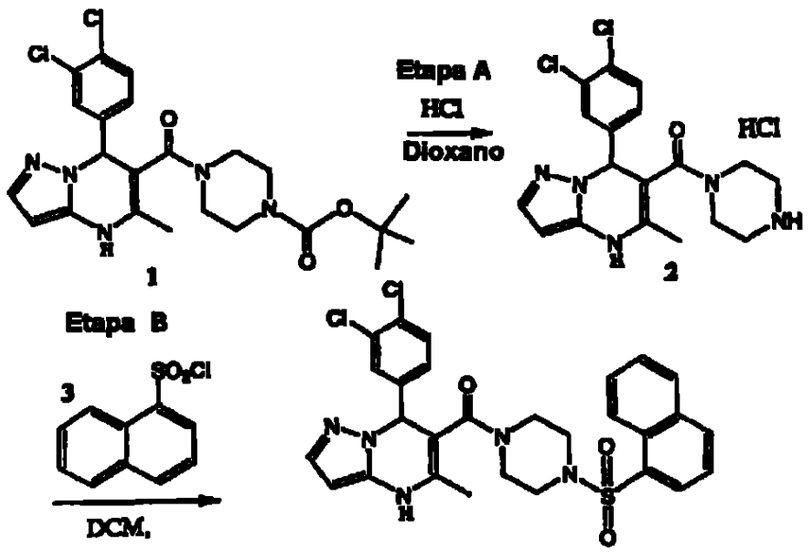
Ejemplo 392

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(1-naftalenilsulfonil)piperazina



1064,188

Método



Compuesto 1 El compuesto 1 (el compuesto del ejemplo 60) se preparó en una manera similar a aquella descrita en el ejemplo 18, del método 2

Etapa A Se agregó HCl (4M en dioxano) a un compuesto solido 1 (0 53 g, 1 1 mmol) Un precipitado gomoso se forma inmediatamente Se agrega diclorometano, el precipitado gomoso permanece El solvente se decantó y el residuo se trituro con acetato de etilo (3X), se concentro para dar 0 63 g (contenido de dioxano residual al 130%) de la sal de clorhidrato del

1065/1589

compuesto 2 como un polvo amarillo ligero LC/MS de fase inversa Columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección de UV a 220 λ, gradiente 4 min , Solvente B/A al 40-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt = 0 57, (92% puro) MS (M+H) 392) El compuesto 2 se usó sin purificación

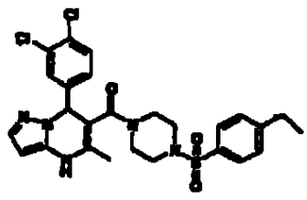
Etapa B El compuesto 2 (0 077 g, 0 18 mmol) y el compuesto 3 (0 049 g, 0 22 mmol) se suspendieron en diclorometano (1 mL) Se agrego trietilamina (0 05 mL, 0 36 mmol) Resultando una solución clara Después de 30 minutos el TLC indicó el consumo del material iniciador La mezcla se cargó directamente en un cartucho Wordlwide Monitoring CLEAN-UP (CUSIL12M6, silice) el cual ha sido equilibrado con hexanos al 100% Eluyendose con hexanos al 100% (40 mL), seguido por acetato de etilo/hexanos al 50% (40 mL) y acetato de etilo al 100% (40 mL) Las fracciones más puras (analisis TLC) se combinaron para dar 0 068 g (rendimiento al 65%) del compuesto del titulo como un solido blanco LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección de UV a 220 λ, gradiente 4 min , Solvente B/A al 40-100% (Solvente A MeOH/H_2O al 10% con TFA

1066 1090

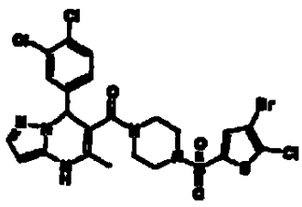
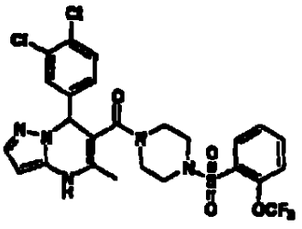
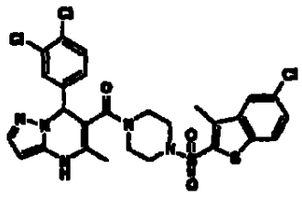
al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/mın Rt = 3 46 mın, (90% puro) MS (M+H) 582) HMR ($CDCl_3$, 400 HMz) 8 60 (1H, d, J = 8), 8 05 (2H, m), 7 95 (1H, m), 7 62 (4H, m), 7 35 (1H, d, J = 2 Hz), 7 17 (1H, d, J = 8 Hz), 7 06 (1H, d, J = 2 Hz), 6 81 (1H, d, J = 6 Hz), 6 17 (1H, m), 5 54 (1H, d, J = 2 Hz), 3 23 (8H, m), 1 86 (3H, s)

Ejemplos 393-396

Los compuestos de los Ejemplos 393-396, mostrados en la tabla proporcıonada abajo, se prepararon en una manera sımılar a aquella descrıta en el Ejemplo 392

Ejemplo	Estructura	Nombre	(M+H)
393		1-[[7-(3,4-Dıcloro-fenıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]-4-[(4-etılfenıl)sulfonıl]-pıperazına	560

1067, 1091

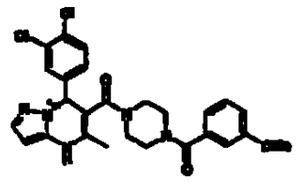
394		1-[(4-bromo-5-cloro-2-tienil)sulfonil]-4-[[7-(3,4-Dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-piperazina	651
395		1-[[7-(3,4-Dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-[[2-(trifluorometoxi)-fenil]sulfonil] piperazina	616
396		1-[(5-cloro-3-metil-benzo[b]tiofen-2-il)sulfonil]-4-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil] piperazina	637

1092

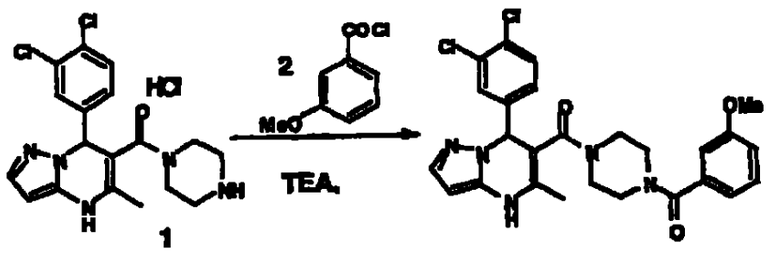
1066

Ejemplo 397

1-[[7-(3,4-Diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-[(3-metoxifenil)carbonil]piperazina



Método



Compuesto 1 El compuesto 1 se preparo como se describe en la Etapa A del Ejemplo 392

Compuesto del titulo El compuesto 1 (0 062 g, 0 15 mmol) y el compuesto 2 (0 025 mL, 0 17 mmol) se suspendieron en diclorometano (1 mL) Se agregó trietilamina (0 040, 0 29 mmol) Resulto una solución clara Después de 30 minutos el TLC indicó el consumo

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1093

del material iniciador La mezcla se cargo directamente en un cartucho Worldwide Monitoring CLEAN-UP (CUSIL12M6) el cuál ha sido equilibrado con hexanos al 100% Eluyéndose con hexanos al 100% (40 mL), seguido por acetato de etilo/hexanos al 50% (100 mL) y acetato de etilo al 100% (100 mL) Las fracciones mas puras (analisis TLC) se combinaron para dar 0 022 g (rendimiento al 29%) del compuesto del titulo como un solido blanco LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, deteccion de UV a 220 λ, gradiente 4 min , Solvente B/A al 40-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt = 2 69 min, (90% puro) MS (M+H) 526)

Ejemplos 398 y 399

Los compuestos de los ejemplos 398 y 399, mostrados en la tabla proporcionada abajo, se prepararon en una manera similar a aquella descrita en el Ejemplo 397

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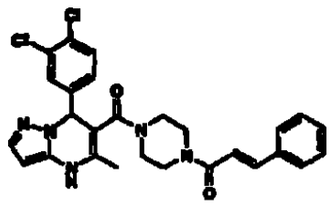
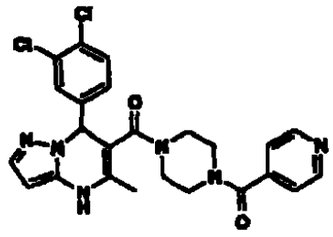
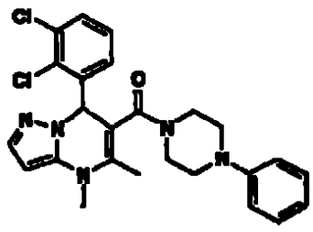
1070

Ejemplo	Estructura	Nombre	(M+H)
398		1-[[7-(3,4-Dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(1-oxo-3-fenil-2-propenil)-piperazina	522
399		1-[[7-(3,4-Dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-piridinilcarbonil) piperazina	497

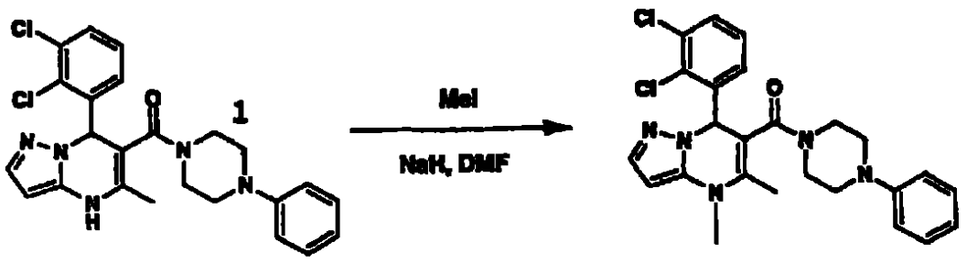
Ejemplo 400

1-[[7-(2,3-Diclorofenil)-4,7-dihidro-4,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina

1095
1077



Método



Compuesto 1 El compuesto 1 se preparo como se describe en el Ejemplo 18

Compuesto del titulo El compuesto 1 (0 08 g, 0 17 mmol) se disolvió en dimetilformamida (1 0 mL) Se agrego NaH (0 005 g, 0 22 mmol, en aceite al 60%) y la mezcla se agitó por 5 minutos Se agregó yodometano (0 012 mL, 0 18 mmol) Cuando el análisis TLC (metanol/diclorometano al 5%) indicó el consumo

1096
1072

del material iniciador, la reacción se enfrio rápidamente con agua, se diluyó con acetato de etilo, se transfirió a un embudo separador, se lavó con agua saturada y salmuera, se seco sobre sulfato de sodio anhidro y se concentro El residuo se purificó por cromatografía de gel de silice eluido con diclorometano al 100% seguido por metanol/diclorometano al 3% para proporcionar 0 06 g (al 75%) del compuesto del titulo como un aceite ámbar LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, detection de UV a 220 λ, gradiente 4 min , Solvente B/A al 40-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con con TFA al 0 1%), 4 mL/min Rt = 2 99 min, (96% puro) MS (M+H 482)

Ejemplos 401-406

Los compuestos de los Ejemplos 401-406, mostrados en la tabla proporcionada abajo, se preparan en una manera similar a aquella descrita en el Ejemplo 400

La resolución de HPLC del Ejemplo 403, columna Chiralpak AD (50 x 500 mm), elución con isopropanol/hexanos al 35% conteniendo trietilamina

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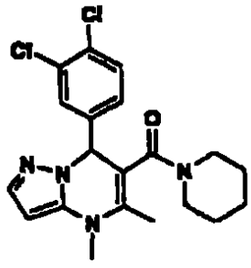
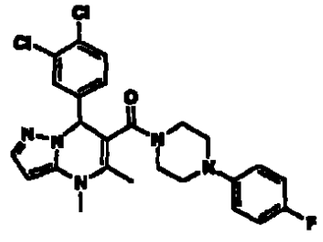
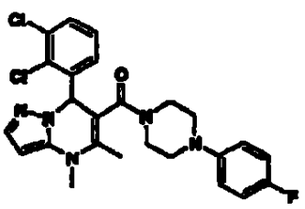
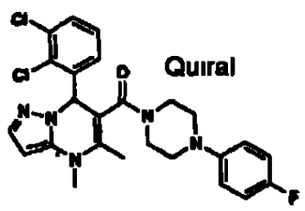
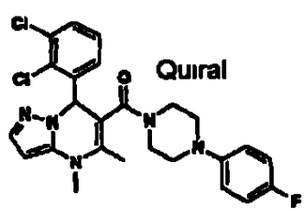
1073

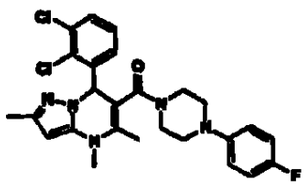
la 0 1% a 50 mL/mın), la detección UV a 254 λ proporcıona enantıómeros A (Ejemplo 405) y B (Ejemplo 404) Columna Chıralpak AD (4 6 x 250 mm) elución cor ısopropanol/hexanos al 30% contenıendo trıetılamına al 0 1% a 1 mL/mın), detección UV a 254 λ, enetıómero A Rt = 14 4 mın, > 99% ee Enantıómero B Rt = 28 7 mın, > 99% ee

Ejemplo	Estructura	Nombre	(M+H)
401		1-[[7-(3,4-Dıcloro-fenıl)-4,7-dıhıdro-4,5-dımetılpırazolo-[1,5-a]pırımıdın-6-ıl]carbonıl]pıperıdına	405
402		1-[[7-(3,4-Dıcloro-fenıl)-4,7-dıhıdro-4,5-dımetılpırazolo [1,5-a]pırımıdın-6-ıl]carbonıl]-4-(4-fluorofenıl) pıperazına	500

1074 1098

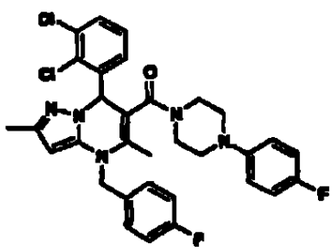
403		1-{[7-(2,3-Dicloro-fenil)-4,7-dihidro-4,5-dimetilpirazolo-[1,5-a]pirimidin-6-il]carbonil}-4-(4-fluorofenil) piperazina	500
404		1-[[7-(2,3-Dicloro-fenil)-4,7-dihidro-4,5-dimetilpirazolo-[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina, enantiómero B	500
405		1-[[7-(2,3-Dicloro-fenil)-4,7-dihidro-4,5-dimetilpirazol-(1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina, enantiómero A	500

1075 1099

406		1-[[7-(2,3-Dicloro-fenil)-4,7-dihidro-2,4,5-trimetilpira-zolo-[1,5-a]pirimi-din-6-il]carbonil]-4-(4-fluorofenil) piperazina	514

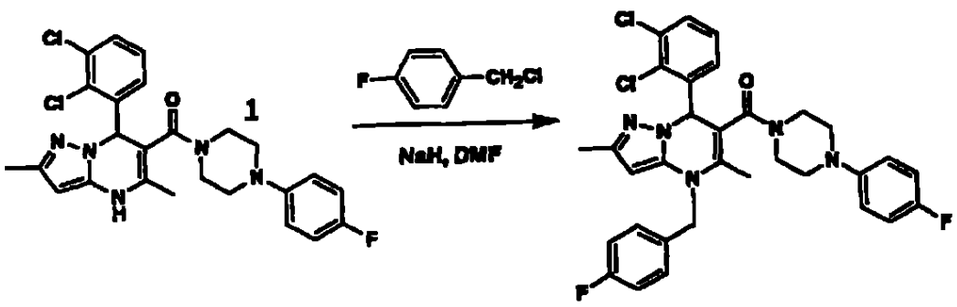
Ejemplo 407

1-[[7-(2,3-Diclorofenil)-4-[(4-fluorofenil)metil]-4,7dihidro-2,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina



1076 1100

Método



Compuesto 1 El compuesto 1 se preparó en una manera similar a aquella descrita en el Ejemplo 18, del método 2

Compuesto del titulo El compuesto 1 (0 10 g, 0 21 mmol) se disolvió en dimetilformamida (1 0 mL), NaH (0 007 g, 0 27 mmol, 60 en aceite) se agrego y la mezcla se agito por 5 minutos Se agregó cloruro de 4-fluorobencilo (0 028 mL, 0 23 mmol) Cuando el analisis TLC (metanol/diclorometano al 5%) indico el consumo del material iniciador, la reaccion se enfrió con agua, se diluyó con acetato de etilo, Se transfirió a un embudo separador, se lavó con agua saturada y salmuera, se secó sobre sulfato de sodio

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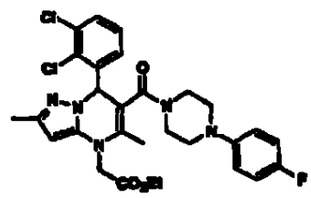
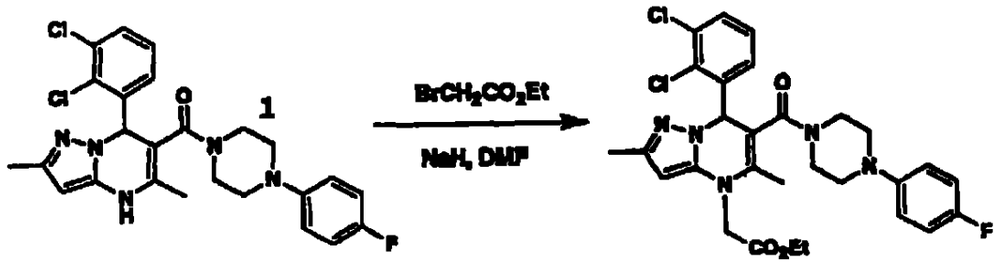
anhidro y se concentro El residuo se purificó por cromatografia en gel de sílice, elución con diclorometano al 100% seguido por metanol/diclorometano al 3% para proporcionar 0 09 g (al 69%) del compuesto del titulo como un aceite ambar LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, deteccion de UV a 220 λ, gradiente 4 min , Solvente B/A al 40-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H O al 90% con con TFA al 0 1%), 4 mL/min Rt = 3 20 min, (93% puro) MS (M+H 608)

Ejemplo 408

Ester etílico del ácido 7-(2,3-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-2,5-dimetilpirazclo[1,5-a]pirimidina-4-(7H)-acético



Metodo



Compuesto 1 El compuesto 1 se preparó en una manera similar a aquella descrita en el Ejemplo 18, del metodo 2

Compuesto del titulo El compuesto 1 (0 10 g, 0 21 mmol) se disolvio en dimetilformamida (1 0 mL) Se agrego NaH (0 006 g, 0 24 mmol, 60% en aceite) y la mezcla se agitó por 5 minutos Se agrego bromoacetato de etilo (0 029 mL, 0 26 mmol) Cuando el análisis TLC (metanol/diclorometano al 5%) indicó el consumo del material iniciador, la reacción se enfrio rapidamente con agua, se diluyó con acetato de etilo, se transfirió a un embudo separador, se lavó con agua

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saturada y salmuera, se secó sobre sulfato de sodio anhidro y se concentró El residuo se purifico por cromatografía en gel de sílice elución con diclorometano al 100% seguido por metanol/diclorometano al 3% para proporcionar 0 086 g (al 74%) del compuesto del titulo como un vidrio amarillo LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, deteccion de UV a 220 λ, gradiente 4 min , Solvente B/A al 40-100% (Solvente A MeOH/H_O al 10% con TFA al 0 1%, Solvente B MeOH/H_O al 90% con con TFA al 0 1%), 4 mL/min Rt = 3 22 min, (97% puro) MS (M+H 586)

Ejemplo 409

7-(2,3-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-N,N,2,5-tetrametilpirazolo[1,5-a]pirimidina-4(7H)-acetamida

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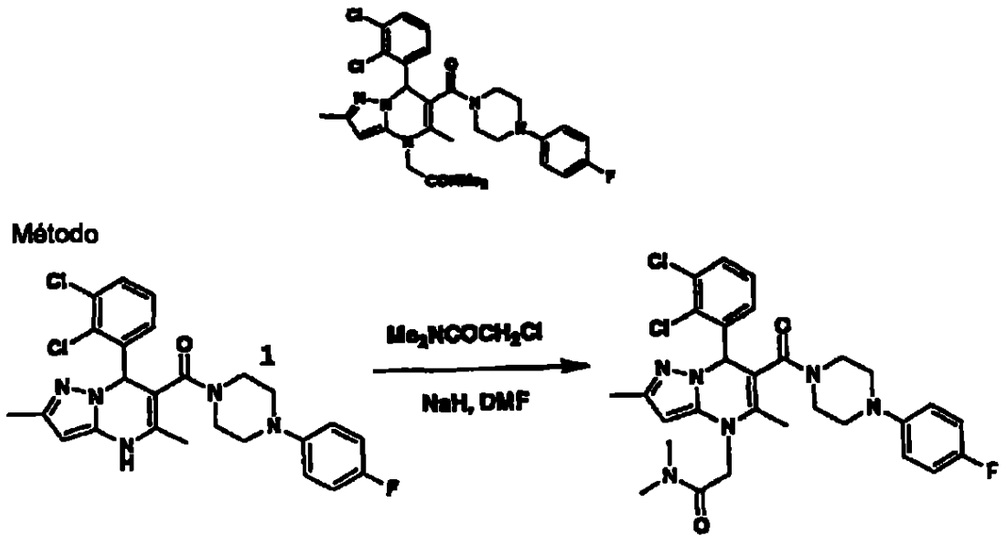

Compuesto 1 El compuesto 1 se preparo en una manera similar a aquella descrita en el Ejemplo 18, del Método 2

Compuesto del titulo El compuesto 1 (0 08 g, 0 16 mmol) se disolvio en dimetilformamida (0 8 mL) Se agrego NaH (0 005 g, 0 19 mmol, 60% en aceite) y la mezcla se agito por 5 minutos Se agregó 2-cloro-N,N-dimetilacetamida (0 021 mL, 0 21 mmol) Cuando el analisis TLC (metanol/diclorometano al 5%) indico el consumo del material iniciador, la reacción se enfrió rapidamente con agua, se diluyo con acetato de etilo, se transfirió a un embudo separador, se lavó con agua y salmuera saturada, se secó sobre sulfato de sodio

anhídro y se concentró El residuo se purificó por cromatografía en gel de sílice elución con diclorometano al 100% seguido por metanol/diclorometano al 3% para proporcionar 0 058 g (al 62%) del compuesto del título como un aceite amarillo LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección de UV a 220 λ, gradiente 4 min , Solvente B/A al 40-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con con TFA al 0 1%), 4 mL/min Rt = 2 63 min, (93% puro) MS (M+H 585)

Ejemplo 410

1-[[7-(2,3-Diclorofenil)-4-[2-(dimetilamino)etil]-4,7-dihidro-2,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina

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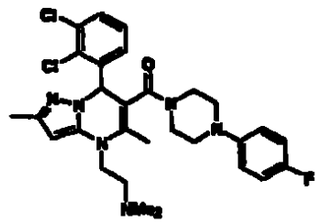
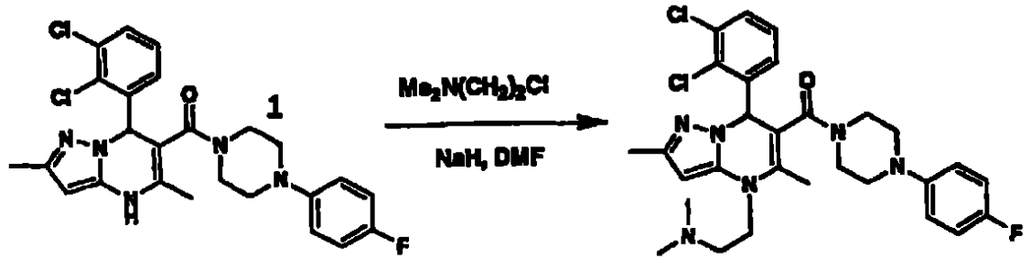


Método



Compuesto 1 El compuesto 1 se preparó en una manera similar a aquella descrita en el Ejemplo 18, del método 2

Compuesto del titulo El compuesto 1 (0 11 g, 0 21 mmol) se disolvio en dimetilformamida (1 0 mL) Se agregó hidruro de sodio (0 054 g, 0 47 mmol, 60% en aceite) y la mezcla se agito por 5 minutos Se agregó clorhidrato de 1-cloro-2-dimetilaminoetano (0 40 g, 0 27 mmol) Despues de 25 minutos la reaccion se enfrió rapidamente con agua, se diluyo con acetato de

etilo, transferido a un embudo separador, se lavó con agua saturada y salmuera, se secó sobre sulfato de sodio anhídro y se concentró El análisis LC/MS del residuo indicó que la mayoría del material iniciador no reaccionó El residuo se disolvio en dimetilformamida (1 0 mL), se agregó hidruro de sodio (0 10 g, 4 2 mmol) y la mezcla se agitó por 5 minutos Se agregó clorhidrato de 1-cloro-2-dimetilaminoetano (0 15 g, 1 05 mmol) Cuando el análisis TLC (metanol/diclorometano al 5%) indico el consumo del material iniciador, la reacción se enfrió rapidamente con agua, se diluyó con acetato de etilo, transferido a un embudo separador, se lavó con agua saturada y salmuera, se secó sobre sulfato de sodio anhídro y se concentró El residuo se purificó por cromatografía en gel de sílice eluido con diclorometano al 100% seguido por metanol/diclorometano al 3% para proporcionar 0 030 g (al 25%) del compuesto del titulo como un vidrio amarillo LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección de UV a 220 λ, gradiente 4 min , Solvente B/A al 40-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H O al 90% con TFA al 0 1%), 4 mL/min Rt = 1 72 min, (92% puro) MS (M+H 571)

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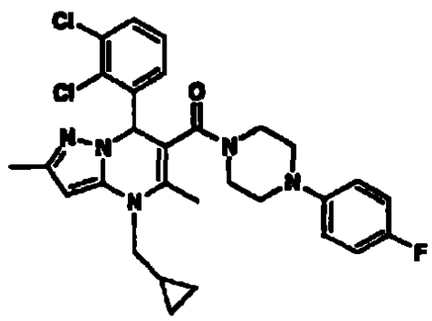
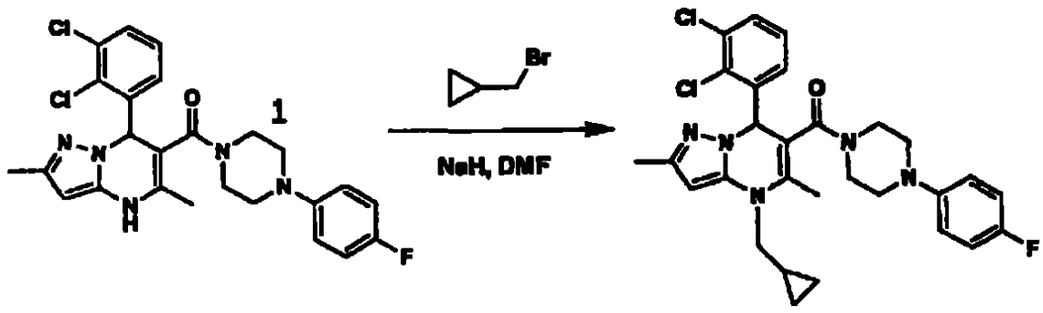
Ejemplo 411

1-[[4-(Ciclopropilmetil)-7-(2,3-diclorofenil)-4,7-dihidro-2,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina



Metodo



Compuesto 1 El compuesto 1 se preparó en una manera similar a aquella descrita en el Ejemplo 18, del Método 2

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Compuesto del titul El compuesto 1 (0 11 g, 0 21 mmol) se disolvió en dimetilformamida (1 0 mL) Se agregó hidruro de sodio (0 006 g, 0 25 mmol, al 60% en aceite) y la mezcla se agito por 5 minutos Se agregó (Bromometil)ciclopropano (0 0251 mL, 0 27 mmol) Cuando al análisis TLC (metanol/diclorometano al 5%) indicó el consumo del material iniciador, la reacción se enfrió rápidamente con agua, se diluyo con acetato de etilo, se transfirió a un embudo separador, se lavo con agua saturada y salmuera, se secó sobre sulfato de sodio anhidro y se concentró El residuo se purificó por cromatografía en gel de silice elucion con diclorometano al 100% seguido por metanol/diclorometano al 3% para proporcionar 0 104 g (al 89%) del compuesto del titulo como un vidrio amarillo LC/MS de fase inversa columna Ballistic iMC S5 ODS 4 6 x 50 mm, deteccion de UV a 220 λ, gradiente 4 min , Solvente B/A al 40-100% (Solvente A MeOH/H O al 10% con TFA al 0 1%, Solvente B MeOH/H O al 90% con TFA al 0 1%), 4 mL/min Rt = 2 99 min, (95· puro) MS (M+H 554)

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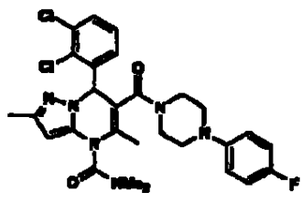
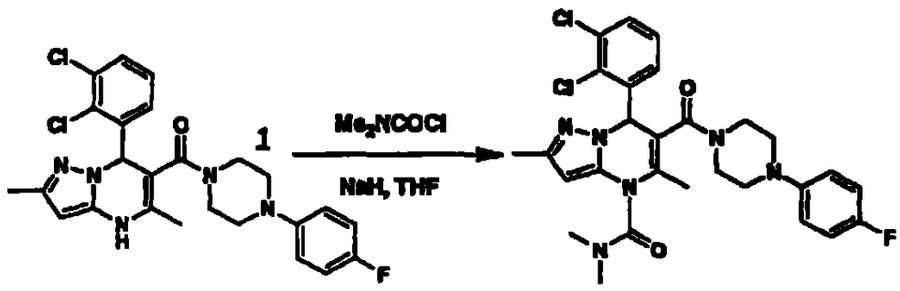
Ejemplo 412

7-(2,3-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-N,N,2,5-tetrametilpirazolo[1,5-a]pirimidina-4(7H)-carboxamida



Método



Compuesto 1 El compuesto 1 se preparo en una manera similar a aquella descrita en el Ejemplo 18, del Método 2

Compuesto del titulo El compuesto 1 (0 22 g, 0 44 mmol) se disolvio en tetrahidrofurano (3 0 mL) Se

agregó hidruro de sodio (0 106 g, 4 44 mmol, al 60% en aceite) y la mezcla se agitó por 5 minutos Se agregó cloruro de N,N-dimetilcarbamoil (0 12 mL, 1 33 mmol) La mezcla se agitó durante la noche El análisis TLC (metanol/diclorometano al 5%) indicó el consumo del material iniciador, la reaccion se enfrio rápidamente con agua, se diluyó con acetato de etilo, se transfirió a un embudo separador, se lavó con agua saturada y salmuera, se secó sobre sulfato de sodio anhidro y se concentró El residuo se purifico por cromatografia en gel de sílice elución con diclorometano al 100%, seguido por metanol/diclorometano al 3% para proporcionar 0 22 g (rendimiento del 87%) del compuesto del titulo El LC/MS indico que el compuesto es impuro El compuesto del titulo se purificó adicionalmente por cromatografia en gel de sílice, elución con acetato de etilo/hexanos al 10%, seguido por acetato de etilo/hexanos al 50% y acetato de etilo al 100% para proporcionar 0 118 g (rendimiento del 47%) del compuesto del titulo como un vidrio blanco LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección de UV a 220 λ, gradiente 4 min , Solvente B/A al 40-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H O al 90% con TFA

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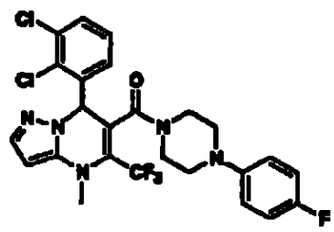
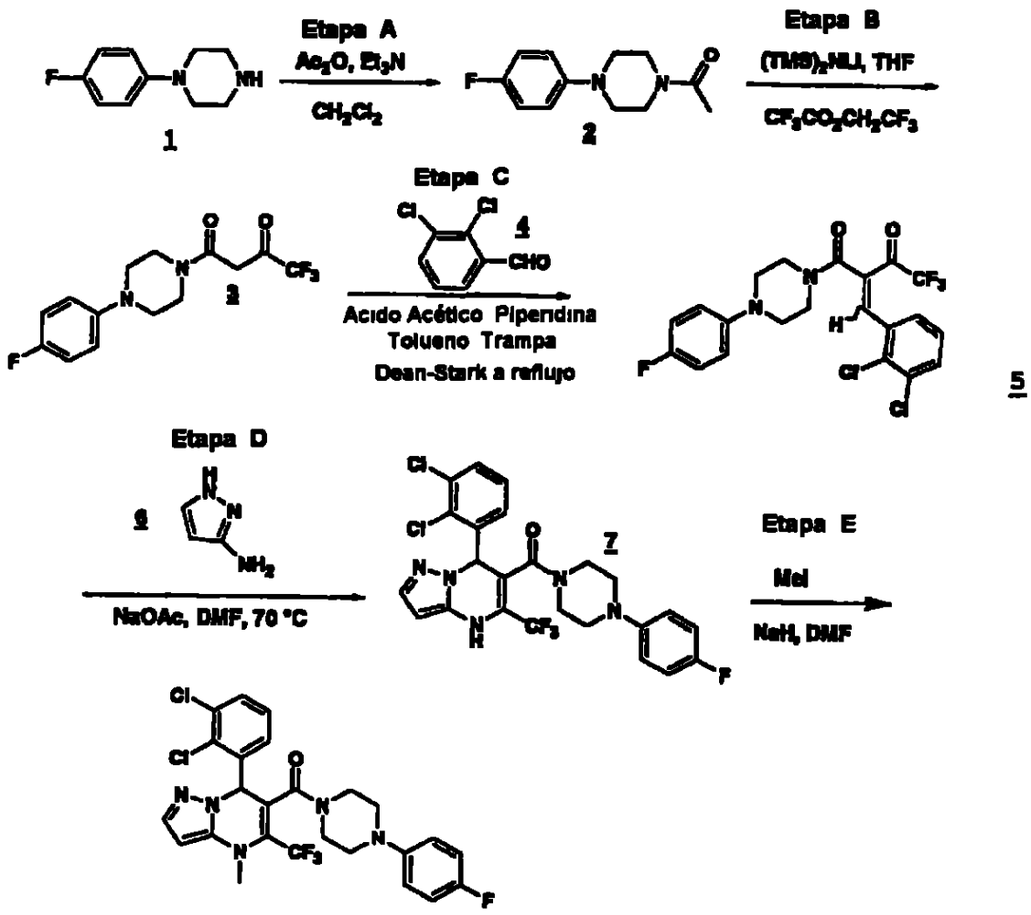
al 0 1%), 4 mL/min Rt = 2 45 min, (95% puro) MS (M+H 571)

Ejemplo 413

1-[[7-(2,3-diclorofenil)-4,7-dihidro-4-metil-5-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina



Método



Etapa A Se agrego en forma de gotas anhídrido acetico (0 77 mL, 8 14 mmol) a una solución de 4-(4-fluorofenil)piperazina 1 (1 17 g, 6 49 mmol) en diclorometano (10 mL) Después de 30 minutos el TLC indico que la reacción se completo La mezcla se transfirió a un embudo separador, se lavó con agua y

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salmuera, se secó sobre sulfato de sodio anhidro y se conentró para dar 1 28 g (rendimiento del 89%) del compuesto 2 como un aceite sólido LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección de UV a 220 λ, gradiente 4 min , Solvente B/A al 40-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt = 1 58 min, (92% puro) MS (M+H 223) HMR (CDCl , 400 MHz) 6 96 (2H, m), 6 89 (2H, m), 3 77 (2H, m), 3 62 (2H, m), 3 07 (4H, m), 2 14 (3H, s) El compuesto 2 se uso sin purificación adicional en la siguiente etapa

Etapa B Se agrego en forma de gotas hexametildisililazida de litio (6 1 mL, 6 1 mmol, 1M en tetrahidrofuran) a una solucion a -78° del compuesto 2 (1 22 g, 5 5 mmol) en terahidrofurano (25 mL) Despues de 40 minutos, se agregó trifluoroacetato de 2,2,2-trifluoroetilo (0 9 mL, 6 6 mmol) a la solución amarilla La reacción se tornó de amarilla a clara Despues de 10 minutos adicionales, el baño frió se removio y la mezcla se dejo calentar a temperatura ambiente Después de 30 minutos más, la reacción se enfrió rápidamente con cloruro de amonio saturado, se diluyó con acetato de etilo, se

transfirió a un embudo separador, se lavó con cloruro de amınıo saturado, agua y salmuera, se seco sobre sulfato de sodıo anhıdro y se concentró en suficıente gel de sílıce de manera que se obtuvo un polvo de flujo suave El polvo resultante se cargo en una columna de cromatografía preenvasada con gel de sılıce y acetato de etılo/hexanos al 30% La elución con acetato de etılo/hexanos al 30% dıo 0 998 g (rendımıento al 57%) del compuesto 3 como un sólıdo amarıllo LC/MS de fase ınversa columna Ballıstıc ıMC S5 ODS 4 6 x 50 mm, detección ae UV a 220 λ, gradıente 4 mın , Soıvente B/A al 40-100% (Solvente A MeOH/H_O al 10% con TFA al 0 1%, Solvente B MeOH/H O al 90% con TFA al 0 1%), 4 mL/mın Rt = 2 87 mın, (90% puro) MS (M+H 319) HMR (CDCl_, 400 MHz) (nota el compuesto exıste en la forma de enol) 7 00 (2H, m), 6 90 (2H, m), 5 80 (1H, s), 3 79 (4H, m), 3 13 (4H, m)

Etapa C El compuesto 3 y el compuesto 4 se condensaron como se describe en el Ejemplo 18 del método 2, etapa B, para proporcıonar el compuesto 5 El compuesto 5 se usó en el sıguıente paso sın purıfıcacıón adıcıonal

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Etapa D El compuesto 5 y el compuesto 6 se condensaron como se describe en el Ejemplo 18 del metodo 2, etapa C1, para proporcionar el compuesto 7 LC/MS de fase inversa del crudo 6 columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección de UV a 220 λ, gradiente 4 min , Solvente B/A al 0-100% (Solvente A MeOH/H O al 10% con TFA al 0 1%, Solvente B MeOH/H O al 90% con TFA al 0 1%), 4 mL/min Rt = 4 12 min, (58% puro) MS (M+H 540) El compuesto 7 se purificó por cromatografia en gel de sílice elucion con acetato de etilo/hexanos al 20-50%, seguido por recristalización de acetato de etilo/hexanos para dar 0 084 g (rendimiento al 6%) del compuesto 7 como un solido blanco LC de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección de UV a 220 λ, gradiente 4 min , Solvente B/A al 0-100% (Solvente A MeOH/H O al 10 con H PO al 0 2%, Solvente B MeOH/H O al 90 con H PO al 0 2%), 4 mL/min Rt = 4 15 min, (92% puro)

Etapa E El compuesto 7 (0 08 g, 0 14 mmol) se disolvio en dimetilformamida (1 0 mL) Se agregó NaH (0 005 g, 0 19 mmol, al 60% en aceite) y la mezcla se agito por 305 minutos Se agregó yodometano (0 010 mL, 0 16 mmol) La mezcla se agitó por 2 horas y

entonces se enfrió rápidamente con cloruro de amonio saturado, se diluyó con acetato de etilo, se transfirió a un embudo separador, se lavó con agua saturada y salmuera, se secó sobre sulfato de sodio anhidro y se concentró El residuo se purificó por preparativa HPLC de fase inversa columna Ballistic YMC S5 ODS 20 x 100 mm, deteccion de UV a 220 λ, gradiente 10 min , Solvente B/A al 30-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H O al 90% con TFA al 0 1%), 20 mL/min Rt = 10 6 min , para proporcionar 0 037 g (al 45%) del compuesto del titulo LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección de UV a 220 λ, gradiente 4 min , Solvente B/A al 0-100% (Solvente A MeOH/H O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt = 3 83 min MS (M+H 568) LC de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección de UV a 220 λ, gradiente 4 min , Solvente B/A al 0-100% (Solvente A MeOH/H_2O al 10% con H_3PO_4 al 0 2%, Solvente B MeOH/H_2O al 90% con H_3PO_4 al 0 2%), 4 mL/min Rt = 4 37 min , 89% puro

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Ejemplos 414-421

Los compuestos de los Ejemplos 414-421, mostrados en la tabla proporcionada abajo, se prepararon en una manera similar a aquella descrita en el Ejemplo 413

La resolución HPLC del Ejemplo 416, columna AD Chiralpak (50 X 500 mm), elución con isopropanol/hexanos al 50%, conteniendo trietilamina al 0 1% a 50 mL/min), detección UV a 254 λ, proporcionó A (Ejemplo 418) y B (Ejemplo 417) Columna AD Chiralpak (4 6 X 250 mm) elucion con isopropanol/hexanos al 50%, conteniendo trietilamina al 0 1 a 1 mL/min), deteccion UV a 254 λ, enantiómero A Rt = 14 4 min, al 89% ee Enantiómero B Rt = 28 7 min, al 87% ee

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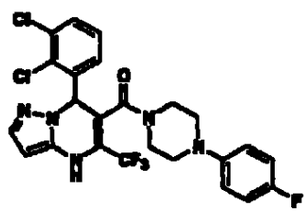
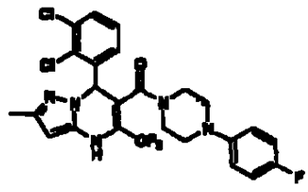
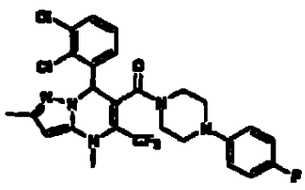
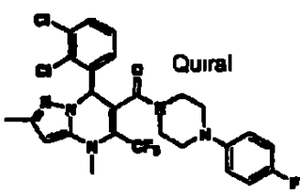
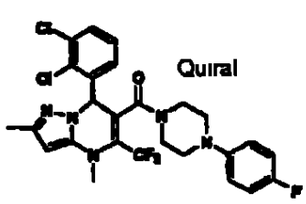
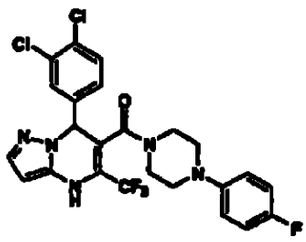
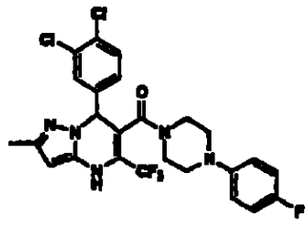
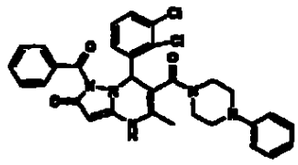
Ejemplo	Estructura	Nombre	(M+H)
414		1-[[7-(2,3-Dıcloro-fenıl)-4,7-dıhıdro-5-(trıfluorometıl) pırazolo-[1,5-a]pırımıdın-6-ıl]carbonıl]-4-(4-fluorofenıl) pıperazına	554
415		1-[[7-(2,3-Dıcloro-fenıl)-4,7-dıhıdro-2-metıl-5-(trıfluorometıl)-pırazolo[1,5-a] pırımıdın-6-ıl] carbonıl]-4-(4-fluorofenıl) pıperazına	554

416		1-[[7-(2,3-Dicloro-fenil)-4,7-dihidro-2,4-dimetil-5-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	568
417		1-[[7-(2,3-Dicloro-fenil)-4,7-dihidro-2,4-dimetil-5-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enantiomero B	568
418		1-[[7-(2,3-Dicloro-fenil)-4,7-dihidro-2,4-dimetil-5-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enantiomero A	568

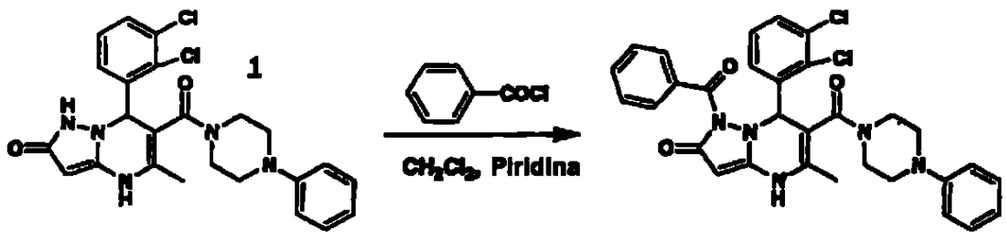
419		1-[[7-(3,4-Dicloro-fenil)-4,7-dihidro-5-(trifluorometil) pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	540
420		1-[[7-(3,4-Dicloro-fenil)-4,7-dihidro-2-metil-5-(tri-fluorometil)pirazolo [1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina	554

Ejemplo 421

1-[[1-Benzoil-7-(2,3-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina



Método



Compuesto 1 El compuesto 1 se preparó en una manera similar a aquella descrita en el ejemplo 18, del metodo 2

Compuesto del titulo Se agrego cloruro de benzoilo (0 007 mL, 0 06 mmol) y piridina (0 008 mL, 0 10 mmol) a 0°C a una solucion del compuesto 1 (0 08 g, 0 17 mmol) en diclorometano (5 mL) Después de 1 hora, el TLC indicó que la reacción se completo La reacción se enfrio rápidamente con metanol y se concentró El residuo se purifico por cromatografía en gel de sílice, elucion con acetato de etilo hexanos al 80 para proporcionar 0 024 g del compuesto del titulo (al 81%) como un solido blanco LC/MS de fase inversa columna Ballistic YMC S5 ODS

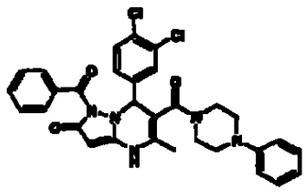
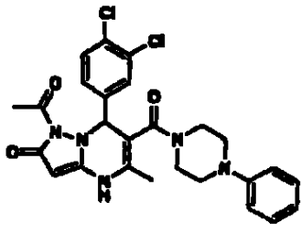
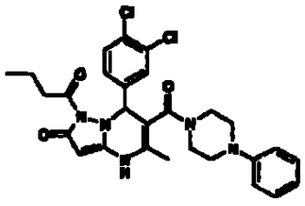
1095 123

4 6 x 50 mm, deteccion UV a 220 λ, gradiente 4 min Solvente B/A del 0-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt = 4 05, (86% puro) (M+H 588) HMR ($CDCl_3$, 400 MHz) 8 08 (1H, s), 8 06 (1H,s), 7 51 (1H, m), 7 37 (2H, t, J = 8 Hz), 7 28 (1H, m), 7 18 (2H, m), 7 08 (1H, m), 6 9-6 7 (3H, m), 6 45 (1H, bs), 5 60 (1H, bs), 4 15-2 8 (6H, m), 2 20 (1H, bs), 1 88 (3H, s), 1 45 (1H, bs)

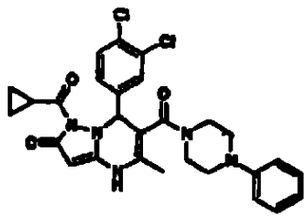
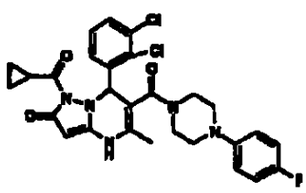
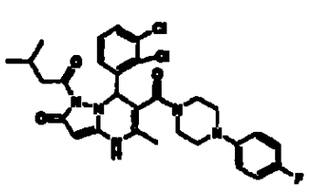
Ejemplos 422-431

Los compuestos de los Ejemplos 422-431, mostrados en la tabla proporcionada abajo, se prepararon en una manera similar a aquella descrita en el Ejemplo 421

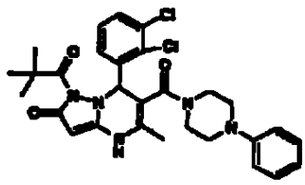
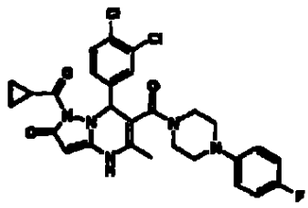
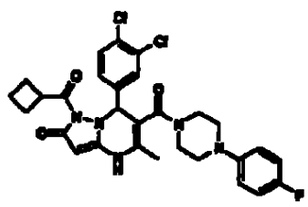
1100 1124

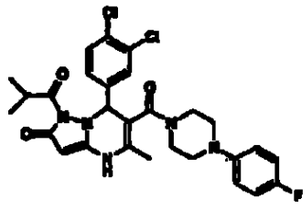
Ejemplo	Estructura	Nombre	(M+H)
422		1-[[1-benzoil-7-(3,4-Diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina	588
423		1-[[1-Acetil-7-(3,4-Diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina	526
424		1-[[7-(3,4-Dicloro-fenil)-1,2,4,7-tetrahidro-5-metil-2-oxo-1-(1-oxo-butil)-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina	554

H01 1125

425		1-[[1-ciclopropil-carbonil)-7-(3,4-Diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a] pirimidin-6-il]carbonil]-4-fenilpiperazina	552
426		1-[[1-ciclopropil-carbonil-7-(2,3-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina	570
427		1-[[7-(2,3-Dicloro-fenil)-1,2,4,7-tetra-hidro-5-metil-1-(3-metil-1-oxobutil)-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina	586

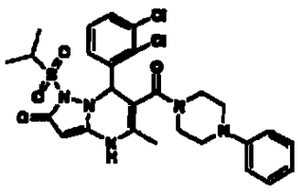
1102 1126

428		1-[[7-(2,3-Dicloro-fenil)-(2,2-dimetil-1-oxopropil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina	568
429		1-[[1-ciclopropil-carbonil)-7-(3,4-Diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazol[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)-piperazina	570
430		1-[[1-Ciclobutil-carbonil-7-(3,4-Diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)-piperazina	584

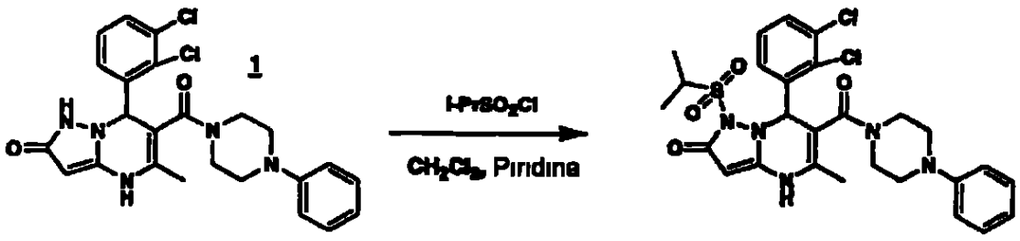
431		1-[[7-(3,4-Dicloro-fenil)-1,2,4,7-tetrahidro-5-metil-1-(2-metil-1-oxopropil)-2-oxopirazolo[1,5-a]p_-rimidin-6-il]carbonil]-4-(4-fluorofenil-piperazina	572

Ejemplo 432

1-[[7-(2,3-diclorofenil)-1,2,4,7-tetrahidro-5-metil-1-[(1-metiletil)sulfonil]-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina



Metodo



1104 1128

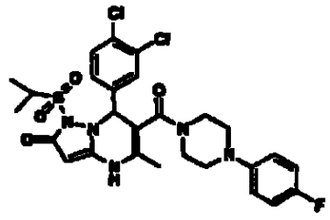
Compuesto 1 El compuesto 1 se preparo en una manera similar a aquella descrita en el Ejemplo 18, del método 12

Compuesto del titulo Se agregó cloruro de isopropilsulfonilo (0 11 mL, 0 97 mmol) y piridina (0 12 mL, 1 46 mmol) a 0°C a una solución del compuesto 1 (0 234 g, 0 487 mmol) en diclorometano (10 mL) La mezcla resultante se dejó calentar a temperatura ambiente Despues de 5 horas, el TLC indicó que la reacción se completo La reacción se enfrio rapidamente con metanol y se concentró El residuo se purifico por cromatografía en gel de silice, elución con metanol/acetato de etilo al 5% para proporcionar 0 095 g del compuesto del titulo (al 33%) como un sólido amarillo pálido LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección UV a 220 λ, gradiente 4 min Solvente B/A del 0-100% (Solvente A MeOH/H O al 10% con TFA al 0 1%, Solvente B MeOH/H O al 90% con TFA al 0 1%), 4 mL/min Rt = 3 57, (92% puro) (M+H 590)

405 1129

Ejemplo 433

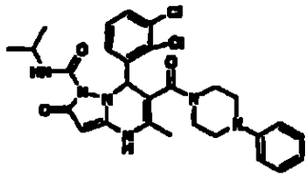
1-[[7-(3,4-diclorofenil)-1,2,4,7-tetrahidro-5-metil-1-[(1-metiletil)sulfonil]-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fuorofenil)piperazina



El compuesto del titulo se preparó en una manera similar a aquella descrita en el Ejemplo 432 (M+H) 608

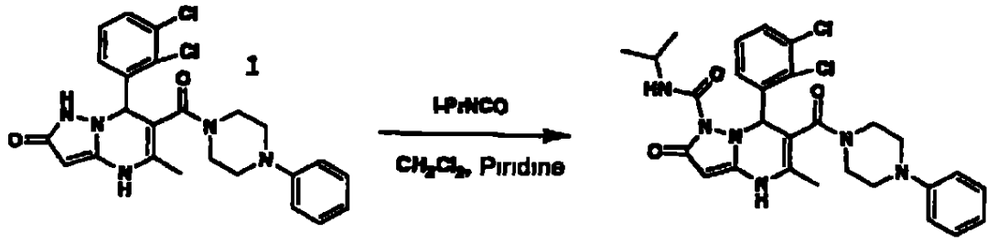
Ejemplo 434

7-(2,3-diclorofenil)-4,7-dihidro-5-metil-N-(1-metiletil)-2-oxo-6-[(4-fenil-1-piperazinil)carbonil]pirazolo[1,5-a]pirimidina-1(2H)-carboxamida



H06 1130

Método



Compuesto 1 El compuesto 1 se preparó en una manera similar a aquella descrita en el Ejemplo 18, del metodo 2

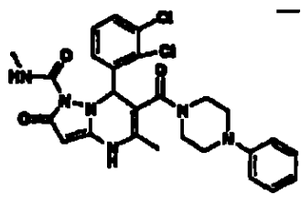
Compuesto del titulo Se agregó isocianato isopropilico (0 034 mL, 0 35 mmol) y piridina (0 057 mL, 0 706 mmol) a 0°C a una solucion del compuesto 1 (0 170 g, 0 350 mmol) en diclorometano (50 mL) La mezcla resultante se dejo calentar a temperatura ambiente Despues de 5 horas, la TLC indicó que la reacción se completo La reaccion se enfrio rapidamente con metanol y se concentro El residuo se purifico por cromatografia en gel de sílice, elución con acetato de etilo/hexanos al 75% para proporcionar 0 027 g del compuesto del titulo (al 13%) como un sólido blanco LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección UV a 220

H07131

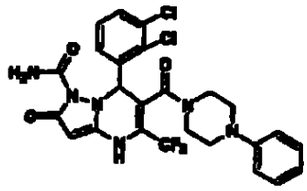
λ, gradiente 4 min Solvente B/A del 0-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt = 3 68, (95% puro) (M+H 569)

Ejemplos 435 y 436

Los compuestos de los Ejemplos 435 y 436, mostrados en la tabla proporcionada abajo, se prepararon en una manera similar a aquella descrita en el Ejemplo 434

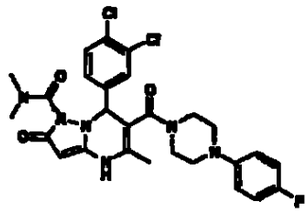
Ejemplo	Estructura	Nombre	(M+H)
435		7-(2,3-Dicloro-fenil)-4,7-dihidro-N,5-dimetil-2-oxo-6-[(4-fenil-1-piperazinil)-carbonil]pirazolo[1,5-a]pirimidin-1(2H)-carboxamida	541

1708
1132

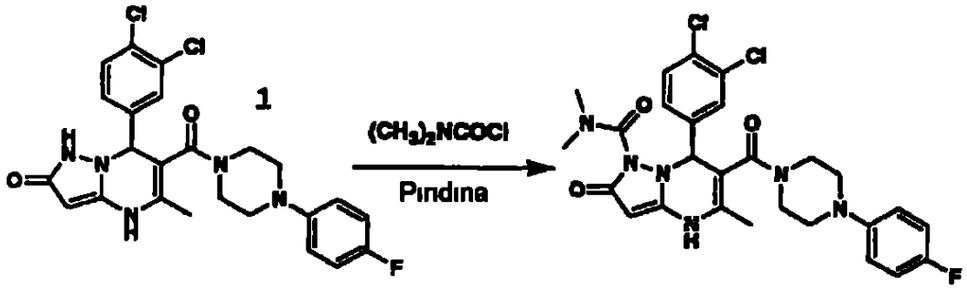
436		7-(2,3-Dicloro-fenil)-4,7-dihidro-5-metil-2-oxo-6-[(4-fenil-1-pipera-zinil)carbonil]pir-azolo[1,5-a]pirimi-din-1(2H)-carboxa-mida	527

Ejemplo 437

7-(3,4-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-4,7-dihidro-N,N,5-trimetil-2-oxopirazolo[1,5-a]pirimidin-1(2H)-carboxamida



Metodo



H09 1133

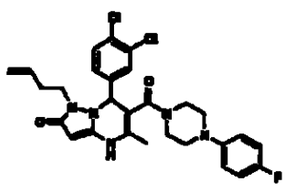
Compuest 1 El compuesto 1 se preparó en una manera similar a aquella descrita en el Ejemplo 18, del método 2

Compuesto del titulo Se agregó cloruro de dimetilcarbamoilo (0 10 mL, 1 1 mmol) a 0°C a una solucion del compuesto 1 (0 52 g, 1 0 mmol) en pirimidina (5 mL) La mezcla resultante se agitó a 0°C por 30 minutos, el baño enfriante se removió, y la mezcla se concentró El residuo se disolvió en acetato de etilo y se lavó con agua y salmuera, se seco sobre sulfato de sodio anhidro y se concentro El residuo se purifico por cromatografía en gel de silice, elución con metano/acetato de etilo al 5% para proporcionar 0 038 g del compuesto del titulo (al 6%) como un solido blanco LC/MS de fase inversa columna 4 6 x 33 TurboPack Pro YMC S5, detección UV a 220 λ, gradiente 2 min Solvente B/A del 0-100% (Solvente A MeOH/H O al 10% con TFA al 0 1%, Solvente B MeOH/H_O al 90% con TFA al 0 1%), 4 mL/min Rt = 1 97, 86% puro) MS (M+H 573)

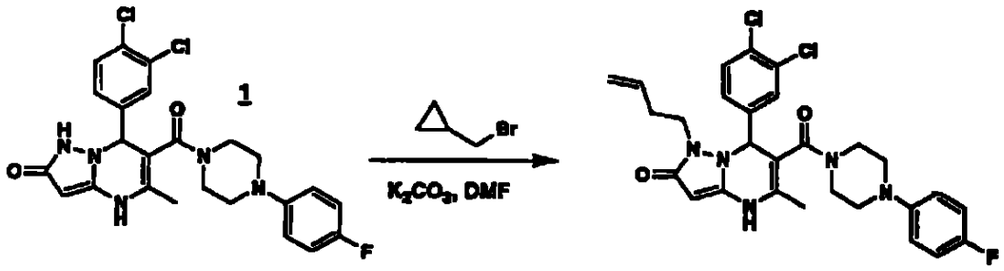
440
1134

Ejemplo 438

1-[[1-(3-Butenil)-7-(3,4-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazol[1,5,a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina



Metodo



Compuesto 1 El compuesto 1 se preparó en una manera similar a aquella descrita en el Ejemplo 18, del Metodo 2

Compuesto del titulo Se agregó (Bromometil)ciclopropano (0 246 mL, 1 82 mmol) a una mezcla del compuesto 1 (0 831 g, 1 66 mmol) y carbonato de potasio (g, mmol) en dimetilformamida

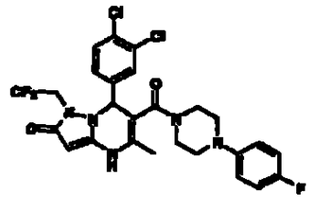
HH 1135

(10 mL) La mezcla resultante se dejó agitar a temperatura ambiente por 4 horas La reaccion se diluyó con acetato de etilo, transferido a un embudo separador, se lavó con agua y salmuera, se secó sobre sulfato de sodio anhidro y se concentró El residuo se purifico por cromatografía en gel de sílice, elución con metanol/acetato de etilo al 5% para proporcionar 0 030 g del compuesto del titulo (al 3%) LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, deteccion UV a 220 λ, gradiente 4 min Solvente B/A del 0-100% (Solvente A MeOH/H O al 10% con TFA al 0 1%, Solvente B MeOH/H_O al 90% con TFA al 0 1%), 4 mL/min Rt = 2 99, (87% puro) (M+H 556)

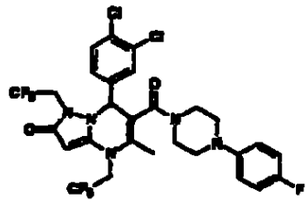
Ejemplos 439 y 440

1-[[7-(3,4-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxo-1-(2,2,2-trifluoro-etil)pirazolo-[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina	1-[[7-(3,4-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxo-1,4-bis(2,2,2-trifluoroetil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluoroenil)piperazina

HR 136

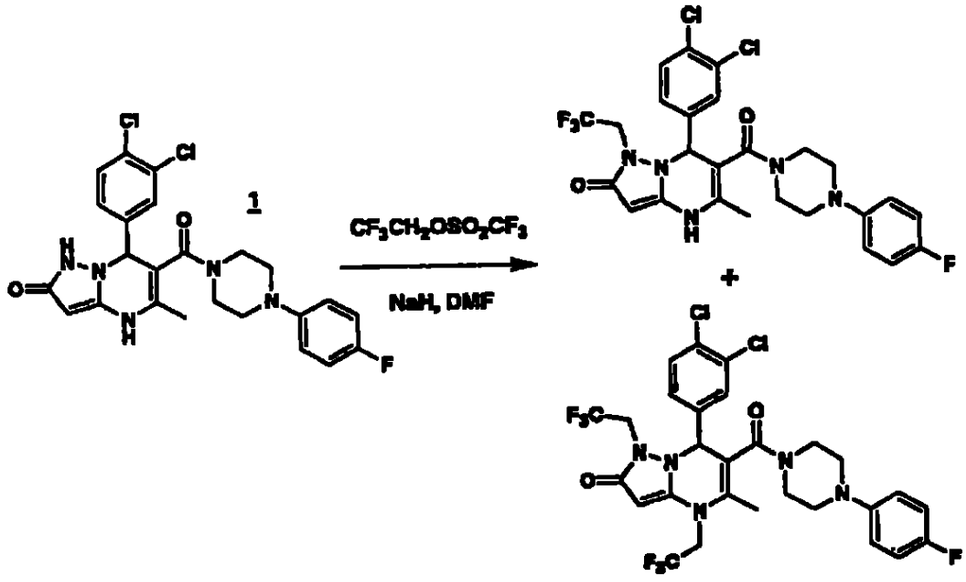


Ejemplo 439



Ejemplo 440

Método



Compuesto 1 El compuesto 1 se preparó en una manera similar a aquella descrita en el Ejemplo 18, del método 2

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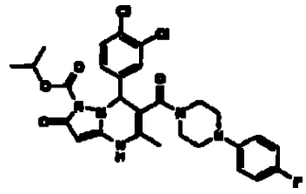
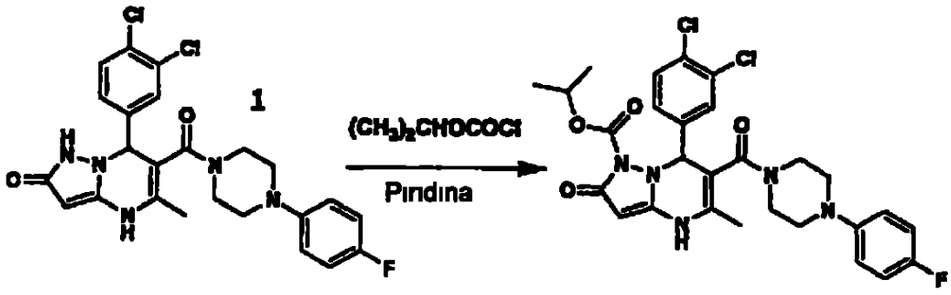
Compuestos del titulo Se agrego trifluormetansulfonato de 2,2,2-trifluoroetilo (0 49 g, 2 1 mmol) a una solución del compuesto 1 (0 967 g, 1 93 mmol) en dimetilformamida (10 mL) Se agrego hidrudro de sodio (0 12 g, 2 89 mmol) La TLC (metanol/acetato de etilo 10%) indicó el consumo del compuesto 1 La mezcla resultante se diluyó con acetato de etilo, se transfirió a un embudo separador, se lavó con agua y salmuera, se secó sobre sulfato de sodio anhidro y se concentró El residuo se purifico por cromatografia en gel de sílice, elucion con acetato de etilo seguido por 100% seguido por metanol/acetato de etilo al 10% para dar una mezcla de los compuestos del titulo Los compuestos del titulo se separaron por columna HPLC YMC S5 ODS 20 X 100 mm preparativa de fase inversa, 25 mL/min, gradiente 15 minutos, elucion con solvente B/A de 50%-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1 , Solvente B MeOH/H_2O al 90% con TFA al 0 1%) Compuesto del ejemplo 439 Rt = 11 05 min, Compuesto del ejemplo 440 Rt = 11 88 min Compuesto del Ejemplo 439 LC/MS de fase inversa columna Ballistic YMC S5 4 6 x 50, deteccion UV a 220 λ, gradiente 4 min Solvente B/A del 0-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA

al 0 1%), 4 mL/min Rt = 2 87 min, 95% puro) MS(M+H 584) Compuesto del Ejemplo 440 LC/MS de fase inversa columna Ballistic YMC S5 4 6 x 50, detecc_on UV a 220 λ, gradiente 4 min Solvente B/A del 0-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_O al 90% con TFA al 0 1), 4 mL/min Rt = 3 25 min, 85% puro) MS(M+H 666)

Ejemplo 441

Ester 1-metiletílico del ácido 7-(3,4-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-4,7-dihidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-1(2H)-carboxílico





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Compuesto 1 El compuesto 1 se prepara en una manera similar a aquella descrita en el Ejemplo 18, del método 2

Compuesto del titulo Se agregó cloroformato de isopropilo (1 0 mL, 1 0 mmol, en 1M de tolueno) a 0°C una solución del compuesto 1 (0 46 g, 0 92 mmol) en piridina (5 mL) La mezcla resultante se agitó a 0°C por 30 minutos, se removio el baño enfriante Despues de 2 horas se agrego metanol la mezcla se enfrió rapidamente y se concentró El residuo se purificó por cromatografía en gel de sílice elución con metanol/acetato de etilo al 5% para proporcionar 0 057 g, del compuesto del titulo (al 11%) como un solido rosado ligero LC/MS de fase inversa columna YMC S5 ODS 4 6 x 50, deteccion UV a 220 λ, gradiente 4 min Solvente B/A del 0-100% (Solvente A MeOH/H_2O al 10 con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt = 3 67 min 95% puro) (M+H 573)

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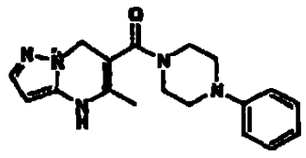
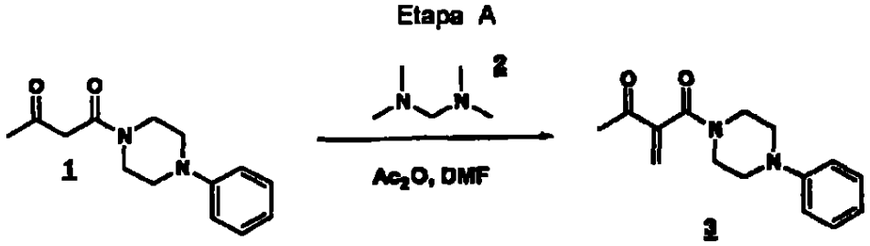
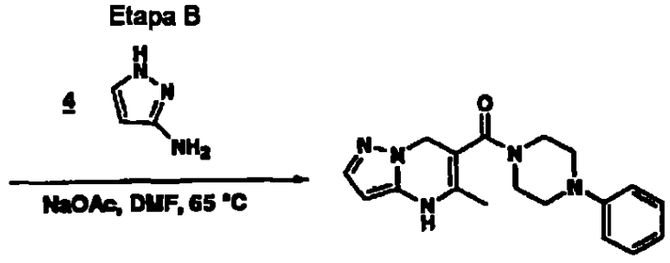
Ejemplo 442

1-[(4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il)carbonil]-4-fenilpiperazina



Método





Compuesto 1 El compuesto 1 se preparó en una manera similar a aquella descrita en el Ejemplo 18, del método 2

Etapa A Se agregó el compuesto 2 (0 6 mL, 4 4 mmol)

y anhidrido acético (0 83 mL, 8 8 mmol) a una solución del compuesto 1 (0 72 g, 2 9 mmol) en dimetilformamida (10 mL) La mezcla se dejo agitar durante la noche, se vertió en agua, se extrajo con diclorometano Los extractos se combinaron, se secaron sobre sulfato de sodio anhidro y se concentraron El residuo se purificó por cromatografía en gel de sílice, elucion con acetato de etilo/hexanos al 50% a acetato de etilo/hexanos al 100% para dar 0 290 g del compuesto 3 (rendimiento de 38%) como un jarabe incoloro (M+H 259)

Etapa B La condensacion del compuesto 3 y compuesto 4 como se describe en el Ejemplo 18, del Método 2 de la etapa C proporcionó el compuesto del titulo LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, deteccion UV a 220 λ, gradiente 4 min Solvente B/A de 0-100- (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt = 1 96 min, (87% puro) (M+H 323)

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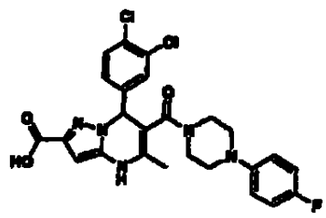
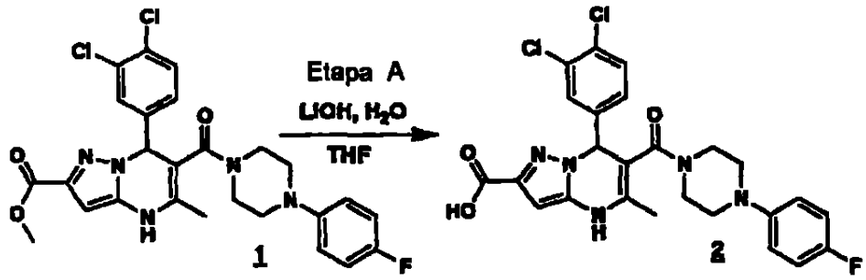
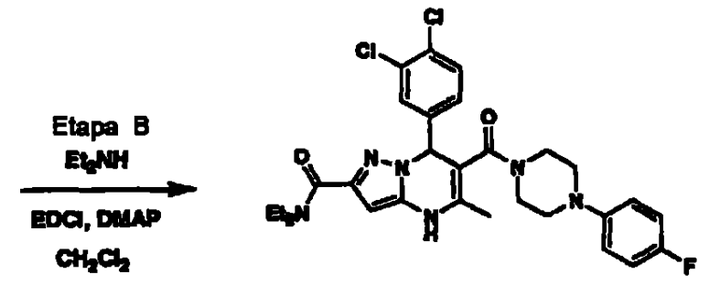
Ejemplo 443

Acido 7-(3,4-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidina-2-carboxilico



Método





1149
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Compuesto 1 El compuesto 1 se preparó en una manera similar a aquella descrita en el Ejemolo 18 oel método 2

Etapa A Se disolvió hidroxido de litio (0 43 g, 1 8 mmol) en agua (3 mL) y se agregó lentamente a temperatura ambiente a una solucion del compuesto 1 en tetrahidrofurano (9 mL) La mezcla resultante se agito agito a temperatura ambiente por 3 horas La TLC indicó que todo el compuesto 1 ha sido consumido La mezcla se enfrio rapidamente por adición de resina Dowex acidica Lo filtrado se diluyó con acetato de etilo, se lavó con agua y salmuera, se secó sobre sulfato de sodio anhidro y se concentró para dar 0 41 g (86% de rendimiento) del compuesto 2 como un sólido amarillo ligero LC/MS oe fase inversa columna YMC S5 ODS 4 6 x 50, deteccion UV a 220 λ, gradiente 4 min Solvente B/A de 0-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt = 3 37 min, 96% puro) MS(M+H 530)

Etapa B Se agregó EDCI (0 025 g, 0 13 mmol), DMPA (0 003 g, 0 02 mmol) a una solucion del compuesto 2 (0 0508 g, 0 1 mmol) y dimetilamina (0 014 mL, 0 13

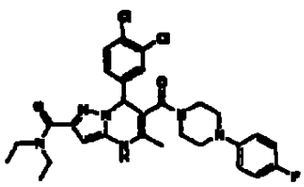
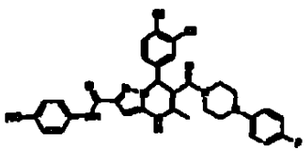
1120
1144

mmol) en diclorometano (3 mL) La mezcla se agitó durante la noche La TLC indicó poco remanente de material iniciador El solvente se removio bajo presion reducida El residuo resultante se purificó por cromatografía en gel de silice, elución con metanol/acetato de etilo al 5% para dar el compuesto del titulo como un solido blanco LC/MS de fase inversa columna Ballistic YMC S5 4 6 x 50, detección UV a 220 λ, gradiente 4 min Solvente B/A de 0-100% (Solvente A MeOH/H O al 10% con TFA al 0 1%, Solvente B MeOH/H_O al 90% con TFA al 0 1%), 4 mL/min Rt = 3 74 min, 91% puro) MS(M+H 585)

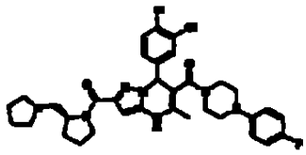
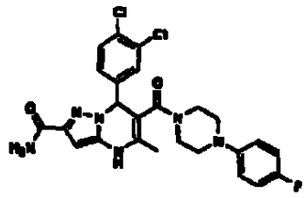
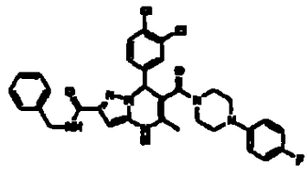
Ejemplos 444-449

Los compuestos de los Ejemplos 445-450, mostrados en la tabla proporcionada abajo, se prepararon en una manera similar a aquella descrita en el Ejemplo 443

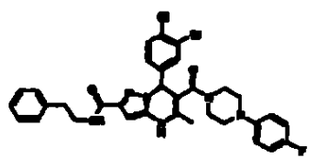
H2T 1145

Ejemplo	Estructura	Nombre	(M+H)
444		7-(3,4-Dicloro-fenil)-N,N-dietil-6-[[4-(4-fluorofenil)-1-piperazinil-carbonil]-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-2-carboxamida	585
445		7-(3,4-Dicloro-fenil)-6-[[4-(4-fluorofenil)-1-piperazinil]-carbonil]-4,7-dihidro-N-(4-hidroxifenil)-5-metilpirazolo[1,5-a]pirimidin-2-carboxamida	621

H22
1146

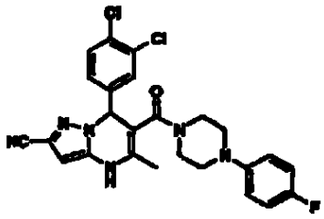
446		1-[[7-(3,4-Dicloro-fenil)-4,7-dihidro-5-metil-2-[[(2S)-2-(1-pirrolidinil-metil)-1-pirroli-dinil]carbonil]-pirazolo[1,5-a]piri-midin-6-il]carbonil]-4-(4-fluorofenil) piperazina	666
447		7-(3,4-Dicloro-fenil)-6-[[4-(4-fluorofenil)-1-pipe-razinil]carbonil]-4,7-dihidro-5-metil-pirazolo[1,5-a]piri-midin-2-carboxamida	529
448		7-(3,4-Dicloro-fenil)-6-[[4-(4-fluorofenil)-1-pipe-razinil]-carbonil]-4,7-dihidro-5-metil-N-(fenilmetil)-pirazolo[1,5-a]piri-midin-2-carboxamida	619

H23
1147

449		7-(3,4-Dicloro-fenil)-6-[[4-(4-fluorofenil)-1-piperazinil]-carbonil]-4,7-dihidro-5-metil-N-(2-fenil-etil)pirazolo[1,5-a]pirimidin-2-carboxamida	633

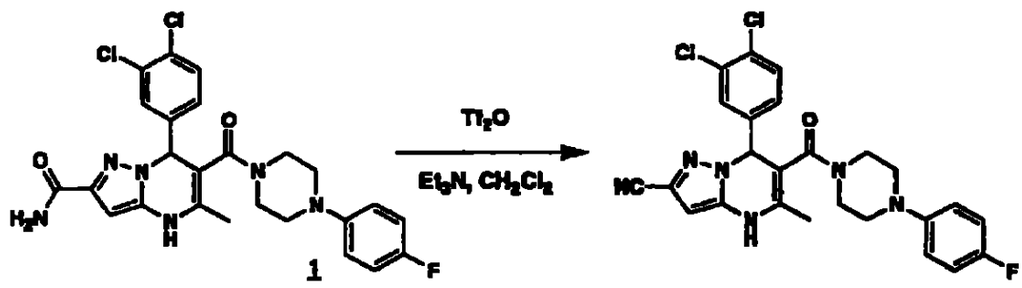
Ejemplo 450

1-[[2-ciano-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina



1148 1124

Método



Compuesto 1 El compuesto 1 (el compuesto del Ejemplo 447) se preparó en una manera similar a aquella descrita en el Ejemplo 443

Compuesto del titulo Se agregó anhidrido triflico (0 036 mL, 0 21 mmol) a 0°C a una solución del compuesto 1 (0 103 g, 0 19 mmol) y trietilamina (0 054 mL, 0 39 mmol) en diclorometano (5 mL) Despues de 10 min, la TLC (metanol/acetato de etilo al 5%) indicó que el compuesto 1 permanecio Adicionalmente se agrega anhidrido triflico (0 036 mL, 0 21 mmol) y trietilamina (0 054 mL, 0 39 mmol) Despues de 10 min, la TLC metanol/acetato de etilo al 5%) indicó que el compuesto 1 permanecio La mezcla se calentó a temperatura ambiente y se agito por unos 30 minutos adicionales La reacción se vertió en

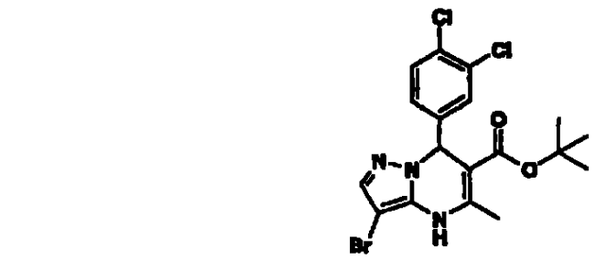
H25 1149

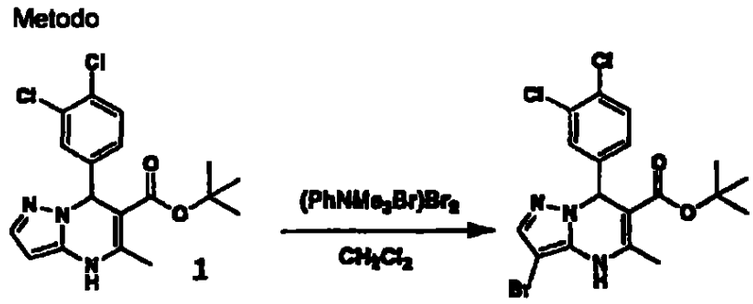
bicarbonato de sodio saturado, se extrajo con diclorometano Los extractos se combinaron, se secaron sobre sulfato de sodio anhidro y se concentró El residuo resultante se purificó por cromatografía en gel de sílice, elució con metanol/acetato de etilo al 2% para 0 018 g (rendimiento al 19%) del compuesto del título como un solido blanco LC/MS de fase inversa columna YMC S5 4 6 x 33, detección UV a 220 λ, gradiente 2 min Solvente B/A de 0-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt = 3 60 min, 81% puro) MS(M+H 511)

Ejemplo 451

Ester 1,1-dimetiletilico del acido 3-bromo-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidina-6-carboxilico

1126 1150





Compuesto 1 El compuesto 1 se preparó como se describe en el Ejemplo 4

Compuesto del título Se agrego tribromuro de feniltrimetilamonio (0 057 g, 0 14 mmol) a 0°C a una solución del compuesto 1 (0 05 g, 0 13 mmol) en diclorometano (2 mL) La mezcla se dejó calentar a temperatura ambiente durante 4 horas El solvente se removió bajo presion reducida El residuo resultante se purificó por TLC preparativa (Analtech, gel de

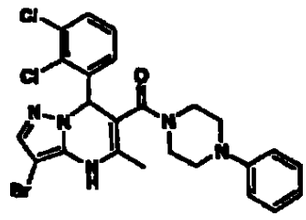
1127
1151

sílice, 20 x 20 cm, 100 µ) Elucion con acetona/hexano al 25% proporciona 0 047 g (rendimiento del 79%) del compuesto del titulo como un sólido blanco LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, deteccion UV a 220 λ, gradiente 4 min Solvente B/A del 0-100% (Solvente A MeOH/H_2O al 10% con H_3PO_4 al 0 2%, Solvente B MeOH/H_2O al 90% con H_3PO_4 al 0 2%), 4 mL/min Rt = 4 67 min, (95% puro) LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección UV a 220 λ, gradiente 4 min Solvente B/A de 0-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt = 4 19 min, MS (EM, M+1 458) HMR ($CDCl_3$, 400 MHz) 7 37 (1H, d, J = 2 0 Hz), 7 36 (1H, d, J = 8 0 Hz), 7 33 (1H, s), 7 12 (1H, dd, J = 2 2 y 8 4 Hz), 6 38 (1H, s), 6 27 (1H, s), 2 53 (3H, s), 1 36 (9H, s)

Ejemplo 452

1-[[3-bromo-7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina

1128
1152

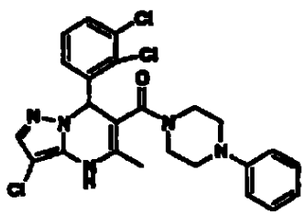


El compuesto del Ejemplo 452 se preparo en una manera similar a aquella descrita en el Ejemplo 451 (M+H) 547

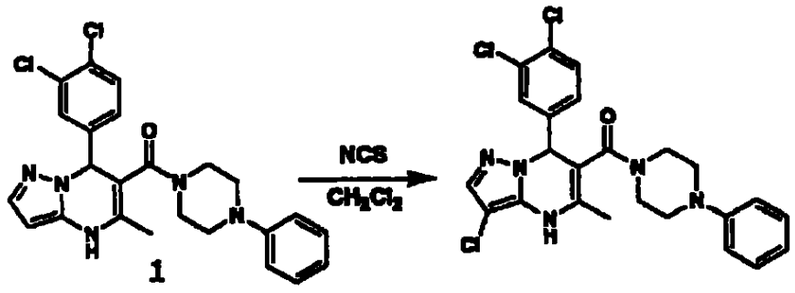
Ejemplo 453

1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina

1153
H29



Metodo



1

Compuesto 1 El compuesto 1 se preparó en una manera similar a aquella descrita en el Ejemplo 18, del método 2

Compuesto del titulo Se agregó N-clorosuccinimida (0 0102 g, 0 076 mmol) a 0°C a una solución del compuesto 1 (0 0343 g, 0 073 mmol) en diclorometano (4 mL) La mezcla se dejó calentar a temperatura ambiente durante 2 horas El solvente se removió bajo presión reducida El residuo resultante se purificó por TLC preparativa (Analtech, gel de sílice, 20 x 20 cm, 100 µ) Elución con acetona/hexano al 50%

1130
1154

proporcionando 0 0287 g (rendimiento de 77%) del compuesto del titulo como un aceite amarillo el cual se solidificó después de reposar HPLC de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, deteccion UV a 220 λ, gradiente 4 min Solvente B/A de 0-100% (Solvente A MeOH/H_2O al 10% con PPA al 0 2%, Solvente B MeOH/H_2O al 90% con PPA al 0 2%), 4 mL/min Rt = 4 21 min, (91% puro) LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, deteccion UV a 220 λ, gradiente 4 min Solvente B/A de 0-100% (Solvente A MeOH/H_2O al 10% con TFA al 0 1%, Solvente B MeOH/H_2O al 90% con TFA al 0 1%), 4 mL/min Rt = 3 72 MS (EM, M+1 501)

Ejemplos 454-463

Los compuestos de los Ejemplos 454-463, mostrados en la tabla proporcionada abajo, se prepararon en una manera similar a aquella descrita en el Ejemplo 453

El ejemplo 456 se obtuvo a partir del enantiómero B sólo del Ejemplo 30, y el Ejemplo 457 se obtuvo a partir del enantiómero A sólo del Ejemplo 29 Columna AD Chiralpak (4 6 x 250 mm) elución con isopropanol/hexanos al 30% conteniendo trietilamina al 1% a 1 mL/min), detección UV a 254 λ, Ejemplo 456

Rt = 5 9 mın, >99% ee, Ejemplo 457 Rt = 6 3 mın, > 99% ee

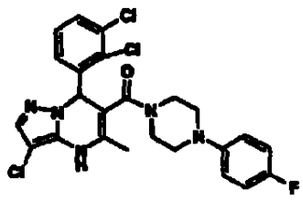
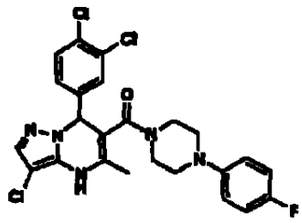
El Ejemplo 458 se obtuvo a partır del enantıomero A sólo del Ejemplo 51, y el Ejemplo 459 se obtuvo a partır del enantıómero B sólo del Ejemplo 52 Columna OD Chıralcel (4 6 x 250 mm), elucıon con ısopropanol/hexanos al 30% contenıendo trıetılamına al 0 1% a 1 mL/mın), detección UV a 254 λ, Ejemplo 458 Rt = 7 8 mın, > 99% ee Ejemplo 459 Rt = 8 4 mın, > 99% ee

El ejemplo 460 se obtuvo a partır del enentıomero A solo del Ejemplo 169, y el Ejemplo 461 se obtuvo a partır del enantıómero B sólo del ejemplo 168 Columna AD Chıralpak (4 6 x 250 mm), elución con ısopropanol/hexanos al 20% contenıendo trıetılamına al 0 1 a 1 mL/mın), oeteccıon UV a 254 ʌ, Ejemplo 461 Rt = 9 2 mın, > 99% ee Ejemplo 460 Rt = 9 4 mın, > 99% ee

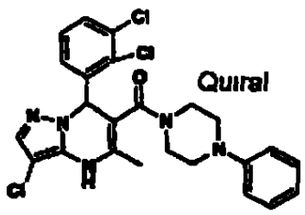
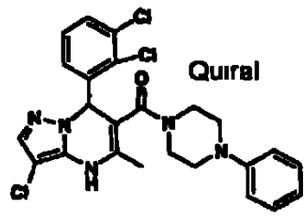
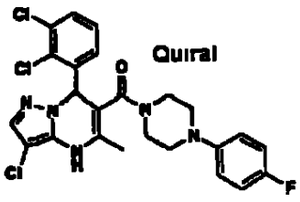
El ejemplo 462 se obtuvo a partır del enantıómero A sólo del Ejemplo 81, y el Ejemplo 463 se obtuvo a partır oel enantıómero B solo del Ejemplo 82 Columna AD Chıralpak (4 6 x 250 mm), elución con ısopropanol/hexanos al 20% contenıendo trıetılamına al 0 1% a 1 mL/mın), detección UV a 254 λ, Ejemplo 462 Rt = 8 25 mın, > 99% ee Ejemplo 463 Rt = 8 28

H32
1156

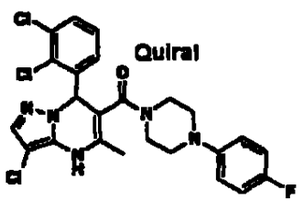
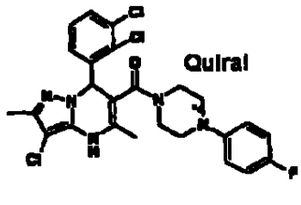
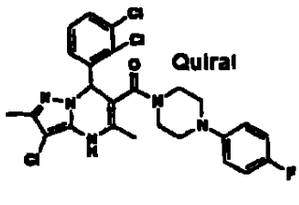
min, > 99% ee

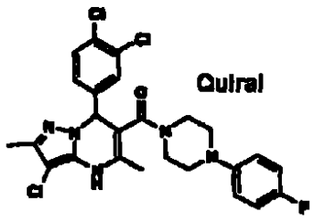
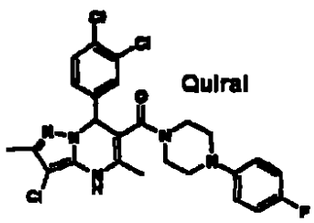
Ejemplo	Estructura	Nombre	(M-1)
454		1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina	520
455		1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina	520

1133
1157

456		1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina, enantiómero B	502
457		1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenil-piperazina, enantiómero A	502
458		1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluoro-fenil)piperazina, enetiómero A	520

H34
1158

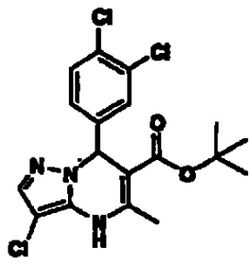
459		1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazol[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil) piperazina, enetiómero B	520
460		1- [3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-2,5-dimetil-pirazol[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enantiómero A	534
461		1- 3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enantiómero B	534

462		1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enantiómero A	534
463		1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enantiómero B	534

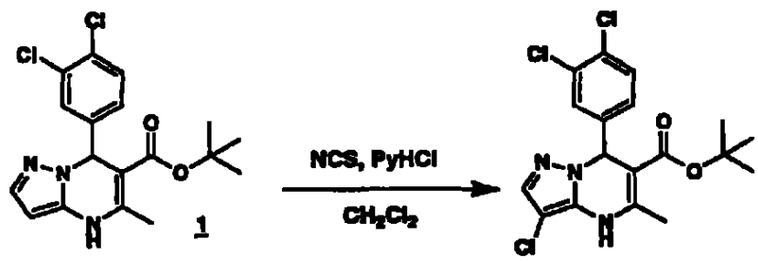
Ejemplo 464

Ester 1,1-dimetiletílico del ácido 3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidina-6-carboxílico

1136 1160



Método



Compuesto 1 El compuesto 1 se preparo como se describe en el Ejemplo 4

Compuesto del titulo Se agrego clornidrato de piridina (0 020 g, 0 173 mmol) a 0°C a una solucion del compuesto 1 (0 060 g, 0 158 mmol) en diclorometano (4 mL) Despues de 2 minutos, se agregó N-clorosucinimida (0 0231 g, 0 174 mmol) La mezcla se dejó calentar a temperatura ambiente y se agito

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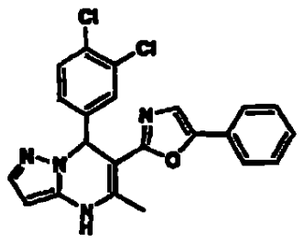
1137

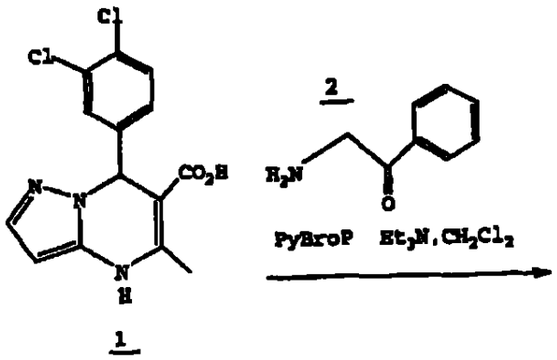
por 13 horas El solvente se removió bajo presion reducida El residuo resultante se purificó por TLC preparativa (Analtech, gel de sílce, 20 x 20 cm, 100 µ) Elución con acetona/hexanos al 20% proporcionado 0 0092 g (rendimiento de 14%) del compuesto del titulo como un aceite amarillo HPLC de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección UV a 220 λ, gradiente 4 min Solvente B/A de 0-100% (Solvente A MeOH/H O al 10% con PPA al 0 2 , Solvente B MeOH/H O al 90% con PPA al 0 2%), 4 mL/min Rt = 4 61 min, (94% puro) LC/MS de fase inversa columna Ballistic YMC S5 ODS 4 6 x 50 mm, detección UV a 220 λ, gradiente 4 min Solvente B/A de 0-100% (Solvente A MeOH/H O al 10% con TFA al 0 1 , Solvente B MeOH/H O al 90% con TFA al 0 1%), 4 mL/min Rt = 4 71 min, MS (EM, M+1 414) HMR (CDCl , 400 MHz) 7 37 (1H, s), 7 36 (1H, d, J = 1 7 Hz), 7 36 (1H, d, J = 8 4 Hz), 7 12 (1H, dd, J = 2 0 y 8 4 Hz), 6 45 (1H, brs), 6 24 (1H, s), 2 52 (3H, s), 1 36 (9H, s)

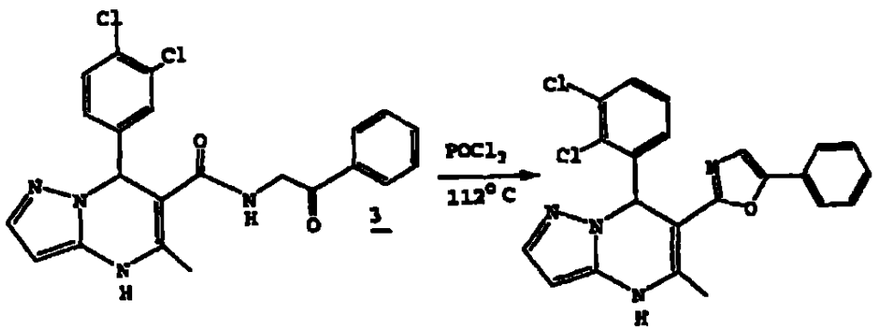
Ejemplo 465

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-6-(5-fenil-2-oxazolilo)pirazolo[1,5-a]pirimidina



Método





Compuesto 1 El compuesto 1 se sintetizó como se describe en el Ejemplo 16

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1163

Compuesto 3 El compuesto 1 (200 mg, 0 62 mmol) se suspendió en 2 mL de diclorometano Se agregó trietilamina (300 µL, 2 2 mmol) y 2-aminoacetofenona 2 (116 mg, 0 68 mmol) seguido por hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (PyBrOP) (312 mg, 0 68 mmol) Todos los sólidos se disolvieron despues de la adición de PyBrOP y la reacción se agitó por 4 horas La mezcla se cargó en gel de sílice y se purifico por cromatografia instantanea en gel de silice, elución con acetona, hexano al 40% para un rendimiento de 106 mg (al 39%) de un sólido rosado H NMR (400 MHz, CDCl3) 44180-148-16, ^{1}H COSY (400 MHz, CD3OD), ^{13}C NMR (100 Mhz, CDCl), HPLC > 99% a 4 0 min (columna YMC S5 ODS 4 6 x 50 mm, metanol al 10-90 , agua con ácido fosforico al 0 2% con gradiente de 4 min , 4 mL/min , deteccion UV a 220 nm)

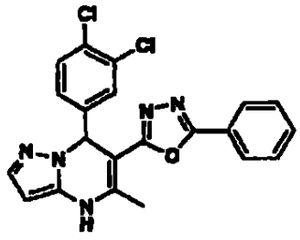
Compuesto del titulo La amida 3 (100 mg, 0 22 mmol) se disolvió en 2 mL de oxicloruro fosforoso y se calento a 112° por 2 horas La mezcla se enfrió rapidamente en hielo y se extrajo con acetato de etilo Los extractos se secaron sobre sulfato de magnesio, se filtraron y el solvente se removió para proporcionar 339 mg de un aceite marrón El aceite se

1440,164

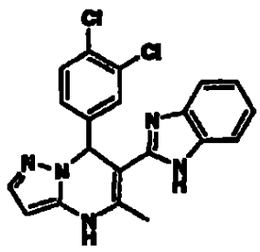
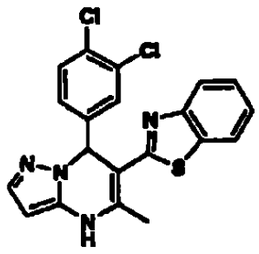
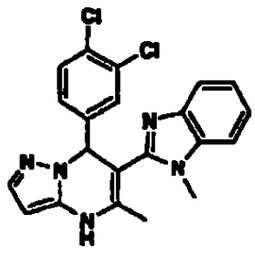
purificó por cromatografía instantánea en gel de sílice, elución con acetona, hexano al 20-40% para rendir 50 mg (al 51%) del compuesto del título como un polvo blanco p f 229-231°, ^{1}H NMR (400 MHz, CD3OD), MS (ESI) *m/z* 423 (MH+), HPLC > 99% a 4 7 min (columna YMC S5 ODS 4 6 x 50 mm, metanol al 10-90 , agua con ácido fosforico al 0 2% de gradiente 4 min, entonces se conserva a 90% de metanol, agua, 4 mL/min , detección UV a 220 nm)

Ejemplos 466-469

Los compuestos de los Ejemplos 466-473, mostrados en la tabla proporcionada abajo, se preparan en una manera similar a aquella descrita en el Ejemplo 465

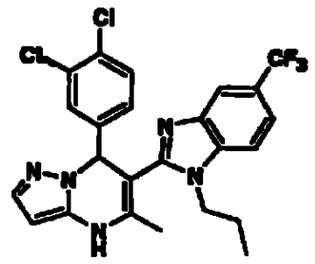
Ejemplo	Estructura	Nombre	(M+H)
466		7-(3,4-Dicloro-fenil)-4,7-dihidro-5-metil-6-(5-fenil-1,3,4-oxadiazol-2-il)pirazolo[1,5-a]pirimidina	424

HMT 1165

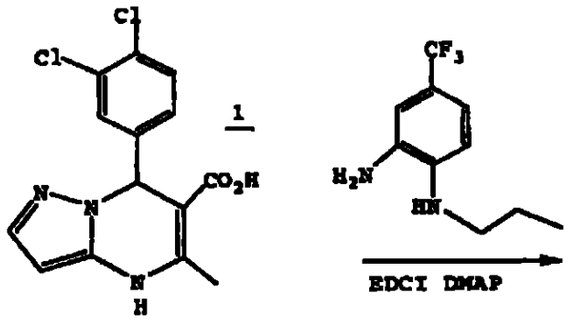
467		6-(1H-Bencimidazol-2-il)-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidina	396
468		6-(2-Benzotiazolil)-7-(3,4-Dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidina	413
469		7-(3,4-Dicloro-fenil)-4,7-dihidro-5-metil-6-(1-metil-1H-bencimidazol-2-il)pirazolo[1,5-a]pirimidina	410

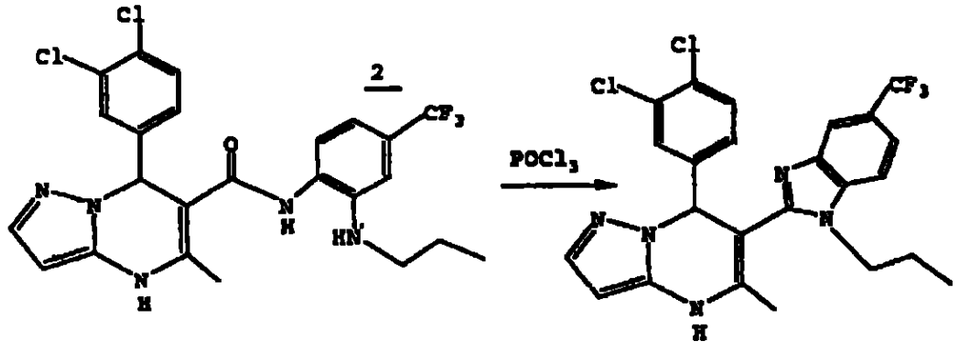
Ejemplo 470

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-6-[5-(trifluorometil)-1-propil-1H-benzimidazol-2-il]pirazolo[1,5-a]pirimidina



Método





Compuesto 2 A una solucion del ácido 1, preparada como se describe en el Ejemplo 16, (0 15 g, 0 463 mmol), 2-(n-propılamıno)-5-trıfluorometılanılına (0 141 g, 0 648 mmol) y se agrego DMAP (5 mg, cat) EDCI (0 124 g, 0 0648 mmol) y la solución se agitó a

1167

temperatura ambiente por 2 horas La reacción se trato con bicarbonato de sodio saturado, la solucion orgánica se seco con sulfato de magnesio y el solvente se evaporó El producto crudo 2 se usó sin purificación adicional

Compuesto del titulo El compuesto 2 se disolvio en oxicloruro fosforoso (4 mL) y se calentó a 80°C por 4 horas La TLC indico que la reaccion no se completo Adicionalmente se agregó oxicloruro fosforoso (2 mL) y la mezcla se calentó por 2 horas y entonces se dejó a temperatura ambiente durante la noche La mezcla entonces se enfrio rapidamente en hielo, hecho basicamente con hidroxido de amino, y se extrajo con acetato de etilo Los extractos se secaron sobre sulfato de magnesio y se concentraron El producto crudo se purificó por cromatografía de fase inversa preparativa (columna YMC PACK ODSA S3 20 x 100 mm, metanol 50 -100, agua con TFA al 0 1% gradiente sobre 10 min , 20 mL/min , deteccion uv a 220 nm) Las fracciones apropiadas se evaporaron, el residuo se dividio entre bicarbonato de sodio saturado y acetato de etilo, la solución orgánica se secó y el solvente se removio bajo vacío dando el producto (27 mg, al 11 5) como un cristal bronceado

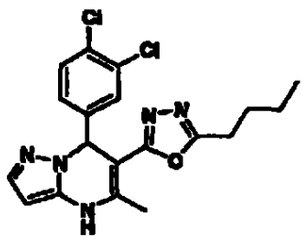
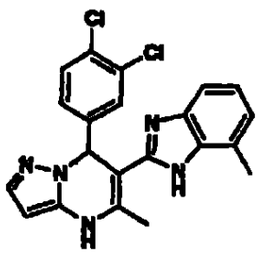
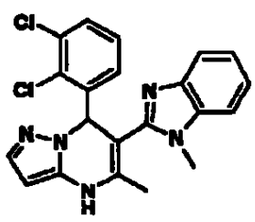
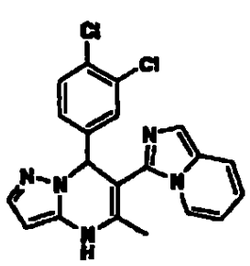
u obscuro [M+H] *m/z* 506 HPLC 91 1% A 4 6 min (columna YMC S5 ODS 4 6 x 50 mm, metanol al 10-90%, agus con ácido fosfórico al 0 2% gradiente sobre 4 min , 4 mL/min , deteccion uv a 220 nm)

Ejemplos 471-482

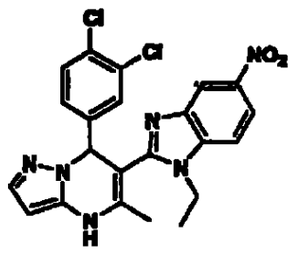
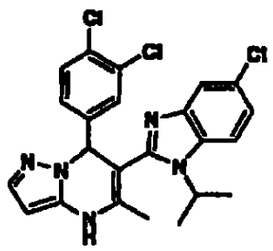
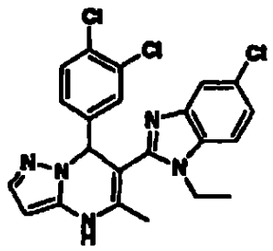
Los compuestos de los Ejemplos 471-482, mostrados en la tabla proporcionada abajo, se prepararon de una manera similar a aquella descrita en el Ejemplo 470

La resolución HPLC del Ejemplo 480, columna Chiralcel OD (50 X 500 mm), elucion con isopropanol/hexanos al 25% conteniendo trietilamina al 0 1 a 50 mL/min), deteccion UV a 254 λ proporcionando enantiomeros A (Ejemplo 481) y B (Ejemplo 482) Columna Analytical Chiralcel OD (4 6 X 250 mm) elución con isopropanol/hexanos al 25% conteniendo trietilamina al 0 1% a 1 mL/min), detección UV a 254 λ, enatiómero A Rt = 7 2 min, > 99 ee Enantiómero B Rt = 10 0 min, > 99% ee

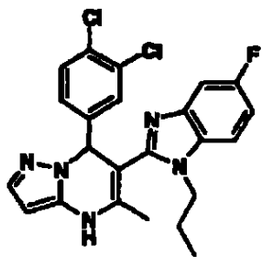
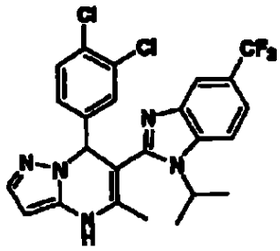
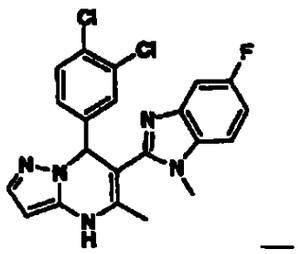
HF5 1169

Ejemplo	Estructura	Nombre	(M+H)
471		6-(5-butil-1,3,4-oxadiazol-2-il)-7-(3,4-Diclorofenil)-4,7dihidro-5-metil-pirazolo[1,5-a]pirimidina	404
472		1-[[7-(3,4-Dicloro-fenil)-4,7-dihidro-5-metil-6-(4-metil-1H-bencimidazol-2-il)pirazolo[1,5-a]pirimidina	410
473		1-[[7-(2,3-Dicloro-fenil)-4,7-dihidro-5-metil-6-(1-metil-1H-bencimidazol-2-il)pirazolo[1,5-a]pirimidina	410
474		7-(3,4-Dicloro-fenil)-4,7-dihidro-6-(imidazol[1,5-a]piridin-3-il)-5-metilpirazolo[1,5-a]pirimidina	510

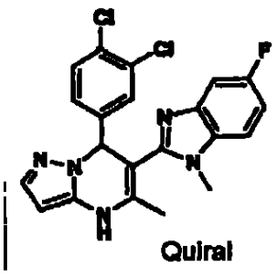
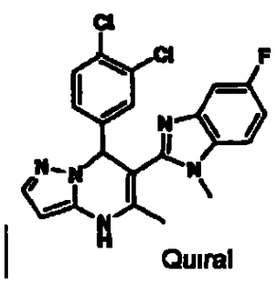
1446 1170

475		7-(3,4-Dıcloro-fenıl)-6-(1-etıl-5-nıtro-1H-bencımı-dazol-2-ıl)-4,7-dıhıdro-5-metıl-pırazolo[1,5-a]pırımıdına	469
476		6-[5-cloro-1-(1-metıletıl)-1H-bencımıdazol-2-ıl)-7-(3,4-Dıcloro-fenıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdına	472
477		6-(5-cloro-1-etıl-1H-bencımıdazol-2-ıl)-7-(3,4-Dıcloro-fenıl)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdına	458

H47 1171

478		7-(3,4-Dicloro-fenil)-6-(5-fluoro-1-propil-1H-benci-midazol-2-il)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidina	456 35
479		7-(3,4-Dicloro-fenil)-4,7-dihidro-5-metil-6-[1-(1-metiletil)-5-(tri-fluorometil)-1H-bencimidazol-2-il] pirazolo[1,5-a]pirimidina	506
480		7-(3,4-Dicloro-fenil)-6-(5-fluoro-1-metil-1H-benci-midazol-2-il)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidina	428

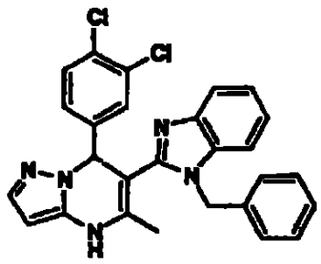
1148/1172

481	 Quiral	7-(3,4-Dicloro-fenil)-6-(5-fluoro-1-metil-1H-bencimidazol-2-il)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidina, enantiómero A	428
482	 Quiral	7-(3,4-Dicloro-fenil)-6-(5-fluoro-1-metil-1H-bencimidazol-2-il)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidina, enantiómero B	428

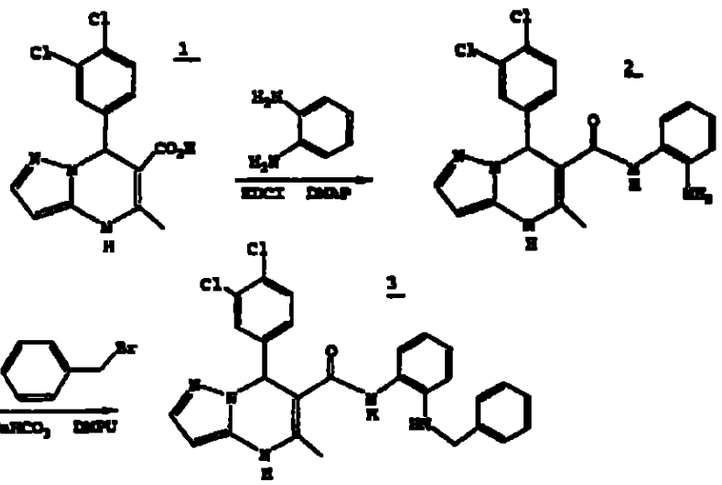
Ejemplo 483

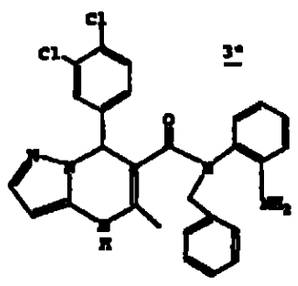
7-(3,4-diclorofenil)-4,7-dihidro-5-metil-6-[1-(fenilmetil)-1H-bencimidazol-2-il]pirazolo[1,5-a]pirimidina

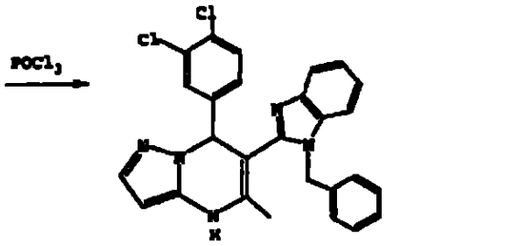
1449 1173



Metodo







1174

Compuesto 1 Preparado como se describe en el Ejemplo 16

Compuesto 2 Preparado a partir del compuesto 1 y fenilenediamina en una manera similar a aquella descrita en el Ejemplo 470

Compuesto 3 Una suspensión de 2 (50 mg 0 121 mmol), $NaHCO_3$ (50 mg, 0 6 mmol) y bromuro de bencilo (20 mg, 0 121 mmol) en DMPU (0 5 mL) se agito a temperatura ambiente durante la noche Otro equivalente de bromuro de bencilo se agrego completando la reacción La suspension se dividió entre agua y acetato de etilo, la fase orgánica se secó ($MgSO_4$), y el solvente se evaporo El residuo se cromatografío instantáneamente a traves de sílice, elución con hexano-acetona 2 1 para proporcionar cualquiera o ambos de los compuestos 3 y 3* (no se determinó exactamente la estructura) (24 8 mg, al 41%) como un sólido blanco P f 135-140, [M+H] *m/z* 504, HPLC al 100% a 4 4 min (columna YMC S5 ODS 4 6 x 50 mm, metanol al 10-90%, agua con ácido fosfórico al 0 2% gradiente sobre 4 min , 4 mL/min , detección uv a 220 nm)

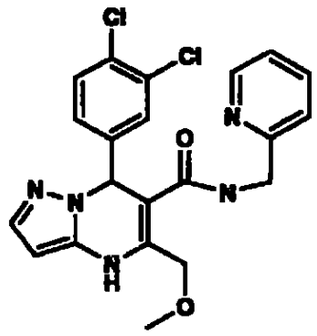
H59 1175

Compuesto del titulo Se disolvieron el (los) compuesto(s) 3/3* en oxicloruro de fósforo (1 5 mL) y se calentó a 80°C por 5 horas, El calentamiento se descontinuó y la mezcla se dejo permanecer a temperatura ambiente durante la noche La mezcla se enfrió rápidamente en hielo, hecho basicamente con hidroxido de amonio y se extrajo con acetato de etilo Los extractos se secaron sobre sulfato de magnesio y se concentraron El residuo se purificó por cromatografía instantánea (gel de sílice, acetona/hexanos al 50%) para dar 6 6 mg del compuesto del titulo como un sólido quemado u obscuro P f 225-230, [M+H] *m/z* 486, HPLC al 100% a 3 8 min (columna YMC S5 ODS 4 6 x 50 mm, metanol al 10-90%, agua con ácido fosforico al 0 2% gradiente sobre 4 min , 4 mL/min , detección uv a 220 nm)

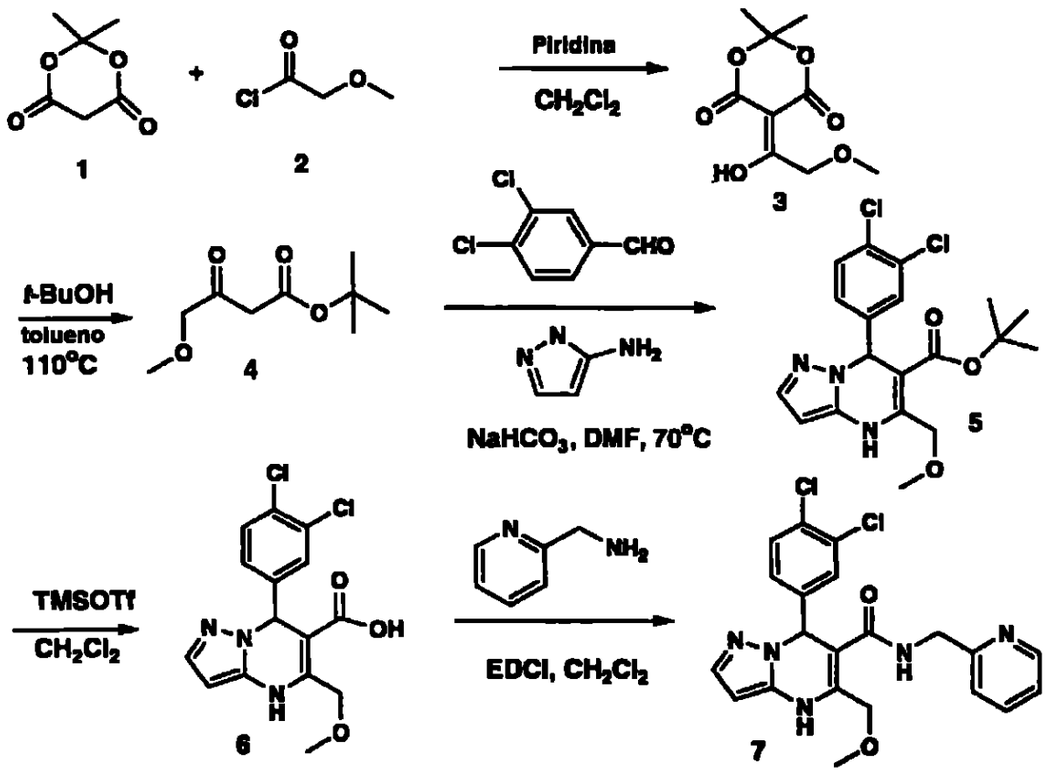
Ejemplo 484

7-(3,4-diclorofenil)-4,7-dihidro-5-(metoximetil)-N-(2-piridinilmetil)pirazolo[1,5-a]pirimidina-6-carboxamida

H52 1176



Esquema



1153 1177

Síntesis de 3 Una solución de 2,2-dimetil-1,3-dioxano-4,6-diona (acetona, hexano) recistalizada (1,25 0 g, 173 5 mmol) en diclorometano (350 mL) se trato con piridina (27 4 g, 346 9 mmol) La mezcla de reaccion se enfrio a -5 1°C A esta solución agitada se agregó una solución de cloruro de metoxiacetilo (2, 20 7 g 190 8 mmol) en dicloroemtano (150 mL) durante 150 minutos, manteniendo la reaccion por de bajo de 1 5°C La mezcla resultante se torno naranja y se formó un precipitado La mezcla de reacción se dejó calentar a 17 5°C durante 40 minutos La mezcla ae reaccion se torno marron y se disolvieron los solidos Después el TLC (acetato de etilo al 100%) mostro que la reacción se completó, la reacción se enfrio rápidamente con 3 7% de ácido clorhídrico acuoso (500 mL) y las capas acuosas se extrajeron con diclorometano Los extractos organicos se combinaron y se lavaron con cloruro de sodio acuoso, se secaron sobre sulfato de magnesio arhidro, y se filtraron El solvente se removio El aceite resultante se seco en alto vació a peso constante para dar 3 (33 11 g) en 88 3% de rendimiento

Síntesis de 4 A una solución de 3 (33 1 g, 153 mmol) en 100 mL de tolueno se agrego 2-metil-2-propanol

(100 mL, 1 05 mol) y la reacción se calento a reflujo Después de 1 5 horas la reacción se concentró para dar 4 (30 2 g) en rendimiento al 100%

Síntesis de 5 A la solución de β-cetoester 4 (30 2 g, 160 6 mmol) en dimetilformamida (120 mL) se agregó 3,4-diclorobenzaldehído (28 13 g, 160 6 mmol), seguido por 3-aminopirazol (14 7 g, 176 7 mmol), despues, carbonato de hidrógeno de sodio (54 g, 642 6 mmol) La mezcla de reacción se calento a 70°C por 48 horas La mezcla de reacción entonces se enfrio a 35°C y se transfirio en agua con rápida agitacion (1 5 L) a temperatura ambiente El sólido blancuzco resultante se filtró El sólido filtrado se suspendio en agua (1 L) y se filtró nuevamente La pasta humeda (165 g) se disolvio en acetato de etilo (1 L), dando una mezcla de dos fases La mezcla se lavo con cloruro de sodio acuoso saturado (500 mL) La capa orgánica se seco sobre sulfato de sodio anhidro y se filtró El solvente se removió El material crudo se purificó por cromatografía en columna usando acetato de etilo al 40% en hexano como eluyente para dar 5 (22 6 g, 34 3%) como un polvo blanco

Síntesis de 6 A una solución de éster ter-butílico de dihidropiridina **5** (10 13 g, 24 7 mmol) en diclorometano (150 mL) se agrego una solución de trimetilsililtrifluorometanosulfonato (11 g, 49 5 mmol) en diclorometano (11 mL) Después de 1 hora, se agregó hexano (300 mL) lentamente y la reaccion se concentró a 250 mL El producto formó una goma y el sobrenadante se decantó Se agregó hexano (250 mL) y la mezcla se dejó agitar por 1 hora La goma ha solidificado y formado un polvo El sobrenadante se decantó nuevamente y se agregaron adicionalmente 250 mL de hexano La mezcla se agito por 10 minutos y se filtró La pasta húmeda resultante se lavó con hexano (250 mL) y resultó un polvo blancuzco fino **6** el cual se dejó para secado por succion

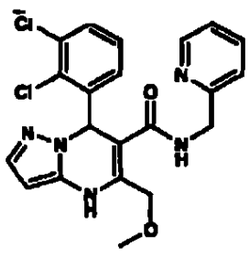
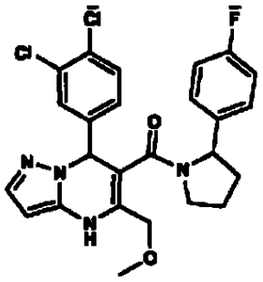
Síntesis de 7 A una suspensión de ácido de hidropiridina **6** (100 mg, 0 28 mmol) en diclorometano (10 mL) se agrego EDCI (76 mg, 0 39 mmol), seguido por una solucion de 2-piridilmetilamina (32 4 mg, 0 39 mmol) en diclorometano (1 mL) Después de 2 5 horas, la reacción se concentro a sequedad y la mezcla cruda se purifico por cromatografia en gel de sílice usando metanol al 10% en diclorometano como eluyente para dar el compuesto del titulo (90 mg,

1175 1180

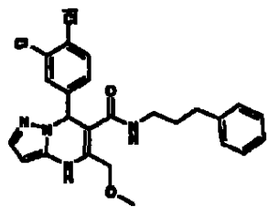
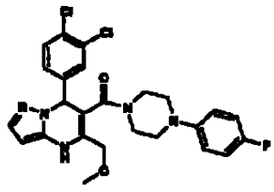
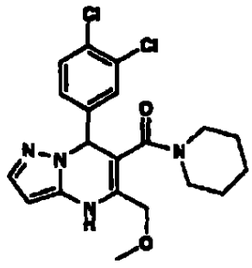
72 4ł) como un polvo blancuzco Espectro de Masa m/z (M+Na) 466

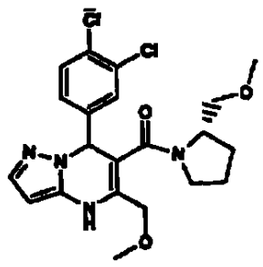
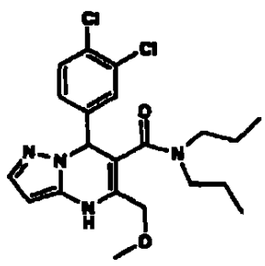
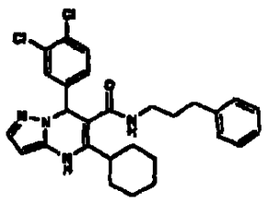
Ejemplos 485-496

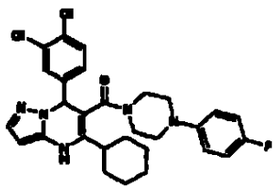
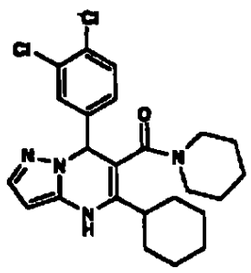
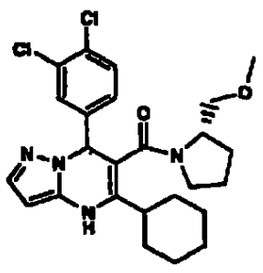
Los siguientes compuestos se prepararon por el método descrito en el ejemplo 484

Ejemplo No	Estructura	Nombre	Espectro de Masa
485		7-(2,3-Dicloro-fenil)-4,7-dihidro-5-(metoximetil)-N-(2-piridinil-metil)pirazolo[1,5-a]pirimidin-6-carboxamida	444 (M+H)
486		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-(metoxi-metil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(4-fluorofenil)pirro-lidina	501 (M+H)⁺

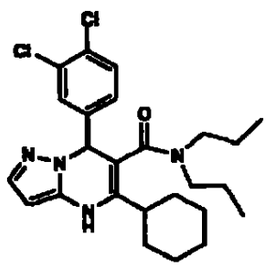
HJ7 1181

487		7-(3,4-dicloro-fenil)-4,7-dihidro-5-(metoximetil)-N-(3-fenil-propil)pirazolo[1,5-a]pirimidin-6-carboxamida	471 (M-F)
488		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-(metoxi-metil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluoro-fenil)piperazina	516 (M+H)$^+$
489		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-(metoxi-metil)pirazolo[1,5-a]pirimidin-6-il]carbonil]piperi-dina	421 (M+H)

490		(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-(metoxi-metil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina	451 (M+H)$^+$
491		7-(3,4-dicloro-fenil)-4,7-dihidro-5-(metoximetil)-N,N-dipropilpirazolo[1,5-a]pirimidin-6-carboxamida	437 (M+H)$^+$
492		5-Ciclohexil-7-(3,4-diclorofenil)-4,7-dihidro-N-(3-fenil-propil)pirazolo[1,5-a]pirimidin-6-carboxamida	509 (M+H)

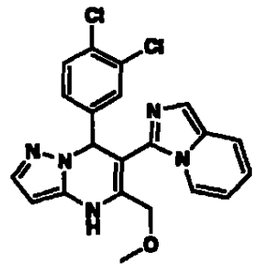
493		1-[[5-ciclohexil-7-(3,4-diclorofenil)-4,7-dihidro-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)pipera-zina	554(M+H)
494		1-[[5-ciclohexil-7-(3,4-diclorofenil)-4,7-dihidropirazolo[1,5-a]pirimidin-6-il]carbonil]piperi-dina	459(M+H)
495		(2S)-1-[[5-ciclohexil-7-(3,4-diclorofenil)-4,7-dihidropirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirro-lidina	489(M+H)

H60, 1134

496		5-Ciclohexil-7-(3,4-diclorofenil)-4,7-dihidro-N,N-dipropilpirazolo[1,5-a]pirimidin-6-carboxamida	475(M+H)

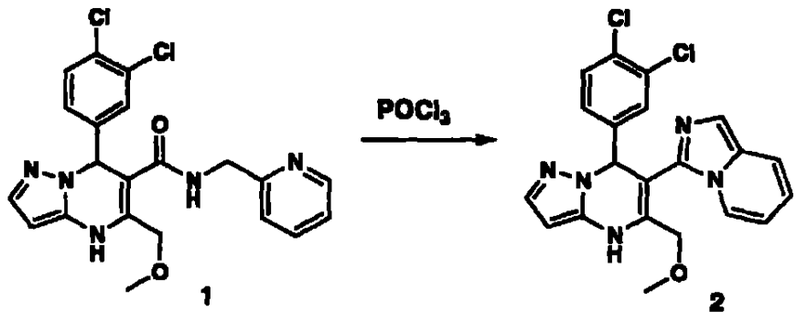
Ejemplo 497

7-(3,4-Diclorofenil)-4,7-dinidro-6-(imidazo[1,5-a]piridin-3-il)-5-(metoximetil)pirazolo[1,5-a]pirimidina



Esquema

1164 1185



1 2

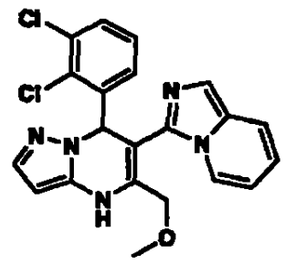
Síntesis de 1 La síntesis 1 se describe en el Ejemplo 484

Síntesis de 2 El compuesto del título se sintetizo en una manera descrita en el Ejemplo 465 El producto se purificó por TLC preparativa en metanol al 10% en diclorometano Espectro de Masa m/z $(M+H)^+$ 426

Ejemplo 498

7-(2,3-diclorofenil)-4,7-dihidro-6-(imidazo[1,5-a]pirimidin-3-il)-5-(metoximetil)pirazolo[1,5-a]pirimidina

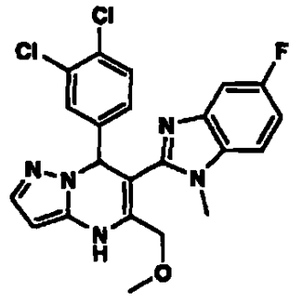
H62 1106



El compuesto del título se sintetizó en una manera similar a aquella descrita en el Ejemplo 497 Espectro de Masa m/z (M+H) 426

Ejemplo 499

7-(3,4-diclorofenil)-6-(5-fluoro-1-metil-1H-bincimidazol-2-il]-4,7-dihidro-5-(metoximetil)pirazolo[1,5-a]pirimidina



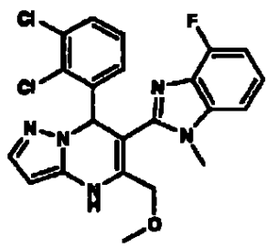
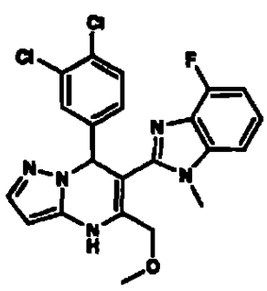
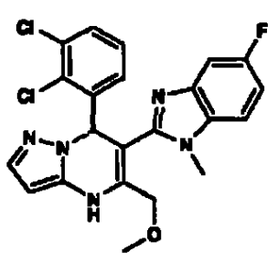
Partiendo con el compuesto 6 del Ejemplo 484, el compuesto del título se sintetizó en una

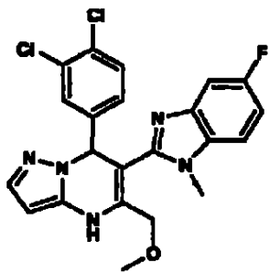
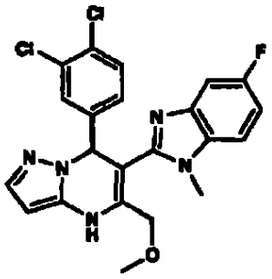
manera similar a aquella descrita en el Ejemplo 470 Espectro de Masa m/z (M+H)⁻ 458 El compuesto del titulo puede ser separado en una forma quiral pura vía HPLC quiral preparativa (columan Chiralpak AD 5 cm x 50 cm, eluido con isopropanol al 25% en hexano con TEA al 0 1% a 50 mL/min con detección UV a 254 nM) El isómero que eluye más rápido (ejemplo 503) es enantiómero A (HPLC tiempo de retencion 6 8 min, columna Chiralpak AD 4 6 x 250, eluido con isopropanol al 25%, hexano con trietilamina al 0 1% a 1 mL/min con deteccion UV a 220 nm) y el isomero que eluye más lento (ejemplo 504) es el enantiómero B (HPLC tiempo de retencion 12 0 min, columna Chiralpak AD 4 6 x 250 mm, eluido con isopropanol al 25%, hexano con trietilamina al 0 1% a 1 mL/min con detección UV a 254 nm)

Ejemplos 500-504

Los siguientes ejemplos se sintetizaron por metodos descritos en el Ejemplo 499

H64 1188

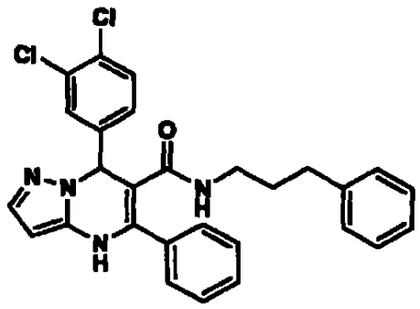
Ejemplo No	Estructura	Nombre	Espectro de Masa
500		7-(2,3-Dicloro-fenil)-6-(4-fluoro-1-metil-1H-bencimidazol-2-il)-4,7-dihidro-5-(metoxi-metil)pirazolo[1,5-a]pirimidina	458 (M+H)
501		7-(3,4-dicloro-fenil)-6-(4-fluoro-1-metil-1H-bencimidazol-2-il)-4,7-dihidro-5-(metoxi-metil)pirazolo[1,5-a]pirimidina	458 (M+H)$^+$
502		7-(2,3-dicloro-fenil)-6-(5-fluoro-1-metil-1H-bencimidazol-2-il)-4,7-dihidro-5-(metoxi-metil)pirazolo[1,5-a]pirimidina	458 (M+H)$^+$

503		7-(3,4-dicloro-fenil)-6-(5-fluoro-1-metil-1H-bencimidazol-2-il)-4,7-dihidro-5-(metoximetil)pirazolo[1,5-a]pirimidina, enantiómero A	458(M+H)
504		7-(3,4-dicloro-fenil)-6-(5-fluoro-1-metil-1H-bencimidazol-2-il)-4,7-dihidro-5-(metoximetil)pirazolo[1,5-a]pirimidina, enatiomero B	458(M+H)

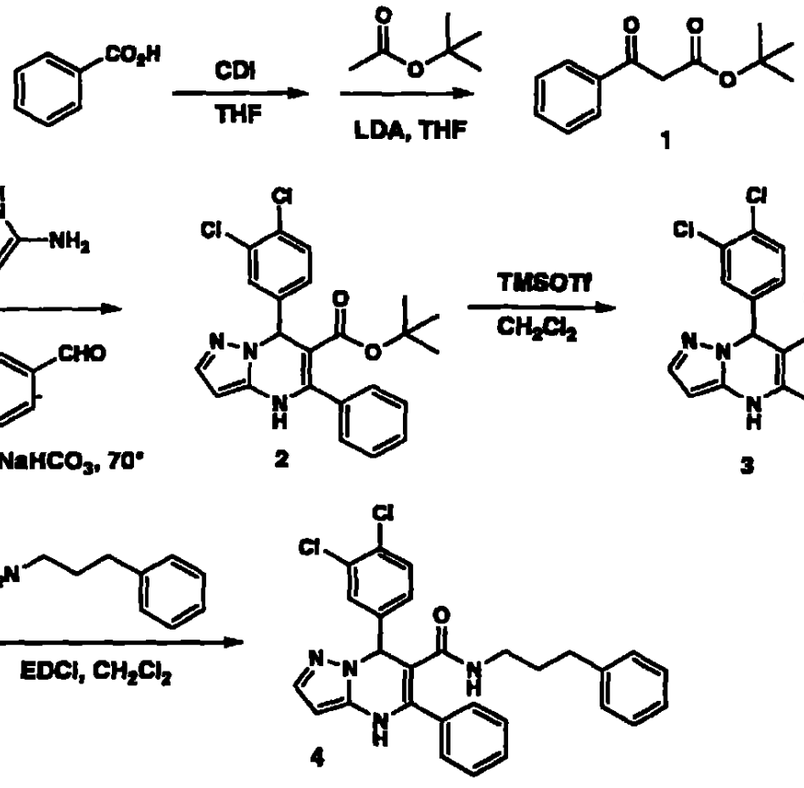
Ejemplo 505

7-(3,4-diclorofenil)-4,7-dihidro-5-fenil-N-(3-fenilpropil)pirazolo[1,5-a]pirimidin-6-carboxamida

1166 1190



Esquema



Síntesis de 1 Una solución de ácido benzóico (3 05 g, 25 mmol) en tetrahidrofurano (25 mL) se trato con

CDI (4 05 g, 25 mmol) a temperatura ambiente En un matraz separado se generó litiodiisopropilamida a -78°C por tratamiento de una solución de tetrahidrofuran (40 mL) de amina diisopropilo (10 6 mL, 76 0 mmol) con 2 5 M de litio de n-butilo en hexanos (30 mL, 75 0 mmol) Se agregó acetato de tert-butilo en forma de gotas y la reaccion se agitó a -78°C por 1 hora El enolato se transfirió a -78°C a una solución agitada del imidazoilbenzoato previamente preparada La solución resultante se enfrio a -78°C Despues de la adición del enolato se completo, resulto una suspensión espesa, la cual se disolvio por medio de sacudimiento de la reacción La mezcla de reaccion se dejo agitar por 1 hora a -78°C Una solucion acuosa 1N de ácido clorhídrico se agregó hasta que el pH fue 4 La mezcla de reacción se dejó calentar a temperatura ambiente con agitacion La mezcla de reaccion se extrajo con eter dietílico Las capas organicas combinadas se lavaron con ácido clorhídrico 1N acuoso, carbonato hidrogenado de sodio al 10% acuoso, cloruro de sodio acuoso saturado, se seco sobre sulfato de magnesio y se filtró El solvente se removio para dar 1 (5 0 g, 91%) como un aceite

H66,1192

Síntesis de 2 El compuesto 2 se sintetizó en una manera similar a aquella del compuesto 5 en el Ejemplo 484

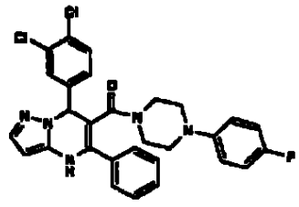
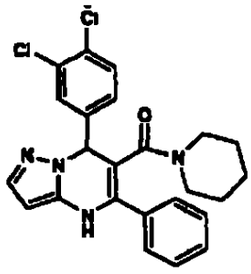
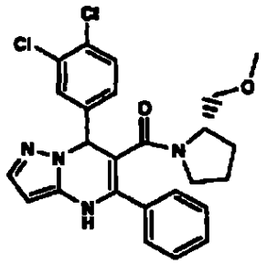
Síntesis de 3 El compuesto 3 se sintetizo en una manera similar a aquella del compuesto 6 en el ejemplo 484

Síntesis de 4 El compuesto del titulo se sintetizó en una manera similar a aquella del compuesto 7 en el ejemplo 484 Espectro de Masa m/z $(M+H)^+$ 503

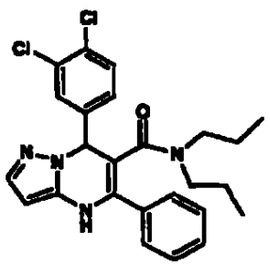
Ejemplos 506-509

Los siguientes Ejemplo 506-509 se sintetizaron en una manera similar a aquella descrita en el Ejemplo 505

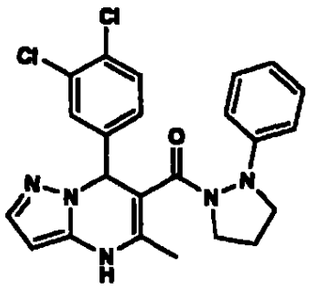
1169 1193

Ejemplo No	Estructura	Nombre	Espectro de Masa
506		1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-fenilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina	448(M+H)
507		1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-fenilpirazolo[1,5-a]pirimidin-6-il]carbonil]piperidina	459(M+H)
508		(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-fenilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina	483(M+H)

H70,194

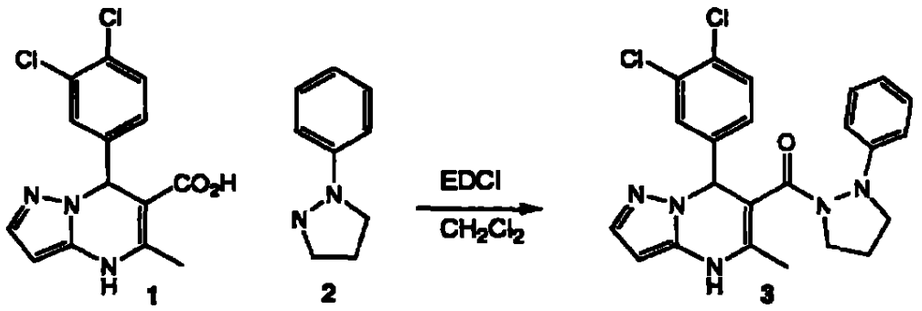
509		7-(3,4-dıcloro-fenıl)-4,7-dıhıdro-5-fenıl-N,N-dıpropılpırazolo[1,5-a]pırımıdın-6-carboxamıda	475(M+H)

Ejemplo 510



Esquema

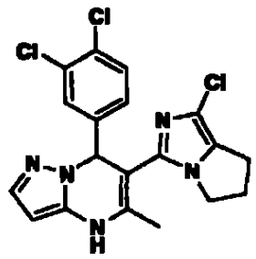
H/T 1195



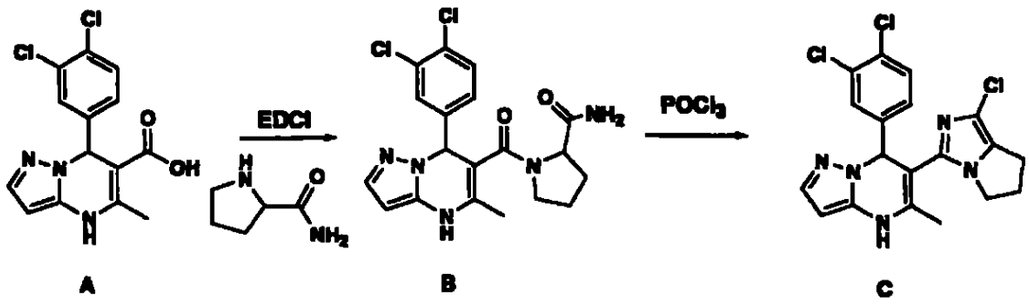
Preparacion de 3 A una solución de ácido dihidropirimidina 1 (0 336 g, 1 mmol) en diclorometano (10 mL) se agregó 1-fenilpirazolidina 2 (0 215 g, 1 5 mmol, se preparo usando el procedimiento descrito en *Tetrahedron*, **1973**, 29, 4045) seguido por clorhidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (0 278 g, 1 5 mmol) y la mezcla se agitó a temperatura ambiente por 2 horas El solvente se evaporó y el residuo se purificó por cromatografía en gel de sílice, eluido con acetato de etilo, para dar el compuesto del titulo 3 (0 184 g, al 39%) como un polvo blanco (M+H) = 455

H72,196

Ejemplo 511



Esquema



Preparacion de B Se agregó EDCI (100 mg, 0 52 mmol) a 20°C, a una suspension agitada de ácido carboxílico **A** (120 mg, 0 37 mmol) en CH_2Cl_2 Después de 5 minutos, se agregó prolinamida (60 mg, 0 52 mmol) y

1173,197

la mezcla de reacción se agitó a temperatura ambiente por 3 horas La suspensión amarilla resultante se concentro bajo presión reducida, se disolvio en 2 mL de acetona y se aplico directamente a una placa de TLC de gel de sílice preparativa, (20x20 cm, espesor 1mm, indicador UV 254 mm) eluyendo con MeOH al 10% en CH_2Cl_2 El producto B se aisló con una relación de 1 1 de diastereomeros (79 mg, 50% de rendimiento como un vidrio amarillo palido) HPLC R_T 2 61 y 2 80 min (columna Ballistic YMC S5 ODS 4 6 x 50 mm) MeOH/agua al 10-90% con gradiente lineal PPA al 0 2% durante 4 minutos, 4 mL/min, deteccion UV a 220 nm LCMS R_T 2 63 y 2 81 minutos (columna Ballistic YMC S5 ODS 4 6 x 50 mm) MeOH/agua al 10-90% con gradiente lineal TFA al 0 1% durante 4 min, 4 mL/min, Detección UV a 220 nm, Espectro de Masa m/z (M+H) 420

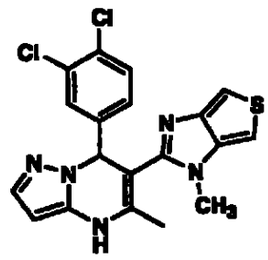
Preparacion de C Se agrego oxicloruro de fosforo (4 mL) al diastereómero B (190 mg, 0 46 mmol) La suspensión se calento a 100°C por 12 horas en que lo precipitado se disolvio hasta proporcionar una solucion coloreada naranja La mezcla de reacción enfriada se vertio cuidadosamente en K_2CO_3 saturado (ca 20 mL) y se extrajo con EtOAc (3x30 mL) Las porciones organicas combinadas se secaron sobre

1174 1198

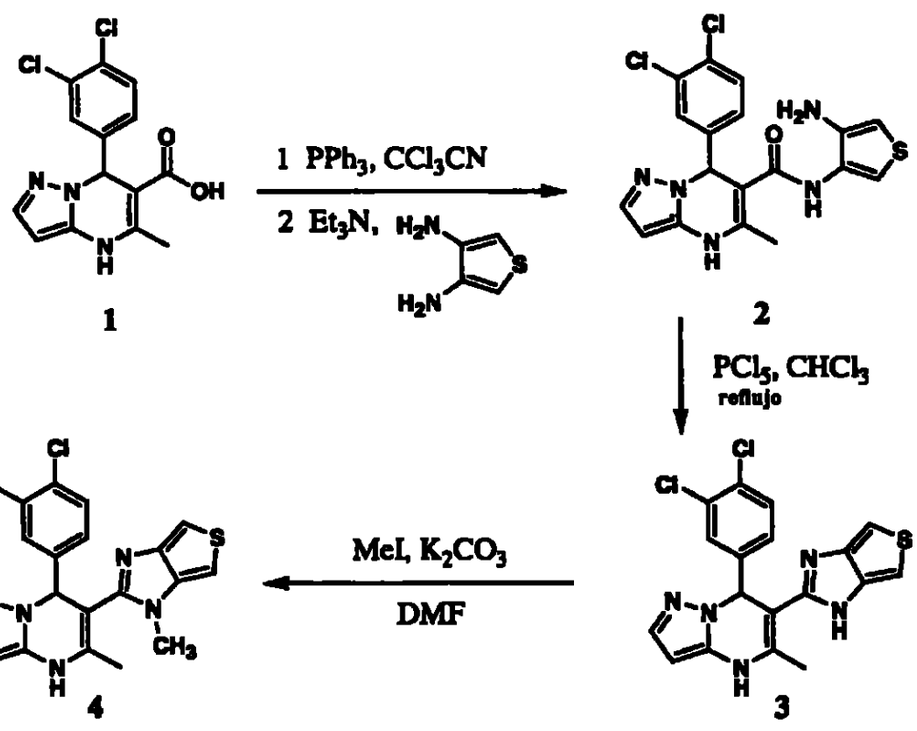
Na_2SO_4, se decantaron y se concentraron que produce un aceite naranja el cual se purificó directamente por HPLC preparativa R- 28 40 min (columna C18 de fase inversa YMC S5 ODS 30 x 250 mm) MeOH/agua al 30-90% con gradiente lineal TFA al 0 1% durante 30 minutos, 25 mL/min, Deteccion UV a 220 nm El Producto C (96 mg, rendimiento de 51%) se obtuvo como una base libre después de la remoción de MeOH de las fracciones HPLC, adicionalmente de 1 0 M de NaOH y extracción en CH_2Cl_2 (3 x 30 mL) Los enantiómeros se separaron por HPLC quiral preparativa R- 42 4 y 59 0 min (columna de fase normal ChiralPak OD 50 x 500 mm) EtOH/hexano isocratico al 15%, 50 mL/min, detección UV a 220 nm Ambos enantiómeros se aislaron como polvos amarillo pálidos, (34 mg de anatiómero A y 38 mg de enantiómero B) Enatiómero B HPLC quiral R_T 7 36 min (columna de fase normal ChiralPak OD 4 6 x 250 mm) EtOH/hexano Isocratico al 15%, 2 mL/min, detección UV a 220 nm 100% ee Enantiómero A HPLC quiral R- 4 94 min (columna de fase normal ChiralPak OD 4 6 x 250 mm) EtOH/hexano Isocratico al 15%, 2 mL/min, detección UV a 220 nm 100 ee

4475 1199

Ejemplo 512



Esquema



H76120

Preparación del c mpuesto 1 como se oescribe en el Ejemplo 16

Preparación del compuesto 2 A una suspension del ácido (152 9 mg, 0 47 mmol) en 5 mL de diclorometano anhidro se agregó tricloroacetonitrilo (57 0 µL, 0 67 mmol) y trifenilfosfina (186 2 mg, 0 71 mmol) La mezcla llego a ser clara y se dejó agitar a temperatura ambiente por 1 hora La mezcla de reacción se transfirio en una solucion de clorhidrato de 3,4-diaminotiofeno (88 5 mg, 0 47 mmol) y trietilamina (198 0 µL, 1 42 mmol) en 5 mL de oiclorometano La reaccion se monitoreo usando TLC o LC/MS Después de la terminacion de acoplamiento, la mezcla oe reacción de cargo directamente en gel de silice y se eluyó con metanol/diclorometano al 5% para proouoir la amioa oeseada como un sólido blanco (132 3 mg al 67%)

Preparacion del compuesto 3 Una suspensión de la amida resultante (107 mg, 0 25 mmol) y pentacloruro de fósforo (53 1 mg, 0 25 mmol) en cloroformo (20 mL) se calentó a reflujo bajo argón anhidro por 5 horas y la mezcla se dejo para enfriar bajo temperatura ambiente y se agitó durante la noche El solvente se

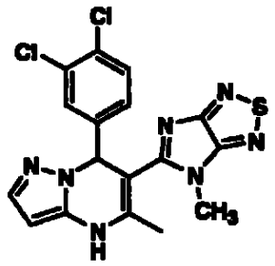
477
201

removió bajo presión reducida, y el residuo se disolvió en acetato de etilo se lavó brevemente con una solución de bicarbonato de sodio acuoso saturado La capa orgánica se separo, se seco sobre sulfato de sodio y se concentró para dar el tienoimidazol crudo, el cual se purifico por cromatografía instantánea usando acetato de etilo al 100% para dar el sólido marrón (73 mg, al 71%)

Preparación del compuesto 4 A una solucion del tienoimidazol (22 4 mg, 0 06 mmol) en 2 mL de DMF anhidro se agrego iodometano (4 5 µL, 0 07 mmol) y carbonato de potasio (15 4 mg, 0 11 mmol) La mezcla se dejó agitar a temperatura ambiente durante la noche La reacción se enfrio rápidamente usando metanol La mezcla se diluyo con acetato de etilo y se lavó con LiCl al 10% (3 x 10 mL) y salmuera (10 mL) La capa orgánica se separo y se secó sobre sulfato de sodio y se concentró para dar un residuo, el cual se purificó adicionalmente usando cromatografía instantanea (MeOH/acetato de etilo al 5%) y MeOH/cloroformo al 6%) para dar el compuesto del titulo como un solido blanco (4 5 mg, al 20%)

1202
1470.

Ejemplo 513



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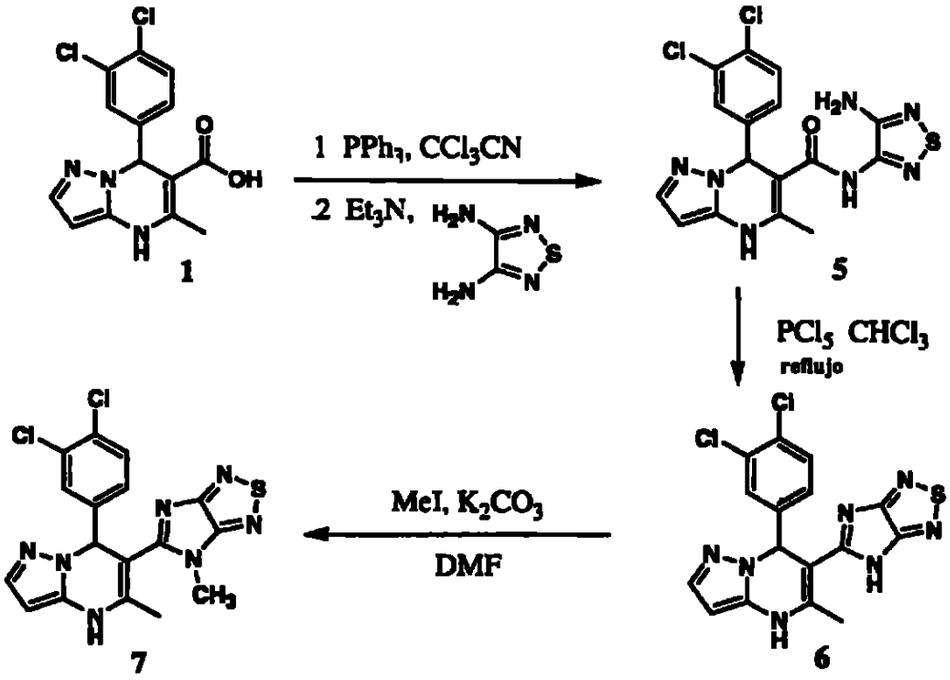


1179 1203

Preparación del compuesto 5 A una suspension del ácido (120 mg, 0 37 mmol) en 5 mL de diclorometano anhidro se agregó tricloroacetonitrilo (55 9 µL, 0 56 mmol) y trifenilfosfina (146 2 mg, 0 56 mmol) La mezcla llegó a ser clara y se dejó agitar a temperatura ambiente por 1 hora La mezcla de reacción se transfirió en una solución de 3,4-diamino-1,2,5-tiadiazol (51 7 mg, 0 45 mmol, se preparo de conformidad a J Heterocycl Chem **1976**, 13, 13) y trietilamina (103 6 µL, 0 74 mmol) en 5 mL de diclorometano La reacción se monitoreó usando TLC o LC/MS Después de la terminación del acoplamiento, la mezcla de reacción se cargó directamente en gel de sílice y se eluyo con acetato de etilo/hexanos al 50% para dar la amina deseada como un sólido amarillo (56 4 mg, al 30%)

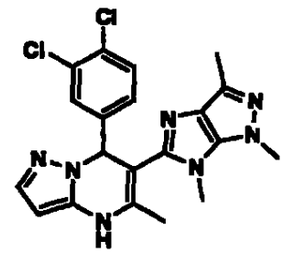
Preparacion del compuesto 6 Una suspension de la amida resultante (80 mg, 0 19 mmol) y pentacloruro de fósforo (79 mg, 0 38 mmol) en cloroformo (10 mL) se agito a temperatura ambiente bajo argón anhidro por una hora y entonces se calentó a reflujo por 2 horas La mezcla se dejo enfriar bajo temperatura ambiente y el solvente se removio bajo presión reducida El residuo se redisolvio en acetato de etilo y se lavó

brevemente con una solucion de bicarbonato de sodio acuoso saturado La capa organica se separo, se secó sobre sulfato de sodio, y se concentró para dar el tiodiazoimidazol crudo, el cual se purifico por cromatografía instantánea usando acetato de etilo/nexanos al 80% para dar un sólido amarillo (29 mg, al 38%)

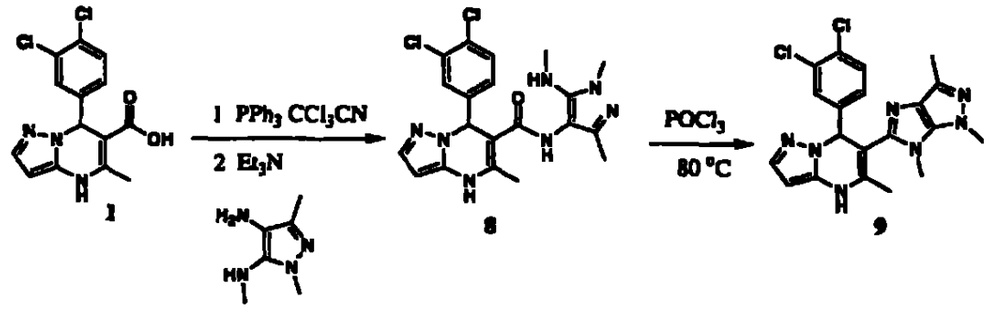
Preparación del compuesto 7 A una solucion del tiadiazoimidazol (29 mg, 0 07 mmol) en 2 mL de DMF annidro se agrego iodometano (4 9 µL, 0 08 mmol) y carbonato de potasio (19 9 mg, 0 14 mmol) La mezcla se dejo agitar a temperatura ambiente bajo argon seco por 3 horas La reaccion se enfrió rápidamente usando metanol y se diluyó con acetato de etilo y se lavó con LiCl al 10% (3 x 10 mL) y salmuera (10 mL) La capa organica se separo y se secó sobre sulfato de sodio y se concentró para dar un residuo, el cual se purificó usando HPLC para dar el compuesto del titulo como un sólido blanco (1 6 mg, al 5%)

1481 1205

Ejemplo 514



Esquema



Preparación del compuesto 8 A una suspensión del ácido (150 mg, 0 46 mmol) en 5 mL de diclorometano anhidro, se agrego tricloroacetonitrilo (69 8 µL, 0 70 mmol) y trifenilfosfina (182 7 mg, 0 70 mmol) La mezcla llegó a ser clara y se dejo agitar a

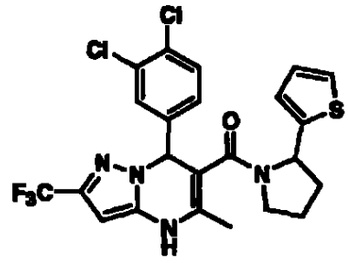
H82,120

temperatura ambiente por 1 hora La mezcla de reacción se transfirió en una solución de diaminopirazol (preparada de conformidad con *J Med Chem* **1995**, 3524) y trietilamina (129 5 µL, 0 93 mmol) en 5 mL de diclorometano La reacción se monitoreó usando TLC o LC/MS Después de la terminación del acoplamiento, la mezcla de reacción se cargó directamente en gel de sílice y se eluyó con metanol/acetato de etilo al 10% para proporcionar la amida deseada como un sólido blanco

Preparación del compuesto 9 Una suspensión de la amida resultante (39 5 mg, 0 09 mmol) en oxicloruro de fósforo (10 mL), se agito a 80°C bajo argón anhidro durante la noche La mezcla se dejo enfriar bajo temperatura ambiente y el solvente se removió bajo presión reducida El residuo se redisolvió en acetato de etilo y se lavo brevemente con una solucion de bicarbonato de sodio acuoso saturado La capa orgánica se separó, se secó sobre sulfato de sodio, y se concentro para dar un residuo, el cual se purificó por cromatografía instantánea usando metanol/diclorometano al 10% para dar el producto deseado como un sólido ligeramente café (13 9 mg, 37%)

1183257

Ejemplo 515



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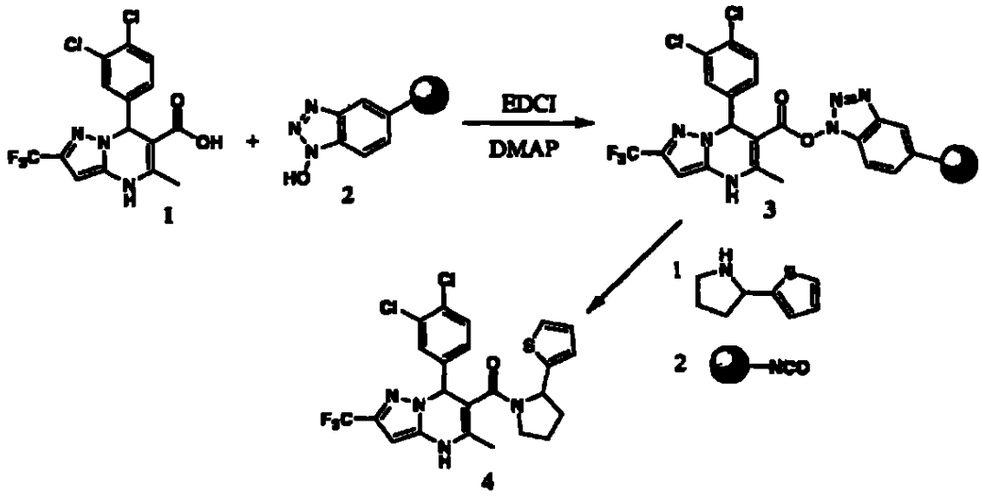


Preparacion del compuesto 1 como se describe en el Ejemplo 17

Preparación del compuest 3 A una suspensión del reactivo HOBt soportado por poliestireno (5 2 g, 8 0 mmol) en 100 mL de diclorometano anhidro se agrego en un recipiente de reacción que tiene un filtro de vidrio y una fitra en la parte inferior, el acido (4 7 g, 12 0 mmol), clorhidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (2 3 g, 12 0 mmol), y 4-dimetilaminopiridina (98 mg, 0 8 mmol) La mezcla se sacudió usando un sacudidor orbital por 3 horas a temperatura ambiente El solvente se dreno a traves de la filtración, y la resina se lavó con DMF anhidro (3 x 30 mL), TF anhidro (3 x 30 mL), y diclorometano anhidro (3 x 30 mL) La resina que contiene el ester activado se dejo secar *in vacuo* durante la noche El rendimiento de acoplamiento se estimo basado en el peso ganado como 84%

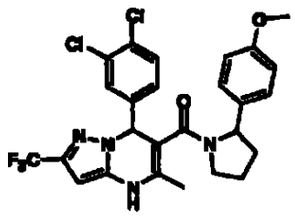
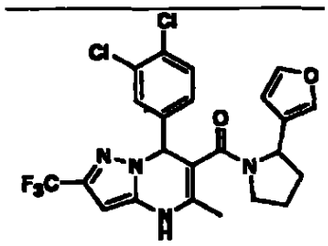
Preparación del compuesto 4 La resina que contiene el ester activado por HOBt (58 mg, 0 55 mmol) se distribuyó en un pozo, al cual se despachó o vació 2-(2'-tienil)-pirrolidina (80 µL de 0 5 M, 0 04 mmol) La suspension se dejo sacudir a temperatura ambiente por 3 horas, y después se agrego el reactivo de isocianato soportado por poliestireno (83 mg, 0 08

mol) y la suspensión se sacudió por 2 horas El solvente se colectó a traves de filtración, y la resina se lavó con diclorometano (2 x 0 5 mL) Todo lo filtrado se combinó y se concentró bajo presion reducida para dar el producto deseado como un sólido blanco (18 mg) La pureza del producto se verificó usando MC/MS como 100%, y m/z es 527

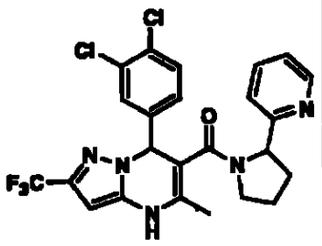
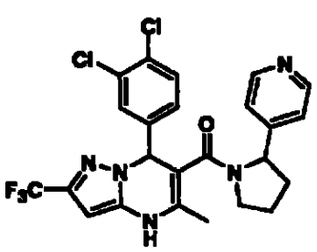
Ejemplos 516-587

Los siguientes compuestos se sintetizaron usando el procedimiento como se describe en el Ejemplo 515 Aquellos compuestos que tienen baja pureza se purificaron usando HPLC preparativo para dar los productos deseados correspondientes

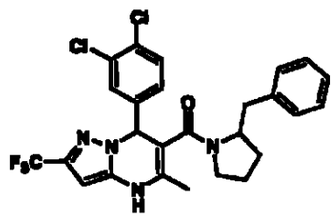
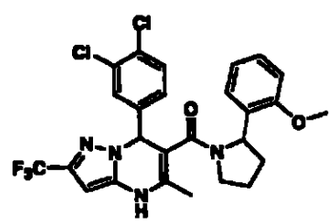
1186/1210

Ejemplo No	Estructura	Nombre	Espectro de Masa
516			551 (M+H)
517			511 (M+H)

1187
1211

518			522 (M+H)
519			522 (M+H)

1188
1212

520			535 (M+H)
521			551 (M+H)

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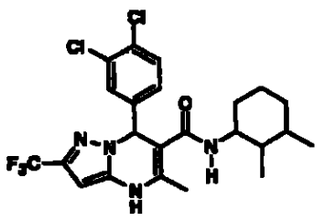
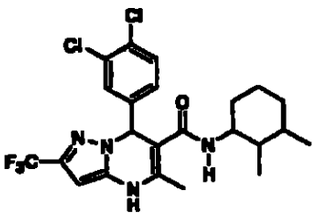
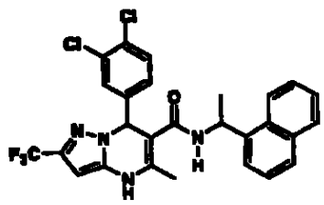
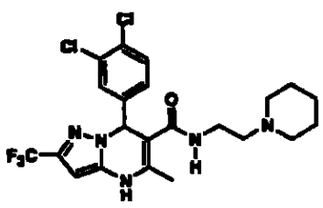
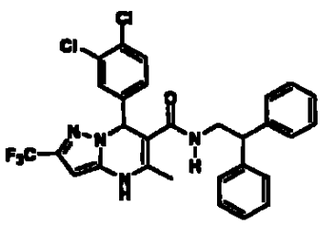
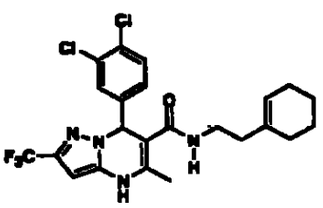
1213

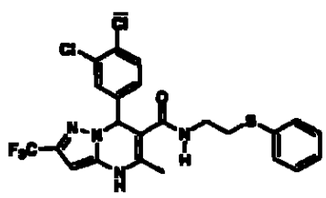
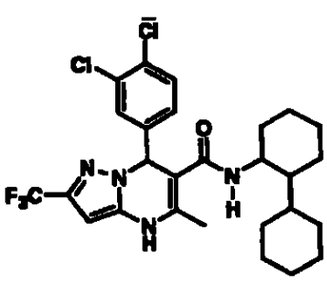
522			549 (M+H)
523			501 (M+H)

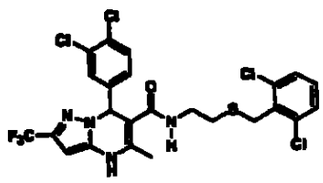
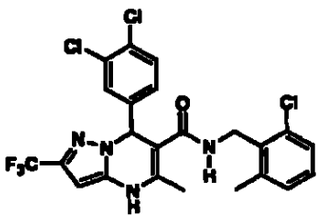
1/90 1204

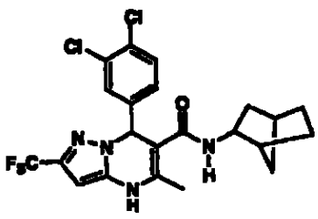
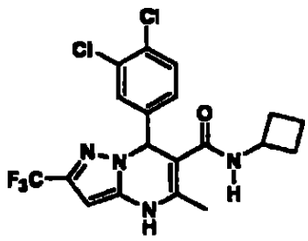
524			545 (M+H)
525			502 (M+H)

526			571 (M+H)
527			499 (M+H)

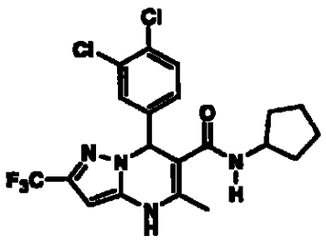
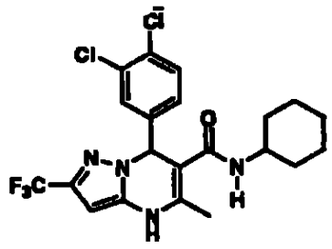
1192
1216

528			527 (M+H)
529			555 (M+H)

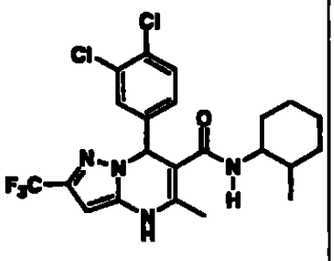
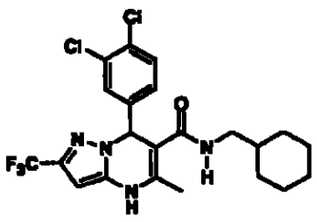
530			610 (M+H)
531			529 (M+H)

532			485 (M+H)
533			445 (M+H)

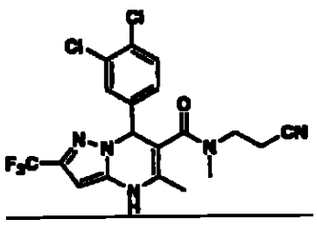
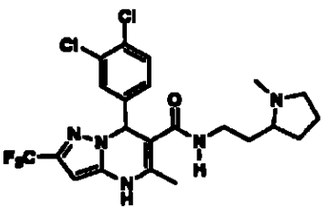
1219 1195

534			458 (M+H)
535			473 (M+H)

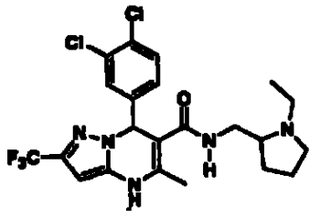
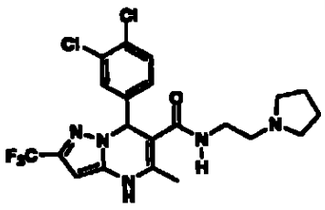
1220
1196

536			487 (M+H)
537			487 (M+H)

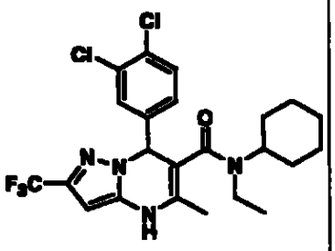
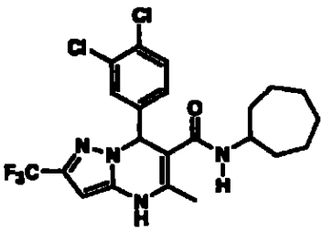
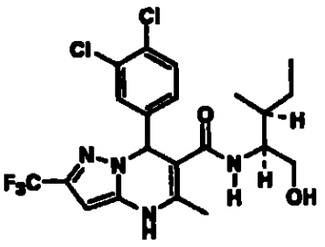
1221
1497

538			458 (M+H)
539			502 (M+H)

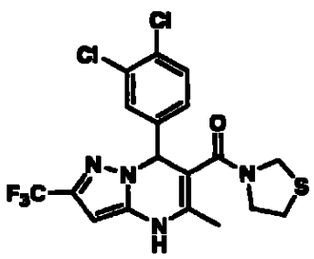
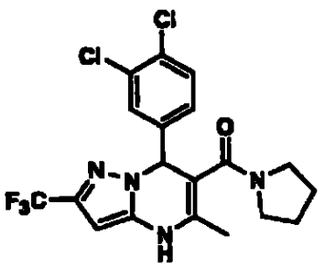
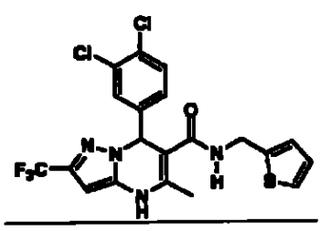
1222
1198

540			502 (M+H)
541			488 (M+H)

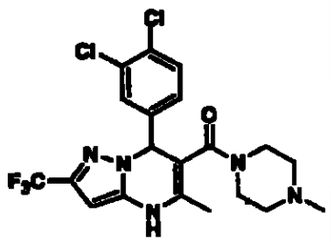
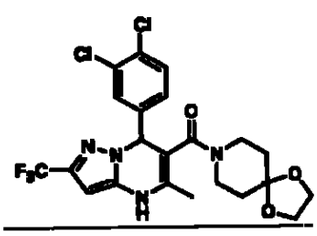
1223
A199

542			501 (M+H)
543			487 (M+H)
544			491 (M+H)

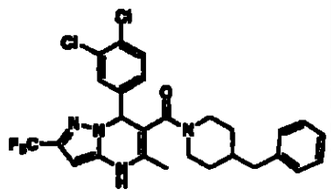
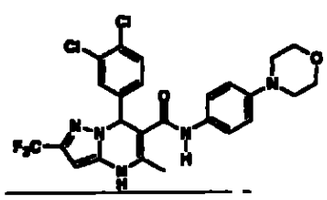
1224

545			463 (M+H)
546			445 (M+H)
547			487 (M+H)

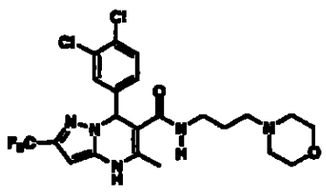
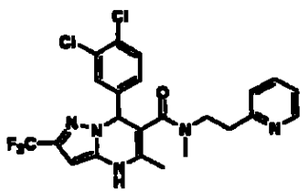
1225
1201

548			474 (M+H)
549			517 (M+H)

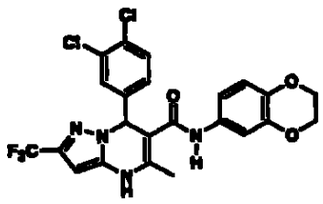
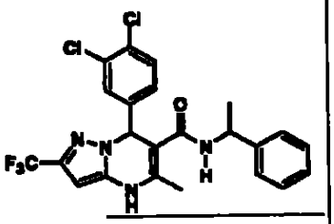
1226 P02

550			549 (M+H)
551			552 $(M+H)^+$

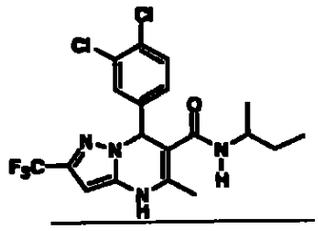
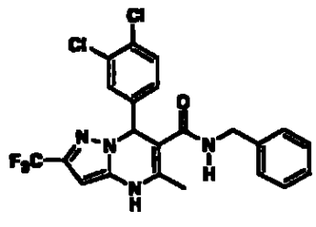
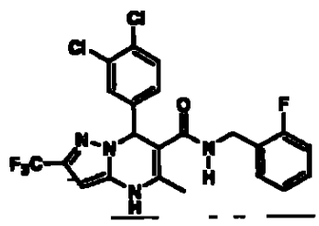
1227 ~~1203~~

552			518 $(M+H)^+$
553			510 $(M+H)^+$

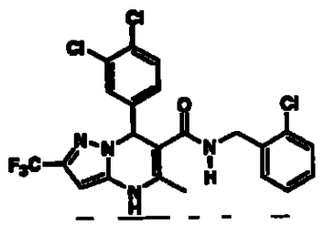
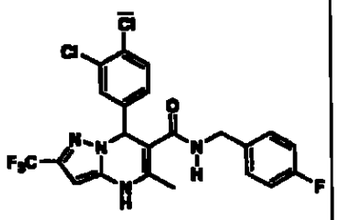
1228 ~~1264~~

554			525 (M+H)$^+$
555			495 (M+H)$^+$

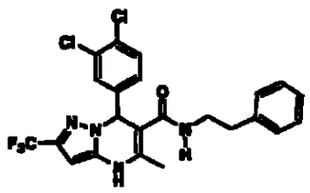
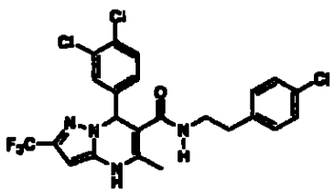
1229 ~~1205~~

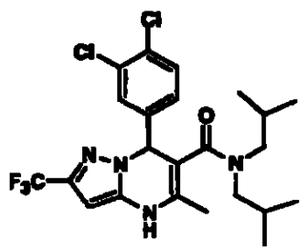
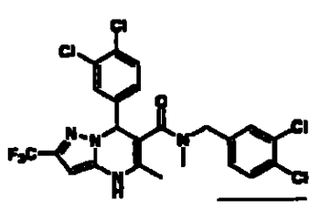
556			447 $(M+H)^+$
557			$(M+H)^+$
558			499 $(M+H)^+$

1230
1206

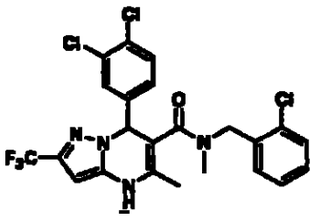
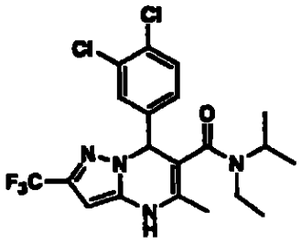
559			515 (M+H)
560			499 (M+H)

1267 P31

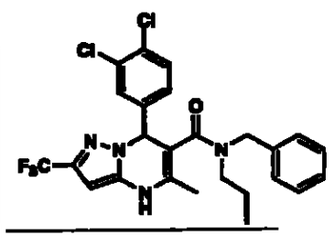
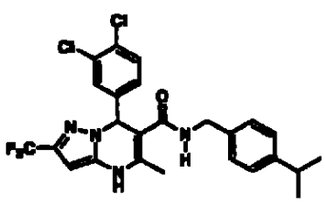
561			495 (M+H)
562			530 (M+H)

563			503 (M+H)
564			564 (M+H)

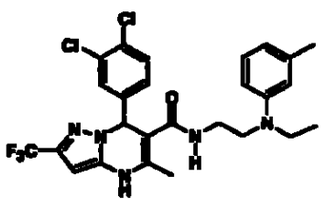
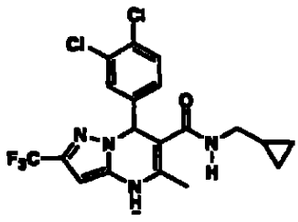
1233

565			530 (M+H)
566			461 (M+H)

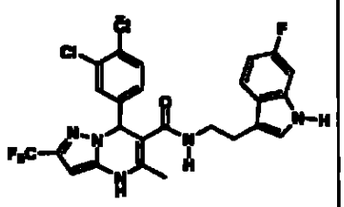
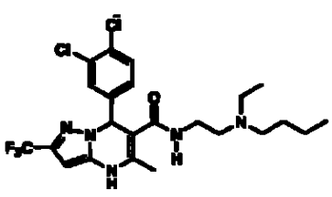
~~1210~~ 1234

567			523 (M+H)
568			523 (M+H)

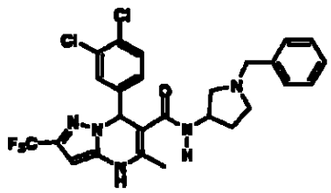
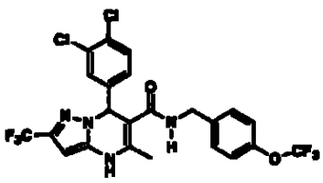
1244 1235

569			552 (M+H)
570			445 (M+H)

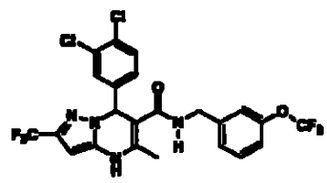
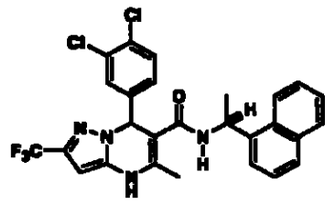
~~1242~~ 1236

571			552 (M+H)
572			518 (M+H)

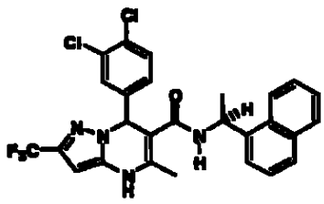
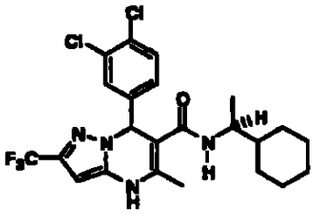
1243
1239

573			550 (M+H)
574			565 (M+H)

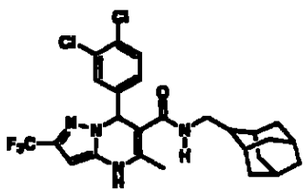
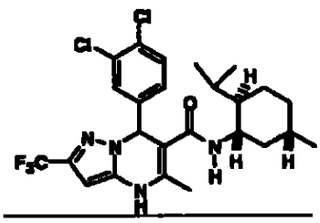
A214 138

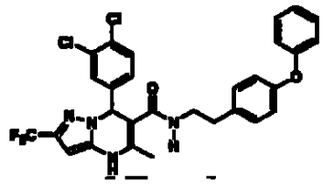
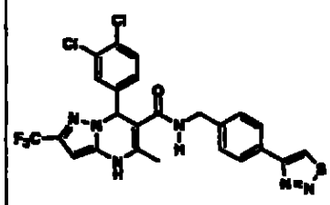
575			565 (M+H)
576			545 (M+H)

125
129

577			545 (M+H)
578			501 (M+H)

1245
1240

579			539(M+H)
580			529(M+H)

581			587 (M+H)
582			565 (M+H)

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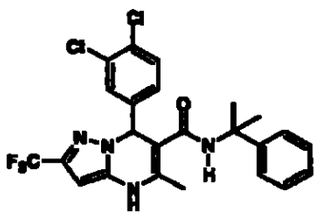
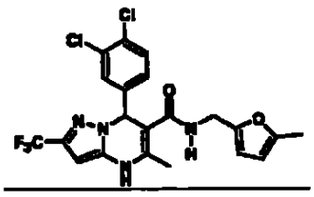
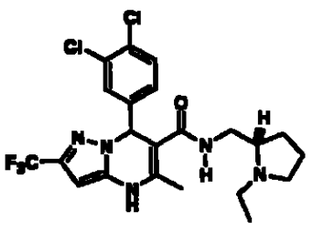
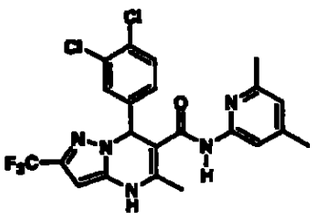
583			509 (M+H)
584			584 (M+H)

1243
1279

585			502 (M+H)
586			596 (M+H)

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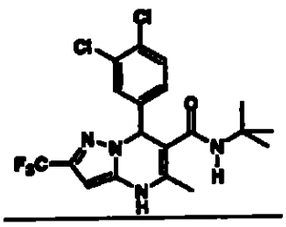
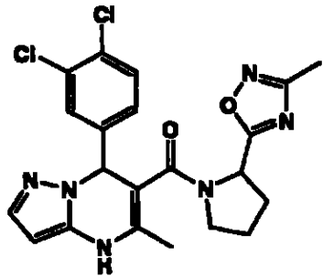
587			447 (M+H)

Ejemplo 588



Esquema

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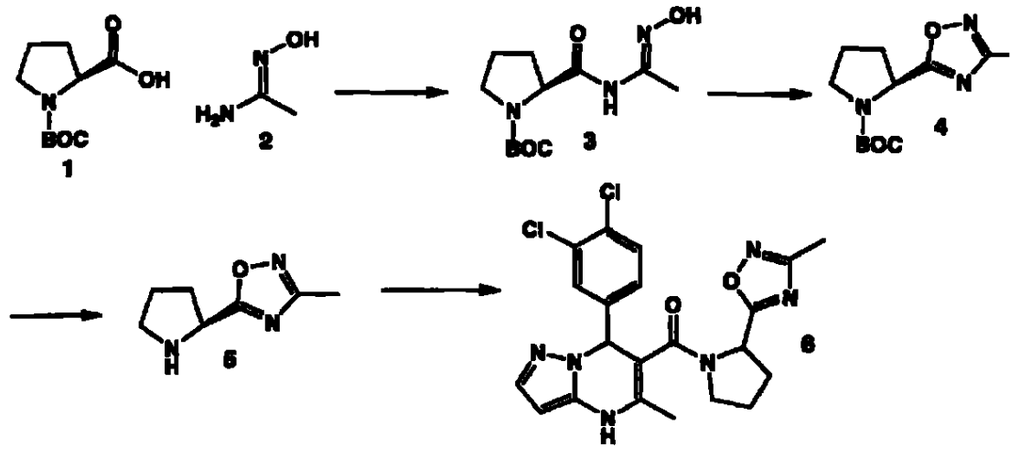

Síntesis de 3 Una mezcla de N-(tert-butoxicarbonil)-L-prolina **1** (0 5 g, 2 3 mmol), hidroxiamidina **2** (0 172 g, 2 3 mmol, se preparo usando el procedimiento comprendido en *J Fluor Chem* **1999**, 95, 127) e hidrato 1-hidroxibenzotriazole (0 323 g, 2 4 mmol) en dimetilformamida al 22% en diclorometano (9 mL) se agitó a temperatura ambiente por 0 5 horas Se agregó entonces clorhidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (0 757 g, 3 9 mmol) y la mezcla se agitó adicionalmente a temperatura ambiente por 2 horas, cuando la HPLC indicó que la reacción se completó La mezcla de

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reacción se diluyo con agua y se extrajo con diclorometano Las capas orgánicas se lavaron sucesivamente con una solución de bicarbonato de sodio acuoso saturado, una solución de cloruro de sodio acuoso saturado y se seco sobre sulfato de magnesio La evaporación del solvente proporciona un sólido blanco con un $(M+H)^+$ de 272 consistente para el producto acoplado **3**

Preparacion de 4 El solido **3** se disolvió en tetrahidrofuran (17 mL), se agregó carbonato de cesio (1 6 g) y la mezcla se calentó a 50-70°C por 18 horas después de lo cual el HPLC indicó el consumo de **3** se completo La reacción se diluyó con agua y se extrajo con acetato de etilo Las capas orgánicas se secaron sobre sulfato de magnesio y se evaporaron para dar un aceite coloreado ligeramente verde que tiene un $(M+H)^+$ de 254 consistente con oxadiazol deseado **4** el cual se usa sin alguna purificacion adicional

Síntesis de 5 A una solucion de **4** (0 288 g, 1 1 mmol) en diclorometano (9 mL) se agregó 0 9 mL de ácido trifluoroacético y la solución se agitó a temperatura ambiente por 18 horas, cuando el HPLC indico la ausencia de **4** La mezcla de reacción se

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concentró y el residuo se purificó por cromatografía de intercambio iónico (usando resina BioRad AG-50W-X2, malla 200-400, en forma de hidrogeno) eluyendo con 2N de amoniaco en metanol para dar la pirrolidina desprotegida **5** como un aceite (0 122 g, al 70%) $(M+H)^+$ = 154

Síntesis de 6 A una solución de ácido de dihidropiridina (0 21 gram, 0 65 mmol) en diclorometano (10 mL) se agregó pirrolidina **5** (0 139 gram, 0 9 mmol) seguido por clorhidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (0 174 gram, 0 9 mmol) y la reaccion se agitó a temperatura ambiente por 1 5 horas El solvente se evaporó y el residuo se purifico por cromatografia en gel de silice, eluyendo con acetato de etilo, para dar dos diastereomeros con movimiento rápido, menos un diastereomero-1 polar y un movimiento lento, más diastereomero-2 polar, ambos como sólidos amorfos con un $(M+H)^+$ de 460

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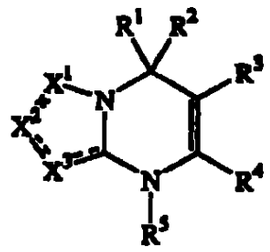
REIVINDICACIONES

1 Un método de tratamiento de arritmias del atrio el cual comprende la administración a un paciente en la necesidad del mismo, una cantidad efectiva de al menos un compuesto de la fórmula I



(I)

enantiomeros, diastereomeros y sales farmacéuticamente aceptables del mismo,

en donde

X^1, X^2 y X^3 son independientemente seleccionados de N, NR^6, $(CR^7)_q$, $(CHR^7)_q$, o C=O, en donde los enlaces que conectan X^1, X^2 y X^3 a los átomos adyacentes, pueden ser enlaces unicos o dobles que forman un anillo aromático de 5 a 7 elementos saturados o parcialmente insaturados,

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R^1, R^2, R^3, R^4, R^5, R^6 y R^7 son seleccionados de manera independiente de los grupos de la fórmula $-(CH_2)_n-(Z^1)_m-(CH_2)_p-Z^2$, o

R^1, R^2, R^3, R^4 y R^5 pueden, en uno o más pares de dos, junto con los atomos a los cuales estan enlazados, formar un grupo carbocíclico, carbociclico substituido, heterociclico o heterociclico substituido, o

R^6 y R^7 pueden, en uno o más pares de dos, junto con los átomos a los cuales están unidos, formar un grupo carbociclico, carbociclico substituido, heterociclico o heterocíclico substituido,

Z^1 es $-CZ^3Z^4-$, $-O-$, $-NZ^3-$, $-S-$, $-SO-$, $-SO_2-$, $-C(O)-$, $-C(O)Z^3-$, $-C(O)NZ^4$, $-C(S)-$, $-C(=NOZ^3)-$, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, carbociclo, carbociclo substituido, arilo, arilo substituido, heterociclo, o heterociclo substituido,

Z^2 es hidrógeno, $-OZ^5$, $-OC(O)Z^5$, $-NZ^5-C(O)-Z^6$, $-NZ^5-CO_2-Z^6$, $-NZ^5(C=O)-NZ^6Z^7$, $-NZ^5Z^6$, $-NO_2$, halo, $-CN$, $-C(O)Z^5$, $-CO_2Z^5$, $-C(S)Z^5$,

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$-(C=NOZ^5)Z^6$, $-C(O)NZ^5Z^6$, $-C(S)NZ^5Z^6$, $-SZ^5$, $-SOZ^5$, $-SO_2Z^5$, $-SO_2NZ^5Z^6$, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, carbociclo, carbociclo substituido, arilo, arilo substituido, heterociclo, o heterociclo substituido,

Z^3, Z^4, Z^5, Z^6 y Z^7 son independientemente hidrógeno, halo, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, carbociclo, carbociclo substituido, arilo, arilo substituido, heterociclo, o heterociclo substituido, o Z^3, Z^4, Z^5, Z^6 y Z^7 pueden, en uno o mas pares de dos, junto con los átomos a los cuales están unidos, formar un grupo carbociclico carbociclico substituido, heterociclico o heterociclico substituido,

n y p son independientemente seleccionados de los enteros a partir de 0 a 10 en donde m es 0, p es también 0,

m es un entero seleccionado de 0 o 1, y

q es un entero seleccionado de 1 a 3

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2 Un método de tratamiento de la fibrilación del atrio, el cual comprende la administración a un paciente en necesidad del mismo de una cantidad efectiva de al menos un compuesto de la reivindicación 1

3 Un metodo de tratamiento de palpitación del atrio, el cual comprende la administración a un paciente en necesidad del mismo en una cantidad efectiva de al menos un compuesto de la reivindicacion 1

4 Un método de tratamiento selectivamente de arritmias supraventricular, el cual comprende la administración a un paciente en necesidad del mismo una cantidad efectiva de al menos uno compuesto de la reivindicación 1

5 Un metodo de tratarmiento de las condiciones asociadas con I_{kur}, el cual comprende la administración a un paciente en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la reivindicación 1

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6 Un método para el tratamiento de esofagitis con reflujo, el cual comprende la administración a un paciente en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la reivindicación 1

7 Un método de tramiento de la dispepsia funcional, el cual comprende la administración a un paciente en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la reivindicación 1

8 Un metodo de tratamiento de la constipación, el cual comprende la administración a un paciente en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la reivindicación 1

9 Un método de tratamiento del asma, el cual comprende la administración a un paciente en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la reivindicación

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10 Un método de tratamiento de la diabetes, el cual comprende la administracion a un paciente en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la reivindicacion 1

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11 Un método de estimulación de la secreción de la hormona de crecimiento, el cual comprende la administracion a un paciente en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la reivindicación 1

12 Un método de tratamiento de las alteraciones proliferativas celulares, el cual comprende la administración a un paciente en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la reivindicación 1

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13 Un método de tratamiento de padecimientos autoinmunes, el cual comprende la administración a un paciente en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la reivindicación 1

14 El método de la reivindicación 1, en el cual en la fórmula I

R^1 es hidrógeno,

R^2 es hidrógeno, alquilo, alquilo substituido, arilo, arilo substituido, heterociclo, heterociclo substituido, carbociclo o carbociclo substituido,

R^3 es $-(CH_2)_n-Z^2$, $-(CH_2)_n-C(O)Z^3-(CH_2)_p-Z^2$, o $-(CH_2)_n-C(O)NZ^4-(CH_2)_p-Z^2$,

R^4 es alquilo o alquilo substituido,

R^5 es hidrogeno, o $-(CH_2)_n-Z^2$, y

X^1, X^2 y X^3, junto con los átomos a los cuales están unidos, forman un anillo, seleccionado de

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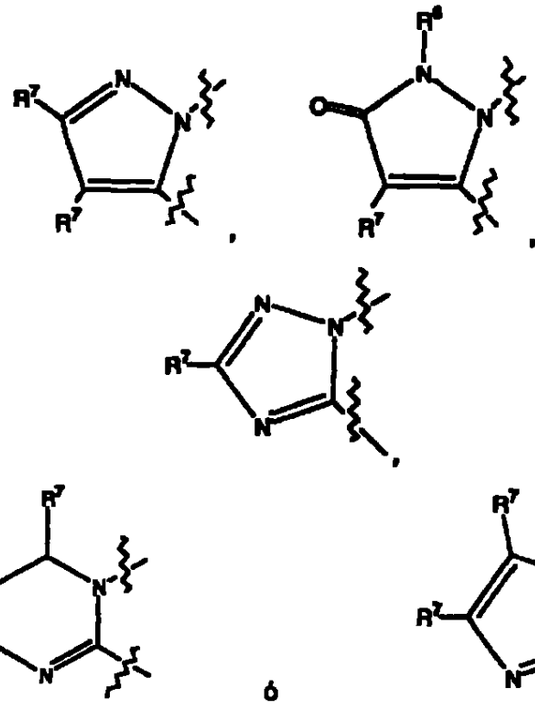

donde los anillos substituyentes son los mismos o diferentes

15 El método de la reivindicación 14, el cual en la fórmula I

R^3 es $-(CH_2)_n-Z^2$, $-(CH_2)_n-C(O)Z^3-(CH_2)_p-Z_2$, o $-(CH_2)_n-C(O)NZ^4-(CH_2)_p-Z^2$,

en donde

Z^2 se selecciona a partir de $-C(O)NZ^5Z^6$, $-CO_2Z^5$, $-SO_2Z^5$, $-NZ^5Z^6$, $-NZ^5CO_2Z^6$,

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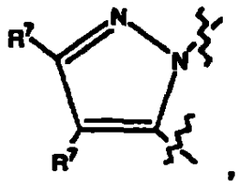
$-NZ^5C(O)Z^6$, $-OZ^5$, arilo, arilo substituido, heterociclo, heterociclo substituido, alquilo o alquilo substituido,

Z^3 es heterociclo o heterociclo substituido, y

n y p son independientemente, seleccionados a partir de los enteros 0 a 3,

R^5 es hidrógeno, o $-(CH_2)_n-Z^2$, en donde Z^2 se selecciona a partir de $-C(O)NZ^5Z^6$, $-CO_2Z^5$, $-NZ^5Z^6$, arilo, arilo substituido, alquilo o alquilo substituido, y

X^1, X^2 y X^3, junto con los átomos a los cuales estan unidos, forman un anillo seleccionado de



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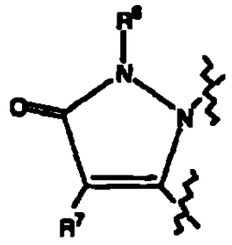

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16 El método de la reivindicación 15, el cual en la fórmula I

R^3 es heterociclo o heterociclo substituido, $-C(O)NZ^5Z^6$, $-CO_2Z^3-CONZ^5Z^6$, $-C(O)Z^3Z^2$, o $-C(O)Z^3-CO_2Z^5$, en donde Z^3 es heterociclo o heterociclo substituido, y Z^2 es arilo o arilo substituido,

17 El metodo de la reivindicacion 1, en el cual el compuesto de la fórmula I se selecciona de

Ester metílico del acido 7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico,

Ester metílico del ácido 7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico,

Ester metílico del ácido 7-(4-clorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico,

Ester 1,1-dimetiletílico del ácido 7-(3,4-diclorofenil)-4,7-dihidro-5-

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metilpirazolo[1,5-a]pirimidin-6-carboxílico,

Ester 1,1-dimetiletílico del ácido 7-(3,4-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-carboxílico,

Ester 1,1-dimetiletílico del acido 7-(2,3-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-carboxílico,

Ester 1,1-dimetiletílico del ácido 7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico,

Ester 1,1-dimetiletílico del ácido 7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico, enantiómero A,

Ester 1,1-dimetiletílico del ácido 7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico, enantiomero B,

Ester 1,1-dimetiletílico del ácido 7-(3,4-diclorofenil)-4,7-dihidro-5-dimetilpirazolo[1,5-a]pirimidin-6-carboxílico,

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Ester 1,1-dimetiletílico del ácido 3-cloro-7-(3-clorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico,

Ester 1,1-dimetiletílico del ácido 7-(2,3-diclorofenil)-4,7-dihidro-4,5-dimetilpirazolo[1,5-a]pirimidin-6-carboxílico,

Ester 1,1-dimetiletílico del ácido 7-(3,4-diclorofenil)-4,7-dihidro-4,5-metilpirazolo[1,5-a]pirimidin-6-carboxílico,

Ester 1,1-dimetiletílico del ácido 4,7-dihidro-5-metil-7-(1-metiletil)pirazolo[1,5-a]pirimidin-6-carboxílico,

Ester 1,1-dimetiletílico del ácido 7-Ciclopropil-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico,

Acido 7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico,

Acido 7-(3,4-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-carboxílico,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-

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fenilpiperazina,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-propilpirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-fenil-pirazolo[1,5-a]pirimidin-6-carboxamida,

4-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]morfolina,

7-(2,3-diclorofenil)-4,7-dihidro-5-metil-N-propilpirazolo[1,5-a]pirimidin-6-carboxamida,

7-(2,3-diclorofenil)-4,7-dihidro-5-metil-N-fenilpirazolo[1,5-a]pirimidin-6-carboxamida,

7-(2,3-diclorofenil)-4,7-dihidro-5-metil-N-(2-feniletil)pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-(2-feniletil)pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-3-piridinilpirazolo[1,5-a]pirimidin-6-carboxamida,

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1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenil-piperazina, enantiómero A,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenil-piperazina, enatiomero B,

1-[[7-(4-clorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-(fenilmetil)pirazolo[1,5-a]pirimidin-6-carboxamida,

4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]morfolina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-metil-piperazina,

7-(2,3-diclorofenil)-4,7-dihidro-5-metil-N-(fenilmetil)pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(4-clorofenil)-4,7-dihidro-5-metil-N-(fenilmetil)pirazolo[1,5-a]pirimidin-6-carboxamida,

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4-[[7-(4-clorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]morfolina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]piperidina,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]piperidina,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-(3-fenilpropil)pirazolo[1,5-a]pirimidin-6-carboxamida,

1-[[5-(3,4-diclorofenil)-5,8-dihidro-7-metil-imidazol[1,2-a]pirimidin-6-il]carbonil]-4-piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(fenil-metil)piperidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(fenil-metil)piperazina,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N,N-dipropilpirazolo[1,5-a]pirimidin-6-carboxamida,

1-[[7-(3-clorofenil)-4,7-dihidro-5-

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metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3,4-difluorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil[1,2,4]triazol[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluoro-fenil)piperazina,

1-(4-fluorofenil)-4-[(4,7-dihidro-5-metil-7-fenilpirazolo[1,5-a]pirimidin-6-il)carbonil]piperazina,

1-(4-fluorofenil)-4-[(4,7-dihidro-5-metil-7-fenilpirazolo[1,5-a]pirimidin-6-il)carbonil]piperazina,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluoro-fenil)piperazina, enantiomero A,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluoro-fenil)piperazina, enantiómero B,

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1-[[5-(2,3-diclorofenil)-5,8-dihidro-7-metil-imidazol[1,2-a]pirimidin-6-il]carbonil]-4-fenil-piperazina,

1-(4-fluorofenil)-4-[[7-(3-fluorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-piperazina,

1-[[7-(3,5-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluoro-fenil)piperazina,

1-[(7-ciclohexil-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il)carbonil]-4-fenilpiperazina,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metil-[1,2,4]triazol[1,5-a]pirimidin-6-il)carbonil]-4-fenil-piperazina,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenil-piperazina,

Ester etílico del ácido 7-(2,3-diclorofenil)-4,7-dihidro-5-metil-6-[(4-fenil-1-piperazinil)-carbonil]pirazolo[1,5-a]pirimidin-3-carboxílico,

1-[[4-(2,3-diclorofenil)-4,6,7,8-tetrahidro-2-metil-1H-pirimido[1,2-a]pirimidin-

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3-il]carbonil]-4-fenil-piperazina,

Ester 1,1-dimetiletilico del ácido 4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-1-piperazincarboxílico,

Ester 1,1-dimetiletilico del ácido 4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-1-piperazincarboxílico,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-2,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-2-fenilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina,

7-(3,4-diclorofenil)-4,7-dihidro-2,5-dimetil-N-(3-fenilpropil)pirazolo[1,5-a]pirimidin-6-carboxamida,

1-[[7-(2,3-diclorofenil)-2-(1,1-dimetiletil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenil-piperidina,

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Ester etílico del ácido 7-(3,4-diclorofenil)-4,7-dihidro-5-metil-6-[[(3-fenilpropil)amino]carbonil]pirazolo[1,5-a]pirimidin-3-carboxílico,

Ester etílico del ácido 7-(2,3-diclorofenil)-4,7-dihidro-5-metil-6-[(4-fenil-1-piperazinil)-carbonil]pirazolo[1,5-a]pirimidin-2-carboxílico,

1-[[3-ciano-7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)-piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)-piperazina,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)-piperazina, enantiómero B,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a]pirimidin-6-

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il]carbonil]-4-(4-fluoro-fenil)-piperazina, enantiómero B,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-(3-fenilpropil)-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-carboxamida,

Ester metílico del ácido 7-(3,4-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-2-carboxílico,

(2S)-1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina,

1-[[7-(2,3-diclorofenil)-2-fluoro-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

(2S)-1-[[2-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina,

(2S)-1-[[2-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina,

(2S)-1-[[7-(2,3-dicloro-fenil)-2-fluoro-

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4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoxi-metil)pirrolidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-2,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-2,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enantiómero A,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluoro-fenil)piperazina, enantiomero B,

7-(2,3-diclorofenil)-4,7-dihidro-5-metil-N,N-dipropilpirazolo[1,5-a]pirimidin-6-carboxamida,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(2,3-difluorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

Ester metílico del ácido 4-[6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-4,7-

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dihidro-5-metilpirazolo[1,5-a]pirimidin-7-il]benzoico,

1-(4-fluorofenil)-4-[[7-(2-fluorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-piperazina,

1-[[7-(2-clorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(2,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-7-(2-metoxifenil)-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(2,3-dimetoxifenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluoro-fenil)piperazina,

1-[[7-(2,3-dimetoxifenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluoro-fenil)piperazina,

1-[[7-(2,5-dimetoxifenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluoro-fenil)piperazina,

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1-[[4,7-dihidro-5-metil-7-[2-trifluorometil)fenil]pirozolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(2-metilfenil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(3-fenoxifenil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3,4-dimetoxifenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3,5-dimetoxifenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-[3-(fenilmetoxi)fenil]pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-7-(3-hidroxifenil)-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-[3-(trifluorometil)fenil]pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

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1-[[4,7-dihidro-5-metil-7-(3-metilfenil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(4-cianofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-(4-fluorofenil)-4-[[7-(4-fluorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-piperazina,

N-[4-[6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-7-il]fenil]acetamida,

1-[[7-(4-(dimetil-amino)fenil]-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-7-(4-metoxifenil)-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-[4-(fenilmetoxi)fenil]pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(4-butoxifenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-

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(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(2-tienil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(3-tienil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-[4-(trifluorometil)fenil]pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(4-metilfenil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(2-nitrofenil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(4-nitrofenil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(2,6-difluorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

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1-[[7-(2,4-difluorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(2,5-difluorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3,5-difluorofenil)-4,7-dirıdro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-[2-(fenilmetoxi)fenil]pirazol[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3,4-dimetilfenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-[4-(trifluorometoxi)fenil]pirazol[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-[3-(trifluorometoxi)fenil]pirazol[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3-cianofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

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1-[[4,7-dihidro-7-(3-metoxifenil)-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(4-clorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(4-(fenoxifenil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(3-nitrofenil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(5-metil-2-furanil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-7-(1H-imidazol-2-il)-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(1H-pirrol-2-il)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(2-piridinil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3-cloro-4-metoxi-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-7-(4-metoxi-1,3-benzodioxol-6-il)-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-7-[5-hidroximetil)-2-furanil]-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-7-[1H-indol-3-il)-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(3-piridinil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(3-quinolinil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(4-quinolinilo)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(2,3-dihidro-1,4-benzodioxin-6-il)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

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1-[[4,7-dihidro-5-metil-7-(2,3,5-tricloro-fenil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7(2,5-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-(4-fluorofenil)-4-[[7-(3-furanil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-piperazina,

1-[[7-(2-benzofuranil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(3-metilbenzo[b]tiofen-2-il)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(2-quinolinil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(2-tiazolil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-(4-fluorofenil)-4-[[7-(2-furanil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-

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il]carbonil]-piperazina,

1-[[4,7-dihidro-7-[3-metoxi-4-(fenilmetoxi)fenil]-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-7-[4-metoxi-3-(fenilmetoxi)fenil]-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(2-naftalenil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-[3,4-Bis(fenil-metoxi)fenil]-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(1,3-Benzodioxol-5-il)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-[3,5-Bis(trifluoro-metil)fenil]-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-[5-[1-metil-3-(trifluorometil)-1H-pirazol-5-il]-2-tienil]pirazolo[1,5-a]pirimidin-6-il]carbonil]-

4-(4-fluorofenil)piperazina,

1-[[7-(5-etil-2-furanil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(2,3-dihidro-5-benzofuranil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3-bromofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-[4-(1-pirrolidinil)-fenil]pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(3-metil-2-tienil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4,7-dihidro-5-metil-7-(5-metil-2-tienil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(1,3-benzodioxol-4-il)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(5-cloro-2-tienil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3,5-dimetilfenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-2,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enantiómero A,

1-[[7-(3,4-diclrofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enantiómero B,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enantiómero B,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enantiomero A,

8-[[7(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,4-dioxa-8-azaspiro[4,5]decano,

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1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(2-metoxi-fenil)piperazina,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-[3-(trifluorometil)-fenil]piperazina,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-nitrofenil)piperazina,

1-(4-acetilfenil)-4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]piperazina,

1-(2-clorofenil)-4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]piperazina,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-metoxi-fenil)piperazina,

1-(3,4-diclorofenil)-4-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]piperazina,

1-(3,4-diclorofenil)-4-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]piperazina,

1-(3,4-clorofenil)-4[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]piperazina,

1-(3-clorofenil)-4[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(3-metoxifenil)piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-metilfenil)piperazina,

1-[[7(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5a]-pirimidin-6-il]carbonil]-4-[4-(trifluorometil)-fenil]piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(2-fluorofenil)piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(3,4-dimetilfenil)piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(2-pirimidinil)piperazina,

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7-(3,4-diclorofenil)-N-[2-[(4-fluorofenil)amino]etil]-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-carboxamida,

Ester fenilmetílico del acido 4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-1-piperazinacarboxílico,

7-(3,4-diclorofenil)-N-etil-N-[(2-fluorofenil)metil]-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida,

N-[(3-cloro-4-metoxifenil)metil]-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-carboxamida,

1-(1,3-Benzodioxol-5-ilmetil)-4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]piperazina,

Ester etílico del ácido 4-[[7-3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1-piperazincarboxílico,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(2-piridinil)piperazina,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina,

1-[Bis(4-fluorofenil)-metil]-4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]piperazina,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(2-furanil-carbonil)piperazina,

1-ciclohexil-4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(2-metoxietil)piperazina,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(9H-fluoren-9-il]piperazina,

(2R)-1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoxi-metil)pirrolidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(2,3-dimetilfenil)piperazina,

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Ester etílico del acido 1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-piperidincarboxilico,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-N,N-dietil-3-piperidincarboxamida,

Ester etílico del ácido 1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3-piperidin-carboxilico,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3-metil-piperidina,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3,5-dimetil-piperidina,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-hidroxi-piperidina,

4-(4-clorofenil)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-hidroxipiperidina,

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Ester etílico del ácido 1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-piperidin-carboxílico,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-metilpiperidina,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,4-tetrahidroquinolina,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-decahidroquinolina,

2-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,4-tetrahidroquinolina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-propilpiperidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(hidroxidifenilmetil)piperidina,

7-(3,4-diclorofenil)-N-[(2-fluorofenil)metil]-4,7-dihidro-5-

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metilpirazolo[1,5-a]pirimidin-6-carboxamida,

2-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2,3,4,9-tetrahidro-1H-pirido[3,4-b]indol,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-[2-(fenilamino)-etil]pirazolo[1,5-a]pirimidin-6-carboxamida,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-[(fenilamino)metil]pirrolidina,

N-ciclohexil-7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetilpirazolo[1,5-a]pirimidin-6-carboxamida,

3-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]tiazol,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]pirrolidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3,4-dihidro-1H-indol,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-

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il]carbonil]azetidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]hexahidro-1H-azepina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]octahidroazocina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,6-tetrahidropiridina,

7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-N-[2-(2-piridinil)-etil]pirazolo[1,5-a]pirimidin-6-carboxamida,

Ester etílico N-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-N-(fenilmetil)glicina,

Trans-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-(2-fenilciclopropil)pirazolo[1,5-a]pirimidin-6-carboxamida,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-metilpirrolidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-

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metilaziridina,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-[[(2,6-dimetilfenil)amino]metil]pirrolidina,

7-(3,4-diclorofenil)-N-etil-4,7-dihidro-5-metil-N-(4-piridinilmetil)pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-N-[(1R)-1-feniletil]pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-N-[(1S)-1-feniletil]pirazolo[1,5-a]pirimidin-6-carboxamida,

6-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,3,3-trimetil-6-azabiciclo[3,2,1]octano,

7-(3,4-diclorofenil)-N-(hexahidro-1H-azepin-1-il)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]aziridina,

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1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]octahidro-1H-azonina,

(2R-trans)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2,5-bis(metoximetil)-pirrolidina,

(2-trans)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2,5-bis-(metoximetil)pirrolidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-L-prolinamida,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-D-prolinamina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2,3-dihidro-2-metil-1H-indol,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2,3-dihidro-5-nitro-1H-indol,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2,3-dihidro-6-nitro-1H-indol,

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4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-tiomorfolina,

Ester metílico 1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-L-prolina,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina, enantiómero A,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina, enantiomero B,

Ester 1,1-dimetiletílico 1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-L-prolina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-N-(2-naftalenil)-L-prolinamida,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,4-tetrahidro-2-metilquinolina,

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1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-6-fluoro-1,2,3,4-tetrahidro-2-metilquinilina,

Ester fenilmetílico 1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-L-prolina,

Ester fenilmetílico 1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-D-prolina,

Ester fenilmetílico 1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-hidroxi-L-prolina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)-2-metilpiperazina,

3-cloro-N-ciclohexil-7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetilpirazolo[1,5-a]pirimidin-6-carboxamida,

4-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-tiomorfolina,

1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2,3-dihidro-1H-indol,

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1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]hexahidro-1H-azepina,

1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-octahidroazocina,

1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,6-tetrahidropiridina,

3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-N-[(1S)-1-feniletil]-pirazolo[1,5-a]pirimidin-6-carboxamida,

3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-N-[(1R)-1-feniletil]-pirazolo[1,5-a]pirimidin-6-carboxamida,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoxi-metil)piperidina,

Ester 1,1-dimetiletílico del ácido [(3R)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3-pirrolidinil]carbámico,

Ester 1,1-dimetiletílico del ácido [(3S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-

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metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3-pirrolidinil]carbámico,

[(3R)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3-(dimetilamino)pirrolidina,

N-[1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3-pirrolidinil]acetamida,

N-[1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3-pirrolidinil]-N-metilacetamida,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N,N-dipentil-pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-N,N-dihexil-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida,

1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]piperidina,

3-cloro-7-(3-clorofenil)-N-ciclohexil-4,7-dihidro-N,5-dimetilpirazolo[1,5-a]pirimidin-6-carboxamida,

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(2S)-1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoxi-metil)pirrolidina,

1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-decahidroquinolina,

2-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,4-tetrahidroisoquinolina,

4-[[3cloro-7-(3-clorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-tiomorfolina,

N-ciclohexil-7-(3,4-diclorofenil)-4,7-dihidro-N,5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-N,N-dietil-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida,

N,N-dibutil-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida,

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7-(3,4-diclorofenil)-N,N-diheptil-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-carboxamida,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-azaciclotridecano,

9-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-dodecahidro-1H-fluoreno,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina,

1-[[3-cloro-7-(3-clorofenil)-4,7-dihidro-5-metil-1pirazolo[1,5-a]pirimidin-6-il]carbonil]-piperidina,

1-[[3-cloro-7-(3-cloro-fenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]hexahidro-1H-azepina,

1-[[3-cloro-7-(3-clorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-octahidroazocina,

1-[[3-cloro-7-(3-clorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-

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il]carbonil]-1,2,3,6-tetrahidropiridina,

3-cloro-7-(3-clorofenil)-4,7-dihidro-N,5-dimetil-N-[(1S)-1-feniletil]pirazolo[1,5-a]pirimidin-6-carboxamida,

(2S)-1-[[3cloro-7-(3-clorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina,

1-[[3cloro-7-(3-clorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-decahidroquinolina,

2-[[3-cloro-7-(3-clorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,4-tetrahidroisoquinolina,

1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]hexahidro-1H-azepina,

1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,6-tetrahidropiridina,

(2S)-1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metil-2-(trifluoro-metil)pirazolo[1,5-

a]pirımıdın-6-il]carbonil]-2,3-dihidro-1H-indol,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirımıdın-6-il]carbonil]hexahidro-1H-azepina,

7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-N-[(1S)-1-feniletil]-2-(trifluorometil)pirazolo[1,5-a]pirımıdın-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-N-[(1R)-1-feniletil]-2-(trifluorometil)pirazolo[1,5-a]pirımıdın-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-N,N-bis(2-metoxietil)-5-metilpirazolo[1,5-a]pirımıdın-6-carboxamida,

7-(3,4-diclorofenil)-N,N-bis(2-etoxietil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirımıdın-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-N-(2-metoxietil)-N,5-dimetilpirazolo[1,5-a]pirımıdın-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-N-(2-metoxietil)-5-metil-N-propilpirazolo[1,5-a]pirımıdın-6-carboxamida,

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1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]piperidina,

2-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,4-tetrahidroisoquinolina,

2-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,4-tetrahidroisoquinolina,

3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-N,5-dimetil-N-[(1S)-1-feniletil]-pirazolo[1,5-a]pirimidin-6-carboxamida,

3-cloro-N-ciclohexil-7-(2,3-diclorofenil)-4,7-dihidro-N,5-dimetil-pirazolo[1,5-a]pirimidin-6-carboxamida,

3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-N-(fenilmetil)pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-N-etil-4,7-dihidro-N-(2-metoxietil)-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida,

Ester etílico N-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-N-metilglicina,

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Ester 1,1-dimetiletílico N-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-N-metilglicina,

Ester etílico N-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-N-(2-etoxi-2-oxoetil)glicina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(3-piridinil)piperidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,4-tetrahidro-6-metilquinolina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-propilpiperidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-[(dietilamino)metil]piperidina,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-(2-fenoxietil)-pirazolo[1,5-a]pirimidin-6-carboxamida,

1-[(7-ciclopropil-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

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1-[[4,7-dihidro-5-metil-7-(1-metiletil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

(2S)-1-[[4,7-dihidro-5-metil-7-(1-metil-etil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina,

1-[[4,7-dihidro-5-metil-7-(1-metil-etil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-2,3-dihidro-1H-indol,

1-[[4,7-dihidro-5-metil-7-(1-metiletil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,6-tetrahidropiridina,

3-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]tiazolidina, enantiómero A,

3-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]tiazolidina, enantiómero B,

7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-N-(fenil-metil)pirazolo[1,5-a]pirimidin-6-carboxmida,

7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-N-(2-feniletil)pirazolo[1,5-a]pirimidin-6-carboxamida,

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7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-(2-feniletil)-N-(fenilmetil)pirazolo[1,5-a]pirimidin-6-carboxamida,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(fenoximetil)pirrolidina,

(2R)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(fenoximetil)pirrolidina,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-[(4-fluorofenoxi)metil]pirrolidina,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-[(4-fluorofenoxi)metil]-pirrolidina,

7-(3,4-diclorofenil)-N-etil-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida,

N-butil-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-pentilpirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-N-(2-metoxietil)-5-metilpirazolo[1,5-a]pirimidin-6-carboxamida,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(hidroxidifenilmetil)pirrolidina,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(hidroxidifenilmetil)pirrolidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(3-piridinil)pirrolidina,

(2S)-1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-fenilpirrolidina,

3-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-feniltiazolidina,

Ester metílico del ácido 3-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-tiazolidincarboxílico,

7-(3,4-diclorofenil)-4,7-dihidro-N,5-dimetil-N-(3-fenilpropil)pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-N-etil-4,7-dihidro-5-metil-N-(3-fenil-propil)pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-(3-fenilpropil)-N-propilpirazolo[1,5-a]pirimidin-6-carboxamida,

N-butil-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-(3-fenil-propil)pirazolo[1,5-a]pirimidin-6-carboxamida,

2-(4-clorofenil)-3-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]tiazolidina,

N-(ciclopropilmetil)-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-propilpirazolo[1,5-a]pirimidin-6-carboxamida,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-

(2,3-dihidro-2-oxo-1H-bencimidazol-1-il)piperidina,

8-[[7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-1-fenil-1,3,8-tiazaspiro[4,5]decan-4-ona,

4-(4-clorofenil)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-1,2,3,6-tetrahidropiridina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(2-feniletil)pirrolidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(4-metoxifenil)pirrolidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(2-metoxifenil)pirrolidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(4-fluorofenil)pirrolidina,

(3R)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-3-fenoxipirrolidina,

(2S)-2-[(ciclohexiloxi)metil]-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]pirrolidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(fenilmetil)pirrolidina,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(fenoximetil)pirrolidina, diastereómero A,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(fenoximetil)pirrolidina, diastereómero B,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(3-metoxifenil)pirrolidina,

(2S)-2-(butoximetil)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]pirrolidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(2-tienil)pirrolidina,

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1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(4-piridinil)pirrolidina,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetoxi)-metil]pirrolidina,

(2S)-2-(1H-benzimidazol-1-ilmetil)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]pirrolidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(3-furanil)pirrolidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(2-piridinil)pirrolidina,

(3S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3-fenoxipirrolidina,

(3S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-3-fenoxipirrolidina,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-

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a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina, enantiómero A,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-metoximetil)pirrolidina, enantiomero B,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-L-propina,

7-(3,4-diclorofenil)-4,7-dihidro-N-[(1R)-2,3-dihidro-1H-inden-1-il]-5-metil-2-(trifluoromeil)pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-N-(2,3-dihidro-1H-inden-2-il)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-carboxamida,

Ester metílico de N-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-D-fenilalanina,

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7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-(1,2,3,4-tetrahidro-1-naftalenil)-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-[3-(2-oxo-1-pirrolidinil)propil]-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-N-(2-furanilmetil)-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-N-[(3,4-doclorofenil)metil]-4,7-dihidro-5-metil-2-(trifluorometil)pirazol[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-N-[(2R)-2-(metoximetil)-1-pirrolidinil]-5-metil-2-(trifluorometil)pirazol[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-N-[(tetrahidro-2-furanil)-metil]-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-

carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-N-[(1S)-2,3-dihidro-1H-inden-1-il]-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-N-[2-(3,4-dicloro-fenil)etil]-4,7-dihidro-5-metil-2-(trifluorometil)pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-2-(trifluorometil)-N-[[4-[(trifluorometil)tio]-fenil]metil]pirazol-[1,5-a]pirimidin-6-carboxamida,

(2S)-1-[[7-(3,4-diclorofenil)-4,7di-hidro-5-metil-2-(trifluorometil)pirazol[1,5-a]pirimidin-6-il]carbonil]-2-(1-pirrolidinilmetil)-pirrolidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(1-naftalenilsulfonilo)piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-[(4-etilfenil)sulfonil]-piperazina,

1-[(4-bromo-5-cloro-2-tienil)sulfonil]-4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-piperazina,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-[[2-(trifluoro-metoxi)fenil]sulfonil]piperazina,

1-[(5-cloro-3-metil-benzo[b]tiofen-2-il)sulfonil]-4-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-[(3-metoxifenil)carbonil]piperazina,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(1-oxo-3-fenil-2-propenil)-piperazina,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-piridinilcarbonil)piperazina,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-4,5-dimetilpirazolo[1,5-a]pirimidin-6-

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il]carbonil]-4-fenilpiperazina,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-4,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]piperidina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-4,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(2,3-dicloro-fenil)-4,7-dihidro-4,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-4,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enatiómero B,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-4,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil)-4-(4-fluorofenil)piperazina, enantiomero A,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-2,4,5-trimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(2,3-diclorofenil)-4-[(4-fluorofenil)metil]-4,7-dihidro-2,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

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Ester etílico del acido 7-(2,3-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil-2,5-dimetilpirazolo[1,5-a]pirimidin-4(7H)-acético

7-(2,3-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-N,N,2,5,-tetrametilpirazolo[1,5-a]pirimidin-4(7H)-acetamida,

1-[[7-(2,3-diclorofenil)-4-[2-(dimetilamino)etil]-4,7-dihidro-2,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[4-(ciclopropilmetil)7-(2,3-diclorofenil)-4,7-dihidro-2,5-dimetilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

7-(2,3-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-N,N,2,5-tetrametilpirazolo[1,5-a]pirimidin-4(7H)-carboxamida,

1-[[7-(2,3-diclorofenil)-4,7-dihidro-4-metil-5-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

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1-[[7-(2,3-diclorofenil)-4,7-dihidro-5-(trifluoro-metil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(2,3-dicloro-fenil)-4,7-dihidro-2-metil-5-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(2,3-dicloro-fenil)-4,7-dihidro-2,4-dimetil-5-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(2,3-dicloro-fenil)-4,7-dihidro-2,4-dimetil-5-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enantiómero B,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-(trifluorometil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-2-metil-5-(trifluoro-metil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

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1-[[1-benzoil-7-(2,3-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina,

1-[[1-benzoil-7-(3,4-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina,

1-[[1-acetil-7-(3,4-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]car-bonil]-4-fenilpiperazina,

1-[[7-(3,4-dicloro-fenil)-1,2,4,7-tetrahidro-5-metil-2-oxo-1-(1-oxobutil)-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina,

1-[[1-(ciclopropil-carbonil)-7-(3,4-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina,

1-[[1-(ciclopropil-carbonil)-7-(2,3-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

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1-[[7-(2,3-dicloro-fenil)-1,2,4,7-tetra-hidro-5-metil-1-(3-metil-1-oxobutil)-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)-piperazina,

1-[[7-(2,3-dicloro-fenil)-(2,2-dimetil-1-oxopropil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenil-piperazina,

1-[[1-(ciclopropil-carbonil)-7-(3,4-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)-piperazina,

1-[[1-(ciclobutil-carbonil)-7-(3,4-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)-piperazina,

1-[[1-(ciclobutil-carbonil)-7-(3,4-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)-piperazina,

1-[[7-(3,4-dicloro-fenil)-1,2,4,7-tetrahidro-5-metil-1-(2-metil-1-oxopropil)-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(2,3-diclorofenil)-1,2,4,7-tetrahidro-5-metil-1-[(1-metiletil)sulfonil]-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina,

1-[[7-(3,4-diclorofenil)-1,2,4,7-tetrahidro-5-metil-1-[(1-metiletil)sulfonil]-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)-piperazina,

7-(2,3-diclorofenil)-4,7-dihidro-5-metil-N-(1-metiletil)-2-oxo-6-[(4-fenil-1-piperazinil)carbonil]pirazolo[1,5-a]pirimidin-1-(2H)-carboxamida,

7-(2,3-diclorofenil)-4,7-dihidro-N,5-dimetil-2-oxo-6-[(4-fenil-1-piperazinil)-carbonil]pirazolo[1,5-a]pirimidin-1(2H)carboxamida,

7-(2,3-diclorofenil)-4,7-dihidro-5-metil-2-oxo-6-[(4-fenil-1-piperazinil)-carbonil]-pirazolo[1,5-a]piri-midin-1(2H)carboxamida,

7-(3,4-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil)-carbonil]-4,7-dihidro-N,N,5-trimetil-2-oxopirazolo[1,5-a]pirimidin-1(2H)carboxamida,

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1-[[1-(3-butenil)-7-(3,4-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3,4-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxo-(2,2,2-trifluoroetil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-trifluorofenil)piperazina,

1-[[7-(3,4-diclorofenil)-1,2,4,7-tetrahidro-5-metil-2-oxo-1,4-bis(2,2,2-trifluoroetil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

Ester 1-metiletílico del ácido 7-(3,4-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-4,7-dihidro-5-metil-2-oxopirazolo[1,5-a]pirimidin-1(2H)-carboxílico,

1-[4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il)carbonil]-4-(fenilpiperazina,

Acido 7-(3,4-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-2-carboxílico,

7-(3,4-diclorofenil)-N,N-dietil-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-4,7-

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dihidro-5-metilpirazolo[1,5-a]pirimidin-2-carboxamida,

7-(3,4-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-4,7-dihidro-N-(4-hidroxifenil)-5-metilpirazolo[1,5-a]pirimidin-2-carboxamida,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metil-2-[[(2S)-2-(1-pirrolidinilmetil)-1-pirrolidinil]carbonil]-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

7-(3,4-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-2-carboxamida,

7-(3,4-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-4,7-dihidro-5-metil-N-(fenilmetil)pirazolo[1,5-a]pirimidin-2-carboxamida,

7-(3,4-diclorofenil)-6-[[4-(4-fluorofenil)-1-piperazinil]carbonil]-4,7-dihidro-5-metil-N-(2-feniletil)-pirazolo[1,5-a]pirimidin-2-carboxamida,

1-[[2-ciano-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

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Ester 1,1-dimetiletílico del ácido 3-bromo-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico,

1-[[3-bromo-7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina,

1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina,

1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-fenilpiperazina, enatiómero B,

1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-il]carbonil]piperazina, enantiómero A,

1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metil-pirazolo[1,5-a]pirimidin-6-

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il]carbonil]-4-(4-fluorofenil)piperazina, enantiómero A,

1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbnil]-4-(4-fluorofenil)piperazina, enantiómero B,

1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enantiómero A,

1-[[3-cloro-7-(2,3-diclorofenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enantiómero B,

1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enatiómero A,

1-[[3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-2,5-dimetil-pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina, enatiómero B,

Ester 1,1-dimetiletílico del ácido 3-cloro-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-carboxílico,

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7-(3,4-diclorofenil)-4,7-dihidro-5-metil-6-(5-fenil-2-oxazolilo)pirazolo[1,5-a]pirimidina,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-6-(5-fenil-1,3,4-oxa-diol-2-il)pirazolo[1,5-a]pirimidina,

6-(1H-benzimidazol-2-il)-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidina,

6-(2-benzotiazolil)-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidina,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-6-(1-metil-1H-benzimi-dazol-2-il)pirazolo[1,5-a]pirimidina,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-6-[5-(trifluorometil)-1-propil-1H-benzimidazol-2-il)pirazolo[1,5-a]pirimidina,

6-(5-butil-1,3,4-oxadiazol-2-il)-7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidina,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-metil-6-(4-metil-1H-benzimidazol-2-il)pirazol[1,5-a]pirimidina,

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1-[[7-(2,3-dıcloro-fenıl)-4,7-dıhidro-5-metil-6-(1-metıl-1H-benzımıdazol-2-ıl)pırazol[1,5-a]pırımıdına,

7-(3,4-dıclorofenıl)-4,7-dıhıdro-6-(ımida-zol[[1,5-a]pırımıdın-3-ıl)-5-metilpırazolo[1,5-a]pırımıdına,

7-(3,4-dıclorofenıl)-6-(1-etil-5-nıtro-1H-benzımıdazol-2-ıl)-4,7-dıhıdro-5-metıl-pırazolo[1,5-a]pırımıdına,

6-[5-cloro-1-(1-metıletıl)-1H-benzımıdazol-2-ıl]-7-(3,4-dıclorofenıl)-4,7-dıhıdro-5-metıl-pırazolo[1,5-a]pırımıdına,

6-[5-cloro-1-etıl-1H-bencımıdazol-2-ıl)-7-(3,4-dıclorofenil)-4,7-dıhıdro-5-metıl-pırazolo[1,5-a]pırımıdına,

7-(3,4-dıclorofenıl)-6-(5-fluoro-1-propıl-1H-benzımıdazol-2-ıl)-4,7-dıhıdro-5-metılpıra-zol[1,5-a]pırımıdına,

7-(3,4-dıclorofenıl)-4,7-dıhıdro-5-metıl-6-[1-(1-metıetıl)-5-(trıfluorometıl)-1H-bencımıdazol-2-ıl]pırazolo[1,5-a]pırimıdına,

7-(3,4-dıclorofenıl)-6-(5-fluoro-1-metıl-1H-bencımıdazol-2-il)-4,7-dıhıdro-5-metılpırazolo[1,5-a]pırımıdına,

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7-(3,4-diclorofenil)-6-(5-fluoro-1-metil-1H-benzimidazol-2-il)-4,7-dihidro-5-metil-pirazolo[1,5-a]piri-midina, enantiómero A,

7-(3,4-diclorofenil)-6-(5-fluoro-1-metil-1H-bencimidazol-2-il)-4,7-dihidro-5-metil-pirazolo[1,5-a]piri-midina, enantiómero B,

7-(3,4-diclorofenil)-4,7-dihidro-5-metil-6-[1-(fenilmetil)-1H-bencimidazol-2-il]pirazolo[1,5-a]pirimidina,

7-(3,4-diclorofenil)-4,7-dihidro-5-(metoximetil)-N-(2-piridinilmetil)pirazolo[1,5-a]pirimidin-6-carboxamida,

7-(2,3-diclorofenil)-4,7-dihidro-5-(metoximetil)-N-(2-piridinilmetil)pirazolo[1,5-a]pirimidin-6-carboxamida

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-(metoximetil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(4-fluorofenil)pirrolidina,

7-(3,4-dicloro-fenil)-4,7-dihidro-5-(metoximetil)-N-(3-fenil-propil)pirazolo[1,5-a]pirimidina-6-carboxamida,

1-[[7-(3,4-dicloro-fenil)-4,7-dihidro-5-(metoxi-metil)pirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluoro-fenil)piperazina,

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1-[[7-(3,4-dıcloro-fenıl)-4,7-dıhıdro-5-(metoxımetıl)pırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]pıperıdına,

(2S)-1-[[7-(3,4-dıclorofenıl)-4,7-dıhıdro-5-(metoxı-metıl)pırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]-2-(metoxımetıl)pırrolıdına,

7-(3,4-dıcloro-fenıl)-4,7-dıhıdro-5-(metoxımetıl)-N,N-dıpropilpırazolo[1,5-a]pırımıdın-6-carboxamıda,

5-Cıclohexıl-7-(3,4-dıclorofenıl)-4,7-dıhıdro-N-(3-fenıl-propıl)pırazolo[1,5-a]pırımıdın-6-carboxamıda,

1-[[5-cıclohexıl-7-(3,4-dıclorofenıl)-4,7-dıhıdropırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]-4-(4-fluorofenıl)pıperazına,

1-[[5-cıclohexıl-7-(3,4-dıclorofenıl)-4,7-dıhıdropırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]pıperıdına,

(2S)-1-[[5-cıclohexıl-7-(3,4-dıclorofenıl)-4,7-dıhıdropırazolo[1,5-a]pırımıdın-6-ıl]carbonıl]-2-(metoxımetıl)pırrolıdına,

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5-Ciclohexil-7-(3,4-diclorofenil)-4,7-dihidro-N,N-dipropilpirazolo[1,5-a]pirimidin-6-carboxamida,

7-(3,4-diclorofenil)-4,7-dihidro-6-(imidazo[1,5-a]piridin-3-il)-5-(metoximetil)pirazolo[1,5-a]pirimidina,

7-(2,3-diclorofenil)-4,7-dihidro-6-(imidazo[1,5-a]piridin-3-il)-5-(metoximetil)pirazolo[1,5-a]pirimidina,

7-(3,4-diclorofenil)-6-(5-fluoro-1-metil-1H-bencimidazol-2-il)-4,7-dihidro-5-(metoximetil)pirazolo[1,5-a]pirimidina,

7-(2,3-Dicloro-fenil)-6-(4-fluoro-1-metil-1H-bencimi-dazol-2-il)-4,7-dihidro-5-(metoxi-metil)pirazolo[1,5-a]pirimidina,

7-(3,4-dicloro-fenil)-6-(4-fluoro-1-metil-1H-bencimi-dazol-2-il)-4,7-dihidro-5-(metoxi-metil)pirazolo[1,5-a]pirimidina enantiómero A,

7-(3,4-dicloro-fenil)-6-(4-fluoro-1-metil-1H-bencimi-dazol-2-il)-4,7-dihidro-5-(metoxi-metil)pirazolo[1,5-a]pirimidina enantiómero B,

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7-(3,4-diclorofenil)-4,7-dihidro-5-fenil-N-(3-fenilpropil)pirazolo[1,5-a]pirimidin-6-carboxamida,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-fenilpirazolo[1,5-a]pirimidin-6-il]carbonil]-4-(4-fluorofenil)piperazina,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-fenilpirazolo[1,5-a]pirimidin-6-il]carbonil] piperidina,

(2S)-1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-fenilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(metoximetil)pirrolidina,

7-(3,4-diclorofenil)-4,7-dihidro-5-fenil-N,N-dipropilpirazolo[1,5-a]pirimidin-6-carboxamida,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(4-fluorofenil)pirrolidina diastereomero 1,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(4-fluorofenil)pirrolidina diastereómero 2,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-

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(4-fluorofenil)pirrolidina enantiómero A,

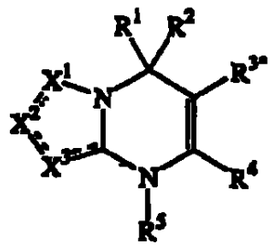
1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(4-fluorofenil)pirrolidina enantiómero B,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(4-fluorofenil)pirrolidina enantiómero C,

1-[[7-(3,4-diclorofenil)-4,7-dihidro-5-metilpirazolo[1,5-a]pirimidin-6-il]carbonil]-2-(4-fluorofenil)pirrolidina enantiómero D,

enantiómeros, diastereomeros y sales de los mismos farmacéuticamente aceptables

18 Un compuesto de fórmula I*



(I*)

enatiómeros, diastereómeros y sales del mismo farmacéuticamente aceptables, en los cuales

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X^1, X^2 y X^3 son independientemente seleccionados de N, NR^6, $(CR^7)_q$, $(CHR^7)_q$, o C=O, en donde los enlaces que conectan X^1, X^2 y X^3 a los átomos adyacentes, pueden ser enlaces unicos o dobles que forman un anillo aromatico de 5 a 7 elementos saturados o parcialmente insaturados,

R^1, R^2, R^3, R^4, R^5, R^6 y R^7 son los mismos o diferentes y son seleccionados de manera independiente de los grupos de la fórmula $-(CH_2)_n-(Z^1)_m-(CH_2)_p-Z^2$, o

R^1, R^2, R^4 y R^5 pueden, en uno o más pares de dos, junto con los atomos a los cuales están enlazados, formar un grupo carbociclico, carbociclico substituido, heterociclico o heterocíclico substituido, o

R^6 y R^7 pueden, en uno o más pares de dos, junto con los atomos a los cuales están unidos, formar un grupo carbocíclico, carbocíclico substituido, heterocíclico o heterocíclico substituido,

Z^1 es $-CZ^3Z^4-$, $-O-$, $-NZ^3-$, $-S-$, $-SO-$, $-SO_2-$, $-C(O)-$, $-C(O)Z^3-$, $-C(O)NZ^4$, $-C(S)-$, -

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$C(=NOZ^3)$-, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, carbociclo, carbociclo substituido, arilo, arilo substituido, heterociclo, o heterociclo substituido,

Z^2 es hidrógeno, $-OZ^5$, $-OC(O)Z^5$, $-NZ^5-C(O)-Z^6$, $-NZ^5-CO_2-Z^6$, $-NZ^5(C=O)-NZ^6Z^7$, $-NZ^5Z^6$, $-NO_2$, halo, $-CN$, $-C(O)Z^5$, $-CO_2Z^5$, $-C(S)Z^5$, $-(C=NOZ^5)Z^6$, $-C(O)NZ^5Z^6$, $-C(S)NZ^5Z^6$, $-SZ^5$, $-SOZ^5$, $-SO_2Z^5$, $-SO_2NZ^5Z^6$, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, carbociclo, carbociclo substituido, arilo, arilo substituido, heterociclo o heterociclo substituido

Z^3, Z^4, Z^5, Z^6 y Z^7 son independientemente hidrógeno, halo, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, carbociclo, carbociclo substituido, arilo, arilo substituido,

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heterociclo, o heterociclo substituido, o

Z^3, Z^4, Z^5, Z^6 y Z^7 pueden, en uno o más pares de dos, junto con los átomos de carbono a los cuales están unidos, formar un grupo carbociclico, carbociclico substituido, heterociclico o heterociclico substituido,

R^{3*} es $-OZ^5$, $-OC(O)Z^5$, $-NZ^5-C(O)_2-Z^6$, $-NZ^5(C=O)-NZ^6Z^7$, $-NZ^5Z^6$, $-(C=NOZ^5)Z^6$, $-C(O)NZ^{5*}Z^{6*}$, $-C(S)NZ^{5*}Z^{6*}$, $-SZ^5$, $-SOZ^5$, $-SO^2Z^5$, $-SO_2NZ^5Z^6$, $-C(O)Z^{3*}-Z^{2*}$, halo, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, carbociclo, carbociclo substituido, arilo, arilo substituido, heterociclo o heterociclo substituido,

Z^{2*} es preferentemente hidrógeno cuando Z^{3*} es heterociclo,

Z^{3*} es heterociclo o heterociclo

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substituido,

Z^{5*} es alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, carbociclo, carbociclo substitudo, arilo, arilo substituido, heterociclo, o heterociclo substituido, y

Z^{6*} es hidrógeno, alquilo, alquilo substituido, alquenilo, alquenilo substituido, alquinilo, alquinilo substituido, carbociclo, carbociclo subsituido, arilo, arilo substituido, heterociclo, o heterociclo substituido, con la condición de que Z^{6*} no sea hidrogeno cuando Z^{5*} es cicloalquilo insubstituido, arilo insubstituido, o bencilo insubstituido,

o Z^{5*} y Z^{6*} pueden, junto con el atomo de nitrógeno al cual están unidos, formar un grupo heterocíclico o un grupo heterociclico substituido, con la condición de que Z^{5*} y Z^{6*} no formen

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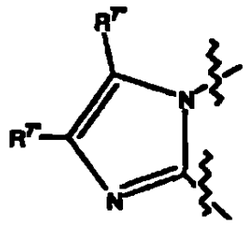
juntos piperidinilo insubstituido, pirrolidinilo insubstituido, o morfolinilo insubstituido, y demas, con la condición de que

(i) R^1 y R^5 sean cada uno hidrógeno, y

(ii) R^2 sea arilo o arilo substituido, y

(iii) R^4 sea heterociclico-arilo substituido, y

(iv) X^1, X^2 y X^3 formen el anillo



donde R^{7*} es H o alquilo,

Z^{5*} y Z^{6*} no formen juntos el piperazinilo insubstituído o piperazinilo N-alquil-substituido,

n y p son independientemente seleccionados de los enteros a partir de 0 a 10 en donde m es 0, p es también 0,

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m es un entero seleccionado de 0 o 1, y

q es un entero seleccionado de 1 a 3

19 Un compuesto de la reivindicación 18, en donde

R^{3*} es heterociclo, heterociclo substituido, $-C(O)NZ^{5*}Z^{6*}$, $-C(O)Z^{3*}-C(O)NZ^{5}Z^{6}$, $-C(O)Z^{3*}-CO_2Z^{5*}$, $C(O)Z^{3}$-(aril), $-C(O)Z^{3}$-(arilo substituido), $-C(O)Z^{3*}$-heterociclo), o $-C(O)Z^{3*}$-(heterociclo substituido)

20 Un compuesto de la reivindicacion 19, en el cual

R^1 es H,

R^2 es arilo, arilo substituido, heterociclo, heterociclo substituido, carbociclo, o carbociclo substituido,

R^4 es alquilo o alquilo substituido, y

X^1, X^2 y X^3, junto con los átomos a los cuales se enlazan, forman un anillo seleccionado de

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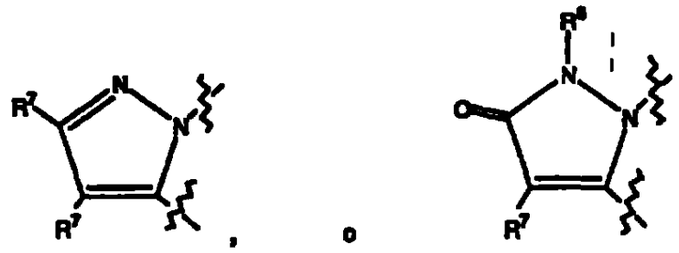

en donde los anillos substituyentes son iguales o diferentes

21 Un compuesto de la reivindicación 18, en el cual R^3 es heterociclo o heterociclo substituido

22 Un compuesto de la reivindicación 21, en donde

R^1 es H,

R^2 es arilo, arilo substituido, heterociclo, heterociclo substituido, carbociclo, o carbociclo substituido,

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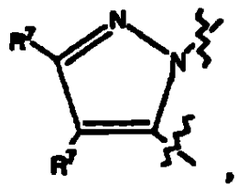
R^4 es alquilo o alquilo substituido, y

X^1, X^2 y X^3, junto con los átomos a los cuales se enlazan, forman un anillo seleccionado de



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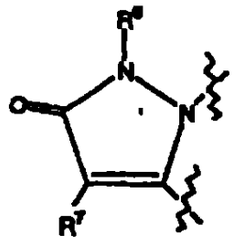

en donde los anillos substitudios son iguales o diferentes

23 Un compuesto de la reivindicación 18, seleccionado de los compuestos del titulo de los ejemplos 18, 19, 25-30, 33, 39-42, 44-82, 84-221, 223-273, 277-282, 286-288, 290-307, 309-312, 314-336, 340-400, 402-450, 452-463, 465-483, 484-488, 490, 493, 495, 497-506, 508, 510-545, 547-555, 557-562, 564, 565, 567-586 y 588

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24 Una composición farmacéutica, la cual comprende una catidad terapeúticamente efectiva de al menos un compuesto de la reivindicación 18 y un vehículo o portador del mismo farmacéuticamente aceptable

25 La composición farmaceutica que comprende una cantidad efectiva terapéuticamente de al menos un compuesto de la reivindicación 19 y un vehículo o portador del mismo farmacéuticamente aceptable

26 Una composición farmacéutica que comprende una cantidad efectiva terapéuticamente de al menos un compuesto de la reivindicación 20 y un vehículo o portador del mismo farmacéuticamente aceptable

27 Una composición farmacéutica que comprende una cantidad efectiva terapéuticamente de al menos un compuesto de la reivindicación 21 y un vehículo o portador del mismo farmacéuticamente aceptable

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28 Una composición farmacéutica que comprende una cantidad efectiva terapéuticamente de al menos un compuesto de la reivindicación 22 y un vehículo o portador del mismo farmacéuticamente aceptable

29 Una composición farmacéutica que comprende una cantidad efectiva terapéuticamente de al menos un compuesto de la reivindicación 23 y un vehículo o portador del mismo farmacéuticamente aceptable

30 Un método de tratamiento de arritmias que comprende la adminsitración a un paciente en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la reivindicación 18

31 Un método de tratamiento de arritmias que comprende la adminsitración a un paciente en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la reivindicación 19

32 Un método de tratamiento de arritmias que comprende la adminsitración a un paciente en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la reivindicación 20

33 Un método de tratamiento de arritmias que comprende la adminsitración a un paciente en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la reivindicación 21

34 Un método de tratamiento de arritmias que comprende la adminsitración a un paciente en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la reivindicacion 22

35 Un método de tratamiento de arritmias que comprende la adminsitración a un paciente en necesidad del mismo, de una cantidad efectiva de al menos, un compuesto de la reivindicación 23

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RESUMEN DE LA INVENCION

Nuevos compuestos de dihidropirimidina heterocíclicos, métodos para usar tales compuestos en la prevención y tratamientos de arritmias y condiciones asociadas con I_{kur}, y composiciones farmacéuticas que contienen tales compuestos