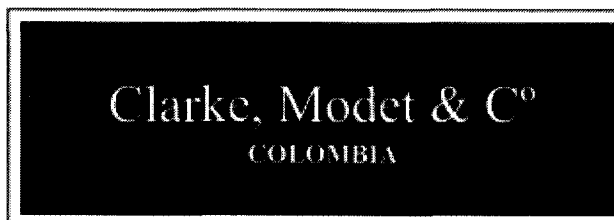


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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

E. S. D.

Ref.: Expediente No. **07-075.247**
Solicitud de Patente a nombre de
ASTEX THERAPEUTICS LIMITED

Yo, **JIMENA ESCOBAR URIBE**, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad **ASTEX THERAPEUTICS LIMITED** con domicilio en Cambridge, Reino Unido de la Gran Bretaña, solicitante de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial el recibo Nr. 08-49,738 de 20 de junio de 2008, por la suma de \$420.000.00, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,


JIMENA ESCOBAR URIBE
C.C.39.779.452 de Usaquén
T.P. 68.228

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NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

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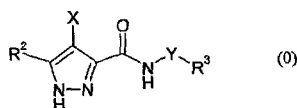
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(54) Title: 3, 4-DISUBSTITUTED 1H-PYRAZOLE COMPOUNDS AND THEIR USE AS CYCLIN DEPENDENT KINASES
(CDK) AND GLYCOGEN SYNTHASE KINASE-3 (GSK-3) MODULATORS



(57) Abstract: The invention provides compounds of the formula (0) or salts or tautomers or N-oxides or solvates thereof for use in the prophylaxis or treatment of disease states and conditions such as cancers mediated by cyclin-dependent kinase and glycogen synthase kinase-3. Formula (0). In formula (0): X is a group R¹-A-NR⁴ or a 5- or 6-membered carbocyclic or heterocyclic ring; A is a bond, SO₂, C=O, NR⁵(C=O) or O(C=O) wherein R⁵ is hydrogen or C₁₋₄ hydrocarbyl optionally substituted by hydroxy or C₁₋₄ alkoxy; Y is a bond or an alkylene chain of 1, 2 or 3 carbon atoms in length; R¹ is hydrogen; a carbocyclic or heterocyclic group having from 3 to 12 ring members; or a C₁₋₈ hydrocarbyl group optionally substituted by one or more substituents selected from halogen (e.g. fluorine), hydroxy, C₁₋₄ hydrocarbyloxy, amino, mono- or di-C₁₋₄ hydrocarbylamino, and carbocyclic or heterocyclic groups having from 3 to 12 ring members, and wherein 1 or 2 of the carbon atoms of the hydrocarbyl group may optionally be replaced by an atom or group selected from O, S, NH, SO, SO₂; R² is hydrogen; halogen; C₁₋₄ alkoxy (e.g. methoxy); or a C₁₋₄ hydrocarbyl group optionally substituted by halogen (e.g. fluorine), hydroxyl or C₁₋₄ alkoxy (e.g. methoxy); R³ is selected from hydrogen and carbocyclic and heterocyclic groups having from 3 to 12 ring members; and R⁴ is hydrogen or a C₁₋₄ hydrocarbyl group optionally substituted by halogen (e.g. fluorine), hydroxyl or C₁₋₄ alkoxy (e.g. methoxy).

When R^a is SO₂NR^c, R^b can be, for example, hydrogen or an optionally substituted C₁₋₈ hydrocarbyl group, or a carbocyclic or heterocyclic group. Examples of R^a-R^b where R^a is SO₂NR^c include aminosulphonyl, C₁₋₄ alkylaminosulphonyl and di-C₁₋₄ alkylaminosulphonyl groups, and sulphonamides formed from a cyclic amino group such as piperidine, morpholine, pyrrolidine, or an optionally N-substituted piperazine such as N-methyl piperazine.

Examples of groups R^a-R^b where R^a is SO₂ include alkylsulphonyl, heteroarylsulphonyl and arylsulphonyl groups, particularly monocyclic aryl and heteroaryl sulphonyl groups. Particular examples include methylsulphonyl, phenylsulphonyl and toluenesulphonyl.

When R^a is NR^c, R^b can be, for example, hydrogen or an optionally substituted C₁₋₈ hydrocarbyl group, or a carbocyclic or heterocyclic group. Examples of R^a-R^b where R^a is NR^c include amino, C₁₋₄ alkylamino (e.g. methylamino, ethylamino, propylamino, isopropylamino, *tert*-butylamino), di-C₁₋₄ alkylamino (e.g. dimethylamino and diethylamino) and cycloalkylamino (e.g. cyclopropylamino, cyclopentylamino and cyclohexylamino).

Specific Embodiments of and Preferences for X, Y, A, R⁵, R¹ to R⁴ and R¹⁰

X

In formula (I), X is a group R¹-A-NR⁴ or a 5- or 6-membered carbocyclic or heterocyclic ring.

In one embodiment, X is a group R¹-A-NR⁴.

In another embodiment, X is a 5- or 6-membered carbocyclic or heterocyclic ring.

A

In formula (I), A is a bond, C=O, NR⁵(C=O) or O(C=O). It will be appreciated that the moiety R¹-A-NR⁴ linked to the 4-position of the pyrazole ring can therefore take the form of an amine R¹-NR⁴, an amide R¹-C(=O)NR⁴, a urea R¹-NR⁵C(=O)NR⁴ or a carbamate R¹-OC(=O)NR⁴.

In one preferred group of compounds of the invention, A is C=O and hence the group R^1-A-NR^4 takes the form of an amide $R^1-C(=O)NR^4$. In another group of compounds of the invention, A is a bond and hence the group R^1-A-NR^4 takes the form of an amine R^1-NR^4 .

5 R⁴

R^4 is hydrogen or a C_{1-4} hydrocarbyl group optionally substituted by halogen (e.g. fluorine), hydroxyl or C_{1-4} alkoxy (e.g. methoxy).

The number of optional substituents on the hydrocarbyl group typically will vary according to the nature of the substituent. For example, where the substituent is halogen, there may be from one to three halogen atoms present, preferably two or three. Where the substituent is hydroxyl or an alkoxy group, typically there will be only a single such substituent present

R^4 is preferably hydrogen or C_{1-3} alkyl, more preferably hydrogen or methyl and most preferably is hydrogen.

15 R⁵

R^5 is hydrogen or a C_{1-4} hydrocarbyl group optionally substituted by hydroxyl or C_{1-4} alkoxy (e.g. methoxy).

When R^5 is C_{1-4} hydrocarbyl substituted by hydroxyl or C_{1-4} alkoxy, typically there is only one such substituent present.

20 Preferably R^5 is hydrogen or C_{1-3} alkyl, more preferably hydrogen or methyl and most preferably R^5 is hydrogen.

R²

R^2 is hydrogen, halogen, C_{1-4} alkoxy, or a C_{1-4} hydrocarbyl group optionally substituted by halogen, hydroxyl or C_{1-4} alkoxy.

25 When R^2 is halogen, preferably it is selected from chlorine and fluorine and more preferably it is fluorine.

When R^2 is C_{1-4} alkoxy, it can be, for example, C_{1-3} alkoxy, more preferably C_{1-2} alkoxy and most preferably methoxy.

When R^2 is an optionally substituted C_{1-4} hydrocarbyl group, the hydrocarbyl group is preferably a C_{1-3} hydrocarbyl group, more preferably a C_{1-2} hydrocarbyl group, for example an optionally substituted methyl group. The optional substituents for the optionally substituted hydrocarbyl group are preferably selected from fluorine, hydroxyl and methoxy.

The number of optional substituents on the hydrocarbyl group typically will vary according to the nature of the substituent. For example, where the substituent is halogen, there may be from one to three halogen atoms present, preferably two or three. Where the substituent is hydroxyl or methoxy, typically there will be only a single such substituent present.

The hydrocarbyl groups constituting R^2 are preferably saturated hydrocarbyl groups. Examples of saturated hydrocarbyl groups include methyl, ethyl, *n*-propyl, *i*-propyl and cyclopropyl.

In one embodiment, R^2 is hydrogen, halogen, C_{1-4} alkoxy, or a C_{1-4} hydrocarbyl group optionally substituted by halogen, hydroxyl or C_{1-4} alkoxy.

In another embodiment, R^2 is hydrogen, fluorine, chlorine, methoxy, or a C_{1-3} hydrocarbyl group optionally substituted by fluorine, hydroxyl or methoxy.

20 In a preferred embodiment, R^2 is hydrogen or methyl, most preferably hydrogen.

R¹

R^1 is hydrogen, a carbocyclic or heterocyclic group having from 3 to 12 ring members, or a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from halogen (e.g. fluorine), hydroxy, C_{1-4} hydrocarbyloxy, amino, mono- or di- C_{1-4} hydrocarbylamino, and carbocyclic or heterocyclic groups having from 3 to 12 ring members, and wherein 1 or 2 of the carbon atoms of the hydrocarbyl group may optionally be replaced by an atom or group selected from

O, S, NH, SO, SO₂. Examples of carbocyclic or heterocyclic groups and hydrocarbyl groups and general preferences for such groups are as set out above in the General Preferences and Definitions section, and as set out below.

In one embodiment, R¹ is an aryl or heteroaryl group.

- 5 When R¹ is a heteroaryl group, particular heteroaryl groups include monocyclic heteroaryl groups containing up to three heteroatom ring members selected from O, S and N, and bicyclic heteroaryl groups containing up to 2 heteroatom ring members selected from O, S and N and wherein both rings are aromatic.

Examples of such groups include furanyl (e.g. 2-furanyl or 3-furanyl), indolyl (e.g.

- 10 3-indolyl, 6-indolyl), 2,3-dihydro-benzo[1,4]dioxinyl (e.g. 2,3-dihydro-benzo[1,4]dioxin-5-yl), pyrazolyl (e.g. pyrazole-5-yl), pyrazolo[1,5-a]pyridinyl (e.g. pyrazolo[1,5-a]pyridine-3-yl), oxazolyl (e.g.), isoxazolyl (e.g. isoxazol-4-yl), pyridyl (e.g. 2-pyridyl, 3-pyridyl, 4-pyridyl), quinolinyl (e.g. 2-quinolinyl), pyrrolyl (e.g. 3-pyrrolyl), imidazolyl and thienyl (e.g. 2-thienyl, 3-thienyl).

- 15 One sub-group of heteroaryl groups R¹ consists of furanyl (e.g. 2-furanyl or 3-furanyl), indolyl, oxazolyl, isoxazolyl, pyridyl, quinolinyl, pyrrolyl, imidazolyl and thienyl.

A preferred sub-set of R¹ heteroaryl groups includes 2-furanyl, 3-furanyl, pyrrolyl, imidazolyl and thienyl.

- 20 Preferred aryl groups R¹ are phenyl groups.

The group R¹ can be an unsubstituted or substituted carbocyclic or heterocyclic group in which one or more substituents can be selected from the group R¹⁰ as hereinbefore defined. In one embodiment, the substituents on R¹ may be selected from the group R^{10a} consisting of halogen, hydroxy, trifluoromethyl, cyano, nitro,

- 25 carboxy, a group R^a-R^b wherein R^a is a bond, O, CO, X³C(X⁴), C(X⁴)X³, X³C(X⁴)X³, S, SO, or SO₂, and R^b is selected from hydrogen and a C₁₋₈ hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy,

oxo, halogen, cyano, nitro, carboxy and monocyclic non-aromatic carbocyclic or heterocyclic groups having from 3 to 6 ring members; wherein one or more carbon atoms of the C₁₋₈ hydrocarbyl group may optionally be replaced by O, S, SO, SO₂, X³C(X⁴), C(X⁴)X³ or X³C(X⁴)X³; X³ is O or S; and X⁴ is =O or =S.

- 5 Where the carbocyclic and heterocyclic groups have a pair of substituents on adjacent ring atoms, the two substituents may be linked so as to form a cyclic group. Thus, two adjacent groups R¹⁰, together with the carbon atoms or heteroatoms to which they are attached may form a 5-membered heteroaryl ring or a 5- or 6-membered non-aromatic carbocyclic or heterocyclic ring, wherein the said
- 10 heteroaryl and heterocyclic groups contain up to 3 heteroatom ring members selected from N, O and S. In particular the two adjacent groups R¹⁰, together with the carbon atoms or heteroatoms to which they are attached, may form a 6-membered non-aromatic heterocyclic ring, containing up to 3, in particular 2, heteroatom ring members selected from N, O and S. More particularly the two
- 15 adjacent groups R¹⁰ may form a 6-membered non-aromatic heterocyclic ring, containing 2 heteroatom ring members selected from N, or O, such as dioxan e.g. [1,4 dioxan]. In one embodiment R¹ is a carbocyclic group e.g. phenyl having a pair of substituents on adjacent ring atoms linked so as to form a cyclic group e.g. to form 2,3-dihydro-benzo[1,4]dioxine.
- 20 More particularly, the substituents on R¹ may be selected from halogen, hydroxy, trifluoromethyl, a group R^a-R^b wherein R^a is a bond or O, and R^b is selected from hydrogen and a C₁₋₄ hydrocarbyl group optionally substituted by one or more substituents selected from hydroxyl, halogen (preferably fluorine) and 5 and 6 membered saturated carbocyclic and heterocyclic groups (for example groups
- 25 containing up to two heteroatoms selected from O, S and N, such as unsubstituted piperidine, pyrrolidino, morpholino, piperazino and N-methyl piperazino).

- The group R¹ may be substituted by more than one substituent. Thus, for example, there may be 1 or 2 or 3 or 4 substituents. In one embodiment, where R¹ is a six membered ring (e.g. a carbocyclic ring such as a phenyl ring), there may be one,
- 30 two or three substituents and these may be located at the 2-, 3-, 4- or 6-positions

around the ring. By way of example, a phenyl group R^1 may be 2-monosubstituted, 3-monosubstituted, 2,6-disubstituted, 2,3-disubstituted, 2,4-disubstituted, 2,5-disubstituted, 2,3,6-trisubstituted or 2,4,6-trisubstituted. More particularly, a phenyl group R^1 may be monosubstituted at the 2-position or disubstituted at positions 2- and 6- with substituents selected from fluorine, chlorine and R^a-R^b , where R^a is O and R^b is C_{1-4} alkyl (e.g. methyl or ethyl). In one embodiment, fluorine is a preferred substituent. In another embodiment, preferred substituents are selected from fluorine, chlorine and methoxy.

Particular examples of non-aromatic groups R^1 include unsubstituted or substituted (by one or more groups R^{10}) monocyclic cycloalkyl groups. Examples of such cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; more typically cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, particularly cyclohexyl.

Further examples of non-aromatic groups R^1 include unsubstituted or substituted (by one or more groups R^{10}) heterocyclic groups having from 3 to 12 ring members, typically 4 to 12 ring members, and more usually from 5 to 10 ring members. Such groups can be monocyclic or bicyclic, for example, and typically have from 1 to 5 heteroatom ring members (more usually 1,2,3 or 4 heteroatom ring members) typically selected from nitrogen, oxygen and sulphur.

When sulphur is present, it may, where the nature of the adjacent atoms and groups permits, exist as $-S-$, $-S(O)-$ or $-S(O)_2-$.

The heterocyclic groups can contain, for example, cyclic ether moieties (e.g. as in tetrahydrofuran and dioxane), cyclic thioether moieties (e.g. as in tetrahydrothiophene and dithiane), cyclic amine moieties (e.g. as in pyrrolidine), cyclic amides (e.g. as in pyrrolidone), cyclic esters (e.g. as in butyrolactone), cyclic thioamides and thioesters, cyclic sulphones (e.g. as in sulpholane and sulfolene), cyclic sulfoxides, cyclic sulphonamides and combinations thereof (e.g. morpholine and thiomorpholine and its S-oxide and S,S-dioxide).

In one sub-set of heterocyclic groups R^1 , the heterocyclic groups contain cyclic ether moieties (e.g. as in tetrahydrofuran and dioxane), cyclic thioether moieties (e.g. as in tetrahydrothiophene and dithiane), cyclic amine moieties (e.g. as in pyrrolidine), cyclic sulphones (e.g. as in sulpholane and sulfolene), cyclic sulfoxides, cyclic sulphonamides and combinations thereof (e.g. thiomorpholine).

Examples of monocyclic non-aromatic heterocyclic groups R^1 include 5-, 6- and 7-membered monocyclic heterocyclic groups such as morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, pyran (2H-pyran or 4H-pyran), dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole, tetrahydrofuran, tetrahydrothiophene, dioxane, tetrahydropyran (e.g. 4-tetrahydropyran), imidazoline, imidazolidinone, oxazoline, thiazoline, 2-pyrazoline, pyrazolidine, piperazine, and N-alkyl piperazines such as N-methyl piperazine.

Further examples include thiomorpholine and its S-oxide and S,S-dioxide (particularly thiomorpholine). Still further examples include N-alkyl piperidines such as N-methyl piperidine.

One sub-group of non-aromatic heterocyclic groups R^1 includes unsubstituted or substituted (by one or more groups R^{10}) 5-, 6- and 7-membered monocyclic heterocyclic groups such as morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, piperazine, and N-alkyl piperazines such as N-methyl piperazine, wherein a particular sub-set consists of pyrrolidine, piperidine, morpholine, thiomorpholine and N-methyl piperazine.

In general, preferred non-aromatic heterocyclic groups include pyrrolidine, piperidine, morpholine, thiomorpholine, thiomorpholine S,S-dioxide, piperazine, N-alkyl piperazines, and N-alkyl piperidines.

Another particular sub-set of heterocyclic groups consists of pyrrolidine, piperidine, morpholine and N-alkyl piperazines, and optionally, N-methyl piperazine and thiomorpholine.

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When R¹ is a C₁₋₈ hydrocarbyl group substituted by a carbocyclic or heterocyclic group, the carbocyclic and heterocyclic groups can be aromatic or non-aromatic and can be selected from the examples of such groups set out hereinabove. The substituted hydrocarbyl group is typically a saturated C₁₋₄ hydrocarbyl group such as an alkyl group, preferably a CH₂ or CH₂CH₂ group. Where the substituted hydrocarbyl group is a C₂₋₄ hydrocarbyl group, one of the carbon atoms and its associated hydrogen atoms may be replaced by a sulphonyl group, for example as in the moiety SO₂CH₂.

When the carbocyclic or heterocyclic group attached to the a C₁₋₈ hydrocarbyl group is aromatic, examples of such groups include monocyclic aryl groups and monocyclic heteroaryl groups containing up to four heteroatom ring members selected from O, S and N, and bicyclic heteroaryl groups containing up to 2 heteroatom ring members selected from O, S and N and wherein both rings are aromatic.

Examples of such groups are set out in the "General Preferences and Definitions" section above.

Particular examples of such groups include furanyl (e.g. 2-furanyl or 3-furanyl), indolyl, oxazolyl, isoxazolyl, pyridyl, quinoliny, pyrrolyl, imidazolyl and thienyl. Particular examples of aryl and heteroaryl groups as substituents for a C₁₋₈ hydrocarbyl group include phenyl, imidazolyl, tetrazolyl, triazolyl, indolyl, 2-furanyl, 3-furanyl, pyrrolyl and thienyl. Such groups may be substituted by one or more substituents R¹⁰ or R^{10a} as defined herein.

When R¹ is a C₁₋₈ hydrocarbyl group substituted by a non-aromatic carbocyclic or heterocyclic group, the non-aromatic or heterocyclic group may be a group selected from the lists of such groups set out hereinabove. For example, the non-aromatic group can be a monocyclic group having from 4 to 7 ring members, e.g. 5 to 7 ring members, and typically containing from 0 to 3, more typically 0, 1 or 2, heteroatom ring members selected from O, S and N. When the cyclic group is a carbocyclic group, it may additionally be selected from monocyclic groups having 3 ring

members. Particular examples include monocyclic cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and 5-, 6- and 7-membered monocyclic heterocyclic groups such as morpholine, piperidine (e.g. 1-piperidinyl, 2-piperidinyl, 3-piperidinyl and 4-piperidinyl), pyrrolidine (e.g. 1-pyrrolidinyl, 2-pyrrolidinyl and 3-pyrrolidinyl), pyrrolidone, piperazine, and N-alkyl piperazines such as N-methyl piperazine. In general, preferred non-aromatic heterocyclic groups include pyrrolidine, piperidine, morpholine, thiomorpholine and N-methyl piperazine.

When R¹ is an optionally substituted C₁₋₈ hydrocarbyl group, the hydrocarbyl group may be as hereinbefore defined, and is preferably up to four carbon atoms in length, more usually up to three carbon atoms in length for example one or two carbon atoms in length.

In one embodiment, the hydrocarbyl group is saturated and may be acyclic or cyclic, for example acyclic. An acyclic saturated hydrocarbyl group (i.e. an alkyl group) may be a straight chain or branched alkyl group.

Examples of straight chain alkyl groups R¹ include methyl, ethyl, propyl and butyl.

Examples of branched chain alkyl groups R¹ include isopropyl, isobutyl, *tert*-butyl and 2,2-dimethylpropyl.

In one embodiment, the hydrocarbyl group is a linear saturated group having from 1-6 carbon atoms, more usually 1-4 carbon atoms, for example 1-3 carbon atoms, e.g. 1, 2 or 3 carbon atoms. When the hydrocarbyl group is substituted, particular examples of such groups are substituted (e.g. by a carbocyclic or heterocyclic group) methyl and ethyl groups.

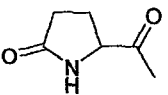
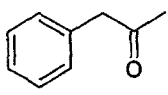
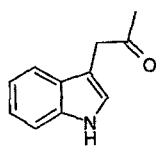
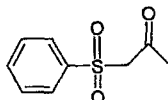
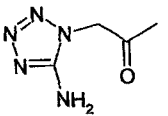
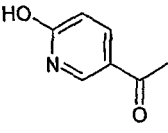
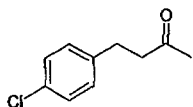
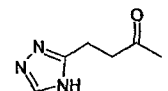
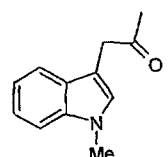
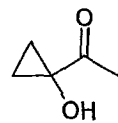
A C₁₋₈ hydrocarbyl group R¹ can be optionally substituted by one or more substituents selected from halogen (e.g. fluorine), hydroxy, C₁₋₄ hydrocarbyloxy, amino, mono- or di-C₁₋₄ hydrocarbylamino, and carbocyclic or heterocyclic groups having from 3 to 12 ring members, and wherein 1 or 2 of the carbon atoms of the hydrocarbyl group may optionally be replaced by an atom or group selected from

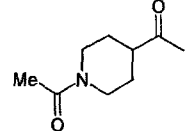
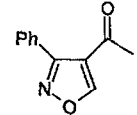
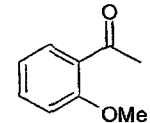
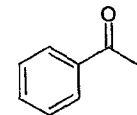
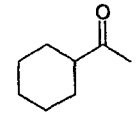
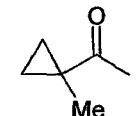
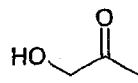
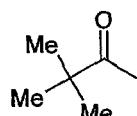
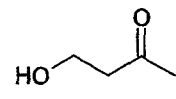
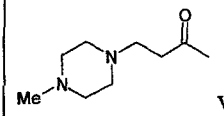
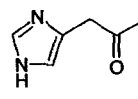
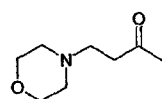
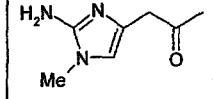
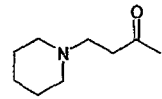
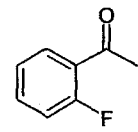
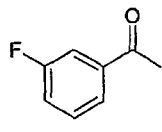
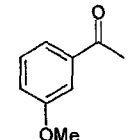
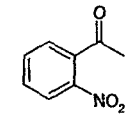
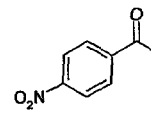
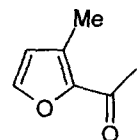
O, S, NH, SO, SO₂. Particular substituents for the hydrocarbonyl group include hydroxy, chlorine, fluorine (e.g. as in trifluoromethyl), methoxy, ethoxy, amino, methylamino and dimethylamino, preferred substituents being hydroxy and fluorine.

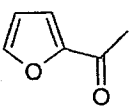
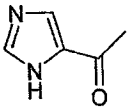
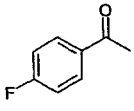
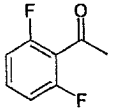
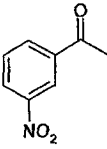
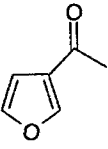
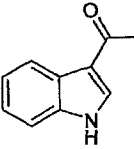
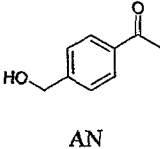
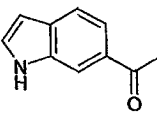
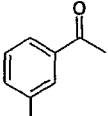
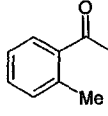
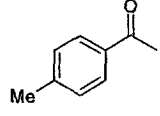
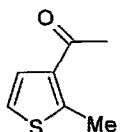
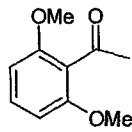
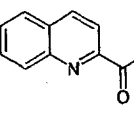
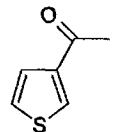
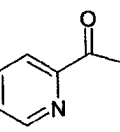
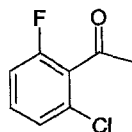
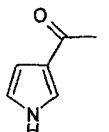
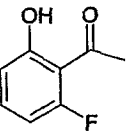
- 5 When A is C=O, particular groups R¹-CO are the groups set out in Table 1 below.

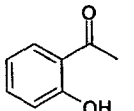
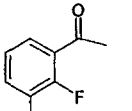
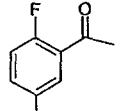
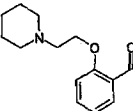
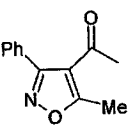
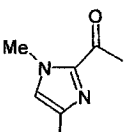
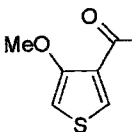
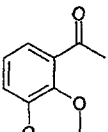
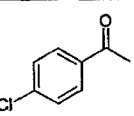
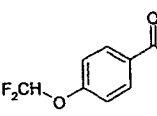
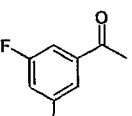
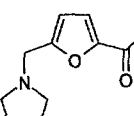
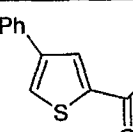
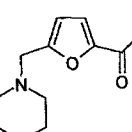
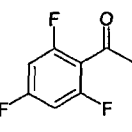
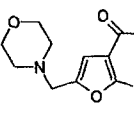
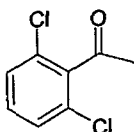
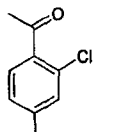
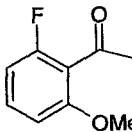
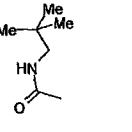
In Table 1, the point of attachment of the group to the nitrogen atom of the pyrazole-4-amino group is represented by the terminal single bond extending from the carbonyl group. Thus, by way of illustration, group B in the table is the trifluoroacetyl group, group D in the table is the phenylacetyl group and group I in the table is the 3-(4-chlorophenyl)propionyl group.

- 10 the table is the 3-(4-chlorophenyl)propionyl group.

Table 1 – Examples of the group R ¹ -CO			
<chem>CH3-C(=O)-</chem> A	<chem>CF3-C(=O)-</chem> B	 C	 D
 E	 F	 G	 H
 I	 J	 K	 L

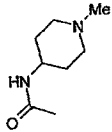
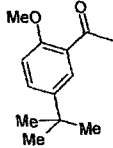
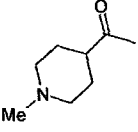
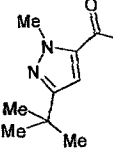
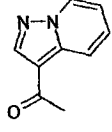
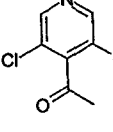
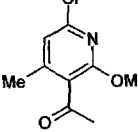
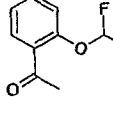
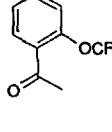
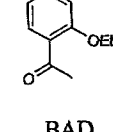
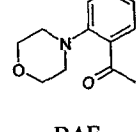
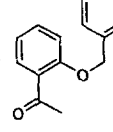
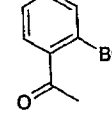
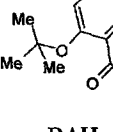
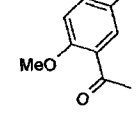
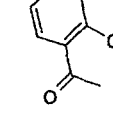
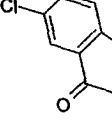
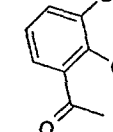
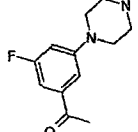
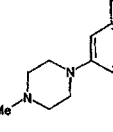
 M	 N	 O	 P
 Q	 R	 S	 T
 U	 V	 W	 X
 Y	 Z	 AA	 AB
 AC	 AD	 AE	 AF

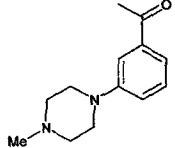
			
AG	AH	AI	AJ
			
AK	AL	AM	AN
			
AO	AP	AQ	AR
			
AS	AT	AU	AV
			
AW	AX	AY	AZ

			
BA	BB	BC	BD
			
BE	BF	BG	BH
			
BI	BJ	BK	BL
			
BM	BN	BO	BP
			
BQ	BR	BS	BT

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BU	BV	BW	BX
			
BY	BZ	BAA	BAB
			
BAC	BAD	BAE	BAF
			
BAG	BAH	BAI	BAJ
			
BAK	BAL	BAM	BAN

			
BAO			

One sub-group of groups R¹-CO consists of groups A to BF in Table 1 above.

Another sub-group of groups R¹-CO consists of groups A to BS in Table 1 above.

One set of preferred groups R¹-CO consists of the groups J, AB, AH, AJ, AL, AS,
5 AX, AY, AZ, BA, BB, BD, BH, BL, BQ, BS and BAI

Another set of preferred groups R¹-CO consists of the groups J, AB, AH, AJ, AL, AS, AX, AY, AZ, BA, BB, BD, BH, BL, BQ and BS.

More preferred groups R¹-CO- are AJ, AX, BQ, BS and BAI.

One particularly preferred sub-set of groups R¹-CO- consists of AJ, BQ and BS.

10 Another particularly preferred sub-set of groups R¹-CO- consists of AJ and BQ.

When X is R¹-A-NR⁴ and A is C=O, and R¹ is a phenyl ring bearing a substituent at the 4-position, the substituent at the 4-position is preferably other than a phenyl group having a group SO₂NH₂ or SO₂Me at the *ortho*-position.

In one general embodiment, R¹ may be other than a substituted or unsubstituted tetrahydroquinoline, chroman, chromene, thiochroman, thiochromene, dihydro-naphthalene or tetrahydronaphthalene group. More particularly, R¹ may be other
15 than a substituted or unsubstituted tetrahydroquinoline, chroman, chromene, thiochroman, thiochromene, dihydro-naphthalene or tetrahydronaphthalene group linked by its aromatic ring to the moiety A-NR⁴-.

In another general embodiment, when R^1 is a substituted or unsubstituted phenyl group, the moiety $Y-R^3$ may be other than hydrogen, unsubstituted C_{1-10} alkyl, unsubstituted C_{5-10} cycloalkyl, unsubstituted phenyl, unsubstituted C_{1-10} alkylphenyl or unsubstituted phenyl- C_{1-10} alkyl.

- 5 In the context of the group R^1-A-NR^4 -, when R^1 is an optionally substituted hydrocarbyl group and the hydrocarbyl group comprises or contains a substituted or unsubstituted alkene group, it is preferred that the carbon-carbon double bond of the alkene group is not directly bonded to the group A.

- 10 Also in the context of the group R^1-A-NR^4 -, when R^1 is an optionally substituted hydrocarbyl group, the hydrocarbyl group may be other than an alkene group.

In another general embodiment, when Y is a bond, R^3 is hydrogen, A is CO and R^1 is a substituted phenyl group, each substituent on the phenyl group may be other than a group $CH_2-P(O)R^xR^y$ where R^x and R^y are each selected from alkoxy and phenyl groups.

15 Y

In the compounds of the formula (I), Y is a bond or an alkylene chain of 1, 2 or 3 carbon atoms in length.

The term "alkylene" has its usual meaning and refers to a divalent saturated acyclic hydrocarbon chain. The hydrocarbon chain may be branched or unbranched.

- 20 Where an alkylene chain is branched, it may have one or more methyl group side chains. Examples of alkylene groups include $-CH_2-$, $-CH_2-CH_2-$, $-CH_2-CH_2-CH_2-$, $CH(CH_3)-$, $-C(CH_3)_2-$, $-CH_2-CH(CH_3)-$, $-CH_2-C(CH_3)_2-$ and $-CH(CH_3)-CH(CH_3)-$.

In one embodiment, Y is a bond.

In another embodiment, Y is an alkylene chain.

When Y is an alkylene chain, preferably it is unbranched and more particularly contains 1 or 2 carbon atoms, preferably 1 carbon atom. Thus preferred groups Y are $-CH_2-$ and $-CH_2-CH_2-$, a most preferred group being $(CH_2)-$.

- 5 Where Y is a branched chain, preferably it has no more than two methyl side chains. For example, it may have a single methyl side chain. In one embodiment, Y is a group $-CH(Me)-$.

In one sub-group of compounds, Y is a bond, CH_2 , CH_2CH_2 or $CH_2CH(CH_3)$.

R^3

- 10 The group R^3 is selected from hydrogen and carbocyclic and heterocyclic groups having from 3 to 12 ring members.

In one sub-group of compounds, Y is a bond and R^3 is hydrogen.

In another sub-group of compounds Y is an alkylene chain as hereinbefore defined and R^3 is hydrogen.

- 15 In a another sub-group of compounds, Y is a bond or an alkylene chain (e.g. a group $-(CH_2)-$) and R^3 is a carbocyclic or heterocyclic group.

In a further sub-group of compounds, Y is a bond and R^3 is a carbocyclic or heterocyclic group.

In a still further sub-group of compounds, Y is an alkylene chain (e.g. a group $-(CH_2)-$) and R^3 is a carbocyclic or heterocyclic group.

- 20 The carbocyclic and heterocyclic groups R^3 can be aryl, heteroaryl, non-aromatic carbocyclic or non-aromatic heterocyclic and examples of such groups are as set out in detail above in the General Preferences and Definitions section, and as set out below.

Preferred aryl groups R^3 are unsubstituted and substituted phenyl groups.

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Examples of heteroaryl groups R^3 include monocyclic heteroaryl groups containing up to three (and more preferably up to two) heteroatom ring members selected from O, S and N. Preferred heteroaryl groups include five membered rings containing one or two heteroatom ring members and six membered rings containing a single heteroatom ring member, most preferably nitrogen. Particular examples of heteroaryl groups include unsubstituted or substituted pyridyl, imidazole, pyrazole, thiazole, isothiazole, isoxazole, oxazole, furyl and thiophene groups.

Particular heteroaryl groups are unsubstituted and substituted pyridyl groups, e.g. 2-pyridyl, 3-pyridyl and 4-pyridyl groups, especially 3- and 4-pyridyl groups. When the pyridyl groups are substituted, they can bear one or more substituents, typically no more than two, and more usually one substituent selected, for example, from C_{1-4} alkyl (e.g. methyl), halogen (e.g. fluorine or chlorine, preferably chlorine), and C_{1-4} alkoxy (e.g. methoxy). Substituents on the pyridyl group may further be selected from amino, mono- C_{1-4} alkylamino and di- C_{1-4} alkylamino, particularly amino.

In one embodiment, when R^3 is an aryl (e.g. phenyl) or heteroaryl group, the substituents on the carbocyclic or heterocyclic group may be selected from the group R^{10a} consisting of halogen, hydroxy, trifluoromethyl, cyano, monocyclic carbocyclic and heterocyclic groups having from 3 to 7 (typically 5 or 6) ring members, and a group R^a-R^b wherein R^a is a bond, O, CO, $X^1C(X^2)$, $C(X^2)X^1$, $X^1C(X^2)X^1$, S, SO, SO_2 , NR^c , SO_2NR^c or NR^cSO_2 ; and R^b is selected from hydrogen, a carbocyclic or heterocyclic group with 3-7 ring members and a C_{1-8} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, cyano, nitro, carboxy, amino, mono- or di- C_{1-4} hydrocarbylamino, a carbocyclic or heterocyclic group with 3-7 ring members and wherein one or more carbon atoms of the C_{1-8} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2 , NR^c , $X^1C(X^2)$, $C(X^2)X^1$ or $X^1C(X^2)X^1$; and R^c , X^1 and X^2 are as hereinbefore defined.

Examples of non-aromatic groups R^3 include optionally substituted (by R^{10} or R^{10a}) cycloalkyl, oxa-cycloalkyl, aza-cycloalkyl, diaza-cycloalkyl, dioxo-cycloalkyl and

aza-oxa-cycloalkyl groups. Further examples include C_{7-10} aza-bicycloalkyl groups such as 1-aza-bicyclo[2.2.2]octan-3-yl.

Particular examples of such groups include unsubstituted or substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyran, morpholine, tetrahydrofuran, piperidine and pyrrolidine groups.

One sub-set of non-aromatic groups R^3 consists of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, tetrahydropyran, tetrahydrofuran, piperidine and pyrrolidine groups.

Preferred non-aromatic groups R^3 include unsubstituted or substituted cyclopentyl, cyclohexyl, tetrahydropyran, tetrahydrofuran, piperidine and pyrrolidine groups,

The non-aromatic groups may be unsubstituted or substituted with one or more groups R^{10} or R^{10a} as hereinbefore defined.

Particular substituents for R^3 (e.g. (i) when R^3 is an aryl or heteroaryl group or (ii) when R^3 is a non-aromatic group) are selected from the group R^{10a} consisting of halogen; hydroxy; monocyclic carbocyclic and heterocyclic groups having from 3 to 6 ring members and containing up to 2 heteroatom ring members selected from O, N and S; and a group R^a-R^b wherein R^a is a bond, O, CO, CO_2 , SO_2 , NH, SO_2NH or $NHSO_2$; and R^b is selected from hydrogen, a carbocyclic or heterocyclic group with 3-6 ring members and containing up to 2 heteroatom ring members selected from O, N and S; and a C_{1-6} hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, oxo, halogen, carboxy, amino, mono- or di- C_{1-4} hydrocarbylamino, a carbocyclic or heterocyclic group with 3-6 ring members and containing up to 2 heteroatom ring members selected from O, N and S; and wherein one or two carbon atoms of the C_{1-6} hydrocarbyl group may optionally be replaced by O, S, SO, SO_2 or NH.

In one embodiment, preferred R^{10a} substituent groups on R^3 (e.g. (i) when R^3 is an aryl or heteroaryl group or (ii) when R^3 is a non-aromatic group) include halogen, a group R^a-R^b wherein R^a is a bond, O, CO, $C(X^2)X^1$, and R^b is selected from

hydrogen, heterocyclic groups having 3-7 ring members and a C₁₋₄ hydrocarbyl group optionally substituted by one or more substituents selected from hydroxy, carboxy, amino, mono- or di-C₁₋₄ hydrocarbylamino, and heterocyclic groups having 3-7 ring members.

- 5 Particularly preferred substituent groups R^{10a} on R³ (e.g. (i) when R³ is an aryl or heteroaryl group or (ii) when R³ is a non-aromatic group) include halogen, especially fluorine, C₁₋₃ alkoxy such as methoxy, and C₁₋₃ hydrocarbyl optionally substituted by fluorine, hydroxy (e.g. hydroxymethyl), C₁₋₂ alkoxy or a 5- or 6-membered saturated heterocyclic ring such as piperidino, morpholino, piperazino
- 10 and N-methylpiperazino.

In another embodiment, the substituents for R³ (whether aromatic or non-aromatic) are selected from:

- halogen (e.g. fluorine and chlorine)
- C₁₋₄ alkoxy (e.g. methoxy and ethoxy) optionally substituted by one or
- 15 substituents selected from halogen, hydroxy, C₁₋₂ alkoxy and five and six membered saturated heterocyclic rings containing 1 or 2 heteroatoms selected from O, N and S, the heterocyclic rings being optionally further substituted by one or more C₁₋₄ groups (e.g. methyl) and wherein the S, when present, may be present as S, SO or SO₂;
- 20 • C₁₋₄ alkyl optionally substituted by one or substituents selected from halogen, hydroxy, C₁₋₄ alkoxy, amino, C₁₋₄ alkylsulphonylamino, 3 to 6 membered cycloalkyl groups (e.g. cyclopropyl), phenyl (optionally substituted by one or more substituents selected from halogen, methyl, methoxy and amino) and five and six membered saturated heterocyclic rings
- 25 containing 1 or 2 heteroatoms selected from O, N and S, the heterocyclic rings being optionally further substituted by one or more C₁₋₄ groups (e.g. methyl) and wherein the S, when present, may be present as S, SO or SO₂;
- hydroxy;
- amino, mono-C₁₋₄ alkylamino, di-C₁₋₄ alkylamino, benzyloxycarbonylamino
- 30 and C₁₋₄ alkoxycarbonylamino;

- carboxy and C₁₋₄ alkoxycarbonyl;
- C₁₋₄ alkylaminosulphonyl and C₁₋₄ alkylsulphonylamino;
- C₁₋₄ alkylsulphonyl;
- a group O-Het^s or NH-Het^s where Het^s is a five or six membered saturated
- 5 heterocyclic ring containing 1 or 2 heteroatoms selected from O, N and S, the heterocyclic rings being optionally further substituted by one or more C₁₋₄ groups (e.g. methyl) and wherein the S, when present, may be present as S, SO or SO₂;
- five and six membered saturated heterocyclic rings containing 1 or 2
- 10 heteroatoms selected from O, N and S, the heterocyclic rings being optionally further substituted by one or more C₁₋₄ groups (e.g. methyl) and wherein the S, when present, may be present as S, SO or SO₂;
- oxo; and
- six membered aryl and heteroaryl rings containing up to two nitrogen ring
- 15 members and being optionally substituted by one or substituents selected from halogen, methyl and methoxy.

- In one preferred sub-group of compounds, R³ is a carbocyclic or heterocyclic group R^{3a} selected from phenyl; C₃₋₆ cycloalkyl; five and six membered saturated non-aromatic heterocyclic rings containing up to two heteroatom ring members selected
- 20 from N, O, S and SO₂; six membered heteroaryl rings containing one, two or three nitrogen ring members; and five membered heteroaryl rings having up to three heteroatom ring members selected from N, O and S;
- wherein each carbocyclic or heterocyclic group R^{3a} is optionally substituted by up to four, preferably up to three, and more preferably up to two (e.g. one) substituents
- 25 selected from amino; hydroxy; oxo; fluorine; chlorine; C₁₋₄ alkyl-(O)_q wherein q is 0 or 1 and the C₁₋₄ alkyl moiety is optionally substituted by fluorine, hydroxy or C₁₋₂ alkoxy; mono-C₁₋₄ alkylamino; di-C₁₋₄ alkylamino; C₁₋₄ alkoxycarbonyl; carboxy; a group R^e-R¹⁶ where R^e is a bond or a C₁₋₃ alkylene chain and R¹⁶ is selected from C₁₋₄ alkylsulphonyl; C₁₋₄ alkylaminosulphonyl; C₁₋₄ alkylsulphonylamino; amino; mono-C₁₋₄ alkylamino; di-C₁₋₄ alkylamino; C₁₋₇-
- 30

hydrocarbyloxycarbonylamino; six membered aromatic groups containing up to three nitrogen ring members; C₃₋₆ cycloalkyl; five or six membered saturated non-aromatic heterocyclic groups containing one or two heteroatom ring members selected from N, O, S and SO₂, the group R¹⁶ when a saturated non-aromatic group being optionally substituted by one or more methyl groups, and the group R¹⁶ when aromatic being optionally substituted by one or more groups selected from fluorine, chlorine, hydroxy, C₁₋₂ alkoxy and C₁₋₂ alkyl.

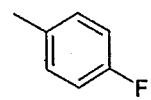
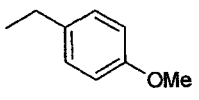
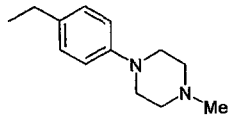
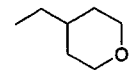
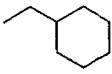
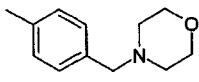
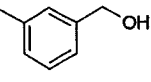
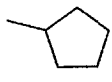
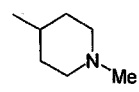
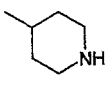
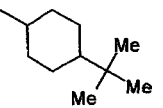
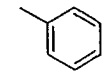
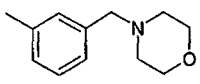
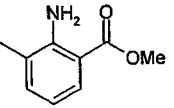
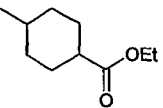
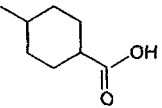
In a further embodiment, R³ is selected from:

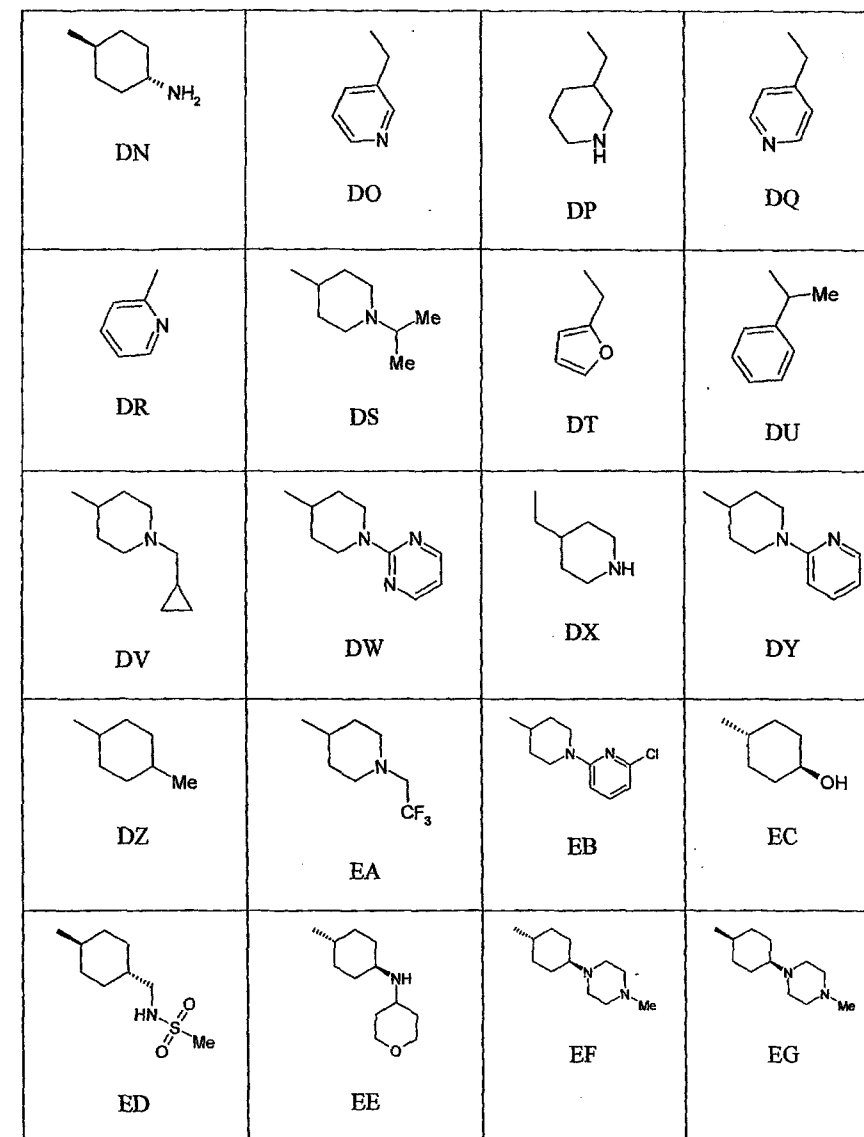
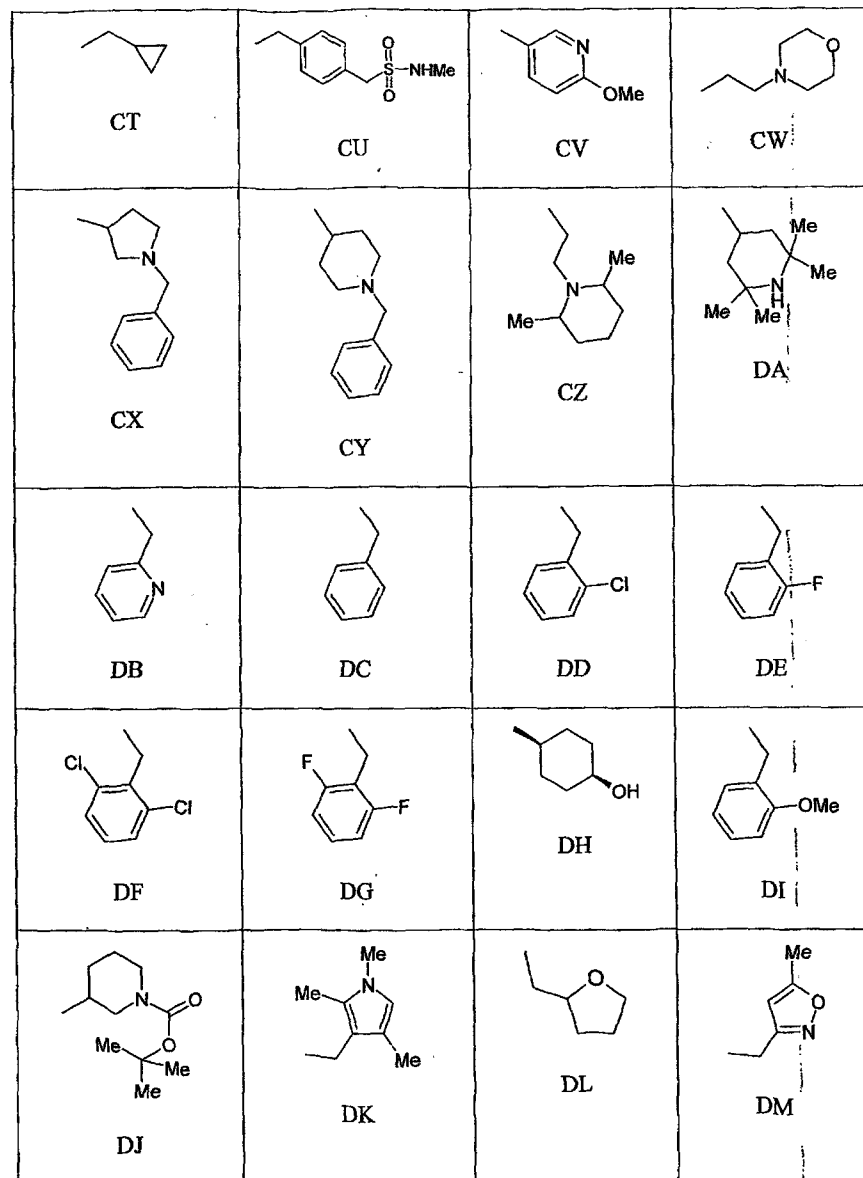
- monocyclic aryl groups optionally substituted by 1-4 (for example 1-2, e.g. 1) substituents R¹⁰ or R^{10a};
- C₃₋₇ cycloalkyl groups optionally substituted by 1-4 (for example 1-2, e.g. 1) substituents R¹⁰ or R^{10a};
- saturated five membered heterocyclic rings containing 1 ring heteroatom selected from O, N and S and being optionally substituted by an oxo group and/or by 1-4 (for example 1-2, e.g. 1) substituents R¹⁰ or R^{10a};
- saturated six membered heterocyclic rings containing 1 or 2 ring heteroatoms selected from O, N and S and being optionally substituted by an oxo group and/or by 1-4 (for example 1-2, e.g. 1) substituents R¹⁰ or R^{10a};
- five membered heteroaryl rings containing 1 or 2 ring heteroatoms selected from O, N and S and being optionally substituted by 1-4 (for example 1-2, e.g. 1) substituents R¹⁰ or R^{10a};
- six membered heteroaryl rings containing 1 or 2 nitrogen ring members (preferably 1 nitrogen ring member) and being optionally substituted by 1-4 (for example 1-2, e.g. 1) substituents R¹⁰ or R^{10a};
- mono-azabicycloalkyl and diazabicycloalkyl groups each having 7 to 9 ring members and being optionally substituted by 1-4 (for example 1-2, e.g. 1) substituents R¹⁰ or R^{10a}.

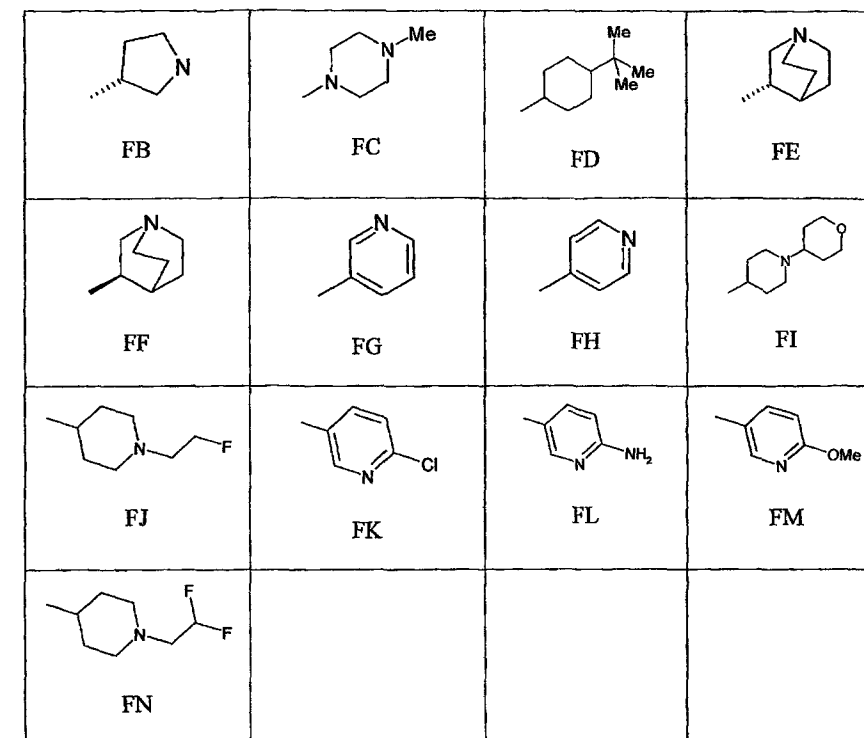
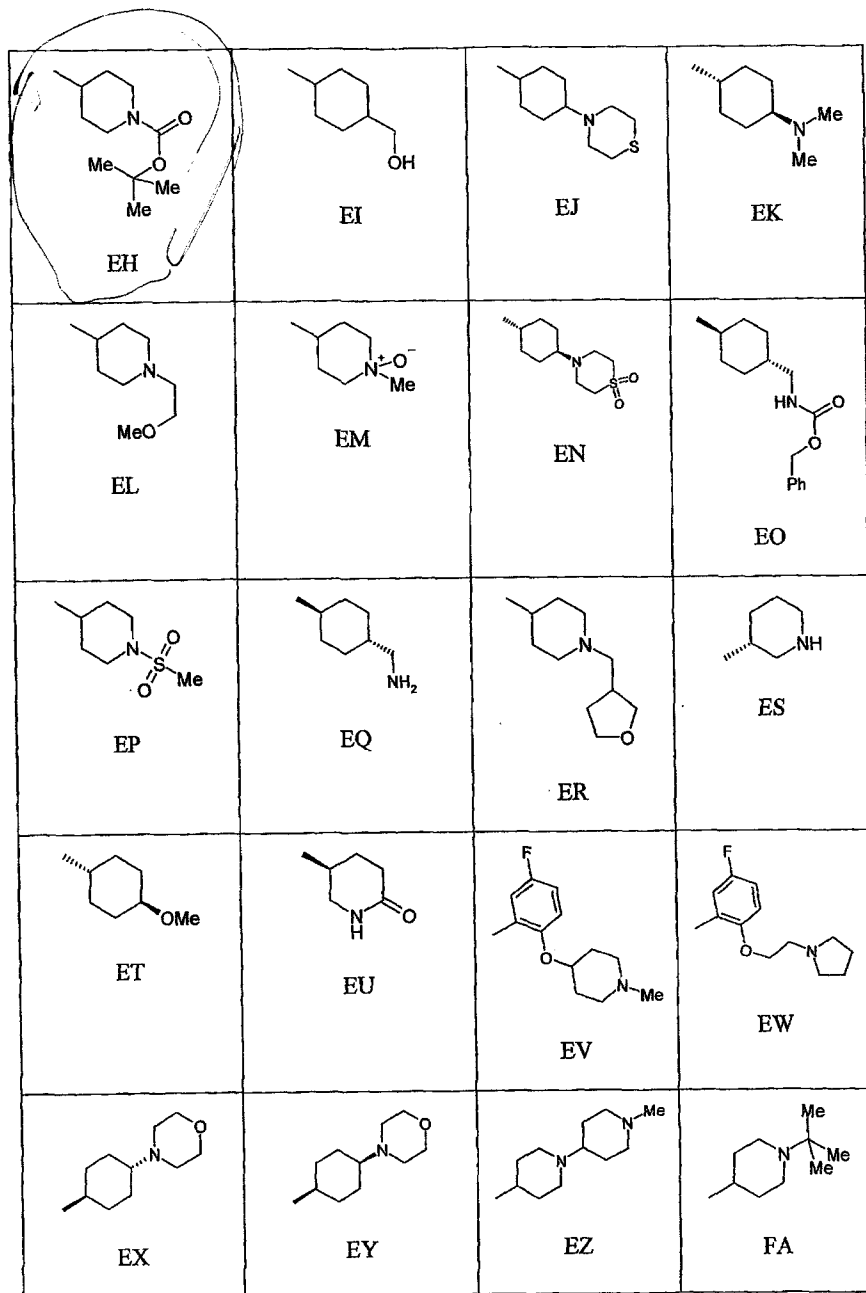
Specific examples of the group Y-R³ are set out in Table 2. In Table 2, the point of attachment of the group to the nitrogen atom of the pyrazole-3-carboxamide group is represented by the terminal single bond extending from the group. Thus, by way

of illustration, group CA in the table is the 4-fluorophenyl, group CB in the table is the 4-methoxybenzyl group and group CC in the table is the 4-(4-methylpiperazino)-phenylmethyl group.

Table 2 – Examples of the Group Y-R³

			
CA	CB	CC	
			
CD	CE	CF	CG
H			
CH	CI	CJ	CK
			
CL	CM	CN	CO
			
CP	CQ	CR	CS





One sub-set of groups selected from table 2 consists of groups CA to EU.

Another sub-set of groups selected from table 2 consists of groups CA to CV.

Preferred groups selected from Table 2 include groups CL, CM, ES, ET, FC, FG

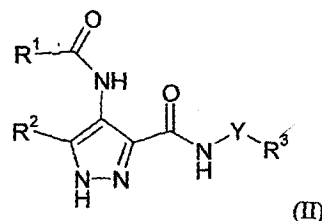
5 and FH.

Particularly preferred groups selected from Table 2 include groups CL, CM and ES, and most preferably CL and CM.

In another general embodiment, when R³ is an aza-cycloalkyl group, the group X in the compound of the formula (I) is preferably R¹-A-NR⁴ wherein A is CO,

10 NR⁵(C=O) or O(C=O). Additionally, or alternatively, when R³ is an aza-cycloalkyl group, the nitrogen atom of the aza-cycloalkyl group is preferably not substituted

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or salts or tautomers or N-oxides or solvates thereof;

wherein R^1 , R^2 , R^3 and Y are each independently selected from R^1 , R^2 , R^3 and Y as defined herein.

- 5 Within formula (II), it is preferred that R^2 is hydrogen or C_{1-4} alkyl (e.g. C_{1-3} alkyl), and more preferably R^2 is hydrogen.

In one sub-group of compounds of the formula (II), R^1 is:

- (i) phenyl optionally substituted by one or more substituents (e.g. 1, 2 or 3) selected from fluorine; chlorine; hydroxy; 5- and 6-membered saturated heterocyclic groups containing 1 or 2 heteroatoms selected from O, N and S, the heterocyclic groups being optionally substituted by one or more C_{1-4} alkyl groups; C_{1-4} hydrocarbyloxy; and C_{1-4} hydrocarbyl; wherein the C_{1-4} hydrocarbyl and C_{1-4} hydrocarbyloxy groups are optionally substituted by one or more substituents chosen from hydroxy, fluorine, C_{1-2} alkoxy, amino, mono and di- C_{1-4} alkylamino, phenyl, halophenyl, saturated carbocyclic groups having 3 to 7 ring members (more preferably 4, 5 or 6 ring members, e.g. 5 or 6 ring members) or saturated heterocyclic groups of 5 or 6 ring members and containing up to 2 heteroatoms selected from O, S and N; or 2, 3-dihydro-benzo[1,4]dioxine; or
- (ii) a monocyclic heteroaryl group containing one or two heteroatoms selected from O, S and N; or a bicyclic heteroaryl group containing a single heteroatom selected from O, S and N; the monocyclic and bicyclic heteroaryl groups each being optionally substituted by one or more substituents selected from fluorine; chlorine; C_{1-3} hydrocarbyloxy; and C_{1-3} hydrocarbyl optionally substituted by hydroxy,

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fluorine, methoxy or a five or six membered saturated carbocyclic or heterocyclic group containing up to two heteroatoms selected from O, S and N; or

- (iii) a substituted or unsubstituted cycloalkyl group having from 3 to 6 ring members; or
- 5 (iv) a C_{1-4} hydrocarbyl group optionally substituted by one or more substituents selected from fluorine; hydroxy; C_{1-4} hydrocarbyloxy; amino; mono- or di- C_{1-4} hydrocarbylamino; and carbocyclic or heterocyclic groups having from 3 to 12 ring members, and wherein one of the carbon atoms of the hydrocarbyl group may optionally be replaced by an atom or group selected from O, NH, SO and SO_2 .
- 10 Within group (i), a sub-group of groups R^1 consists of phenyl optionally substituted by one or more substituents selected from fluorine; chlorine; hydroxy; C_{1-3} hydrocarbyloxy; and C_{1-3} hydrocarbyl wherein the C_{1-3} hydrocarbyl group is optionally substituted by one or more substituents chosen from hydroxy, fluorine, C_{1-2} alkoxy, amino, mono and di- C_{1-4} alkylamino, saturated carbocyclic groups
- 15 having 3 to 7 ring members (more preferably 4, 5 or 6 ring members, e.g. 5 or 6 ring members) or saturated heterocyclic groups of 5 or 6 ring members and containing up to 2 heteroatoms selected from O, S and N.

In another sub-group of compounds of the formula (II), R^1 is selected from (i) and (iii) above and additionally from a sub-set (aii) where sub-set (aii) consists of 2-furanyl, 3-furanyl, imidazolyl, 2-pyridyl, indolyl, 2-thienyl and 3-thienyl, each optionally substituted by one or more substituents selected from fluorine, chlorine, C_{1-3} hydrocarbyloxy, and C_{1-3} hydrocarbyl optionally substituted by hydroxy, fluorine or methoxy.

- Within the group of compounds defined by the formula (II), where R^1 is (i) an optionally substituted phenyl group, it may be, for example, an unsubstituted phenyl group or a 2-monosubstituted, 3-monosubstituted, 2,3 disubstituted, 2,5 disubstituted or 2,6 disubstituted phenyl group or 2, 3-dihydro-benzo[1,4]dioxine, where the substituents are selected from halogen; hydroxyl; C_{1-3} alkoxy; and C_{1-3} alkyl groups wherein the C_{1-3} alkyl group is optionally substituted by hydroxy,

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fluorine, C₁₋₂ alkoxy, amino, mono and di-C₁₋₄ alkylamino, or saturated carbocyclic groups having 3 to 6 ring members and/or saturated heterocyclic groups of 5 or 6 ring members and containing 1 or 2 heteroatoms selected from N and O.

- In one embodiment, R¹ is selected from unsubstituted phenyl, 2-fluorophenyl, 2-hydroxyphenyl, 2-methoxyphenyl, 2-methylphenyl, 2-(2-(pyrrolidin-1-yl)ethoxy)-phenyl, 3-fluorophenyl, 3-methoxyphenyl, 2,6-difluorophenyl, 2-fluoro-6-hydroxyphenyl, 2-fluoro-3-methoxyphenyl, 2-fluoro-5-methoxyphenyl, 2-chloro-6-methoxyphenyl, 2-fluoro-6-methoxyphenyl, 2,6-dichlorophenyl and 2-chloro-6-fluorophenyl, and is optionally further selected from 5-fluoro-2-methoxyphenyl.
- 10 In another embodiment, R¹ is selected from unsubstituted phenyl, 2-fluorophenyl, 2-hydroxyphenyl, 2-methoxyphenyl, 2-methylphenyl, 2-(2-(pyrrolidin-1-yl)ethoxy)-phenyl, 3-fluorophenyl, 3-methoxyphenyl, 2,6-difluorophenyl, 2-fluoro-6-hydroxyphenyl, 2-fluoro-3-methoxyphenyl and 2-fluoro-5-methoxyphenyl.

- Particular groups R¹ are 2,6-difluorophenyl, 2-fluoro-6-methoxyphenyl and 2,6-dichlorophenyl.

One particularly preferred group R¹ is 2,6-difluorophenyl.

Another particularly preferred group R¹ is 2,6-dichlorophenyl.

- When R¹ is (ii) a monocyclic heteroaryl group containing one or two heteroatoms selected from O, S and N or a bicyclic heteroaryl group containing a single heteroatom, examples of monocyclic and bicyclic heteroaryl groups include furanyl (e.g. 2-furanyl and 3-furanyl), imidazolyl, pyridyl (e.g. 2-pyridyl), indolyl, thienyl (e.g. 2-thienyl and 3-thienyl) groups. The optional substituents for such groups can include chlorine, fluorine, methyl, methoxy, hydroxymethyl, methoxymethyl, morpholinomethyl, piperazinomethyl, N-methylpiperazinomethyl and piperidinylmethyl groups. Particular examples of groups (ii) include unsubstituted 2-furanyl, 3-methyl-2-furanyl, unsubstituted 4-(1H)-imidazolyl, unsubstituted 5-(1H)-imidazolyl, unsubstituted 3-furanyl, unsubstituted 3-thienyl, 2-methyl-3-thienyl and unsubstituted 3-pyrrolyl, and further examples include 4-methoxy-3-

thienyl, 5-(1-pyrrolidinyl)methyl-2-furyl and 5-(4-morpholino)methyl-2-furyl groups.

- When R¹ is (iii) an optionally substituted cycloalkyl group, it can be for example a substituted or unsubstituted cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group. When the cycloalkyl group is substituted, preferred substituents include methyl, fluorine and hydroxyl. Particular examples of cycloalkyl groups include 1-methylcyclopropyl, 1-hydroxycyclopropyl, and unsubstituted cyclohexyl, cyclopentyl and cyclobutyl.

- In the context of formula (II) and the group R¹, examples of optionally substituted hydrocarbyl groups are optionally substituted methyl, ethyl and propyl groups wherein one of the carbon atoms of the hydrocarbyl group is optionally replaced by O, NH, SO or SO₂. Particular examples of such groups include methyl, ethyl, trifluoromethyl, methyl and ethyl substituted with a carbocyclic or heterocyclic group having from 3 to 12 ring members, sulphonylmethyl substituted with a carbocyclic or heterocyclic group having from 3 to 12 ring members, hydroxymethyl, hydroxyethyl, 3-hydroxy-2-propyl, propyl, isopropyl, butyl and tertiary butyl. Examples of hydrocarbyl groups and carbocyclic and heteroacyclic groups are as set out above in the general definitions of such groups. Particular carbocyclic and heterocyclic groups include unsubstituted or substituted phenyl, indolyl, tetrazolyl, triazolyl, piperidinyl, morpholinyl, piperazinyl, N-methylpiperazinyl, imidazolyl wherein the optional substituents may be selected from the group R¹⁰, and sub-groups thereof, as defined herein.

- In another sub-group of compounds of the formula (II), R¹ is a C₁₋₄ hydrocarbyl group optionally substituted by one or more substituents selected from fluorine, hydroxy, C₁₋₄ hydrocarbyloxy, amino, mono- or di-C₁₋₄ hydrocarbylamino, and carbocyclic or heterocyclic groups having from 3 to 12 ring members, and wherein 1 of the carbon atoms of the hydrocarbyl group may optionally be replaced by an atom or group selected from O, NH, SO and SO₂.

In one embodiment, R¹ is a group R^{1a}-(V)_n where:

- n is 0 or 1;
V is selected from CH₂, CH₂CH₂ and SO₂CH₂; and
R^{1a} is a carbocyclic or heterocyclic group selected from phenyl;
five membered heteroaryl rings having up to 4 heteroatom ring members selected
5 from N, O and S;
six membered heteroaryl rings containing one or two nitrogen ring members;
five or six membered saturated non-aromatic heterocyclic rings containing one or
two heteroatom ring members selected from N, O, S and SO₂;
C₃₋₆ cycloalkyl groups; indole; and quinoline;
10 wherein each of the carbocyclic and heterocyclic groups R^{1a} can be optionally
substituted by one or more substituents selected from five or six membered
saturated non-aromatic carbocyclic and heterocyclic groups containing up to two
heteroatom ring members selected from N, O, S and SO₂; hydroxy; amino; oxo;
mono-C₁₋₄ alkylamino; di-C₁₋₄ alkylamino; fluorine; chlorine; nitro; C₁₋₄ alkyl-(O)_q-
15 wherein q is 0 or 1 and the C₁₋₄ alkyl moiety is optionally substituted by fluorine,
hydroxy, C₁₋₂ alkoxy or a five or six membered saturated non-aromatic carbocyclic
or heterocyclic group containing up to two heteroatom ring members selected from
N, O, S and SO₂; phenyl and C₁₋₂-alkylene dioxy.

Specific examples of groups R¹-CO- in formula (II) are set out in Table 1 above.

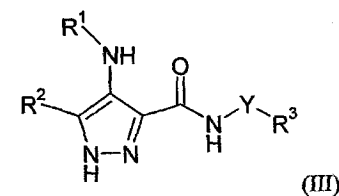
- 20 One sub-group of preferred groups R¹-CO consists of the groups J, AB, AH, AJ,
AL, AS, AX, AY, AZ, BA, BB, BD, BH, BL, BQ and BS.

Another sub-group of groups R¹-CO consists of the groups A to BF.

A further sub-group of groups R¹-CO consists of the groups A to BS.

- Particularly preferred groups are the groups AJ, BQ and BS in Table 1, e.g. the sub-
25 set consisting of AJ and BQ.

Another group of compounds of the invention is represented by the formula (III):



or salts or tautomers or N-oxides or solvates thereof;

wherein R¹, R², R³ and Y are as defined herein.

- Examples of, and preferences, for the groups R¹, R², R³ and Y are as set out above
5 for compounds of the formulae (0), (I⁰), (I), (Ia), (Ib) and (II) unless the context
indicates otherwise.

Particular sub-groups of compounds of the formula (III) include:

- (i) compounds wherein R¹ is a heteroaryl group containing 1, 2 or 3 heteroatom
ring members selected from N, O and S;
10 (ii) compounds wherein R¹ is a C₁₋₆ hydrocarbyl group optionally substituted by
one or more substituents selected from fluorine, hydroxy, C₁₋₄ hydrocarbyloxy,
amino, mono- or di-C₁₋₄ hydrocarbylamino, and carbocyclic or heterocyclic groups
having from 3 to 12 ring members, and wherein 1 of the carbon atoms of the
hydrocarbyl group may optionally be replaced by an atom or group selected from
15 O, NH, SO and SO₂; and
(iii) compounds wherein R¹ is a non-aromatic carbocyclic or heterocyclic group
having from 3 to 12 ring members.

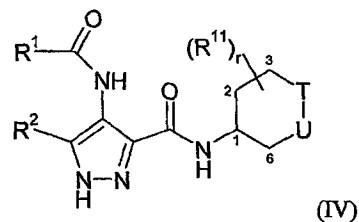
- Examples of compounds of the formula (III) wherein R¹ is (i) a heteroaryl group
include 5- and 6-membered monocyclic heteroaryl groups, e.g. containing 1 or 2
20 heteroatom ring members selected from O, N and S. In one embodiment, the
heteroaryl group is a monocyclic group containing 1 or 2 nitrogen ring members.
In another embodiment, the heteroaryl groups are selected from 6-membered rings
containing 1 or 2 nitrogen ring members, for example pyridine, pyrimidine,
pyrazine and pridazine groups, one particular sub-group consisting of pyrazinyl and
25 pyridyl.

The heteroaryl groups can be unsubstituted or substituted by one or more groups R^{10} as defined herein.

- Examples of compounds of the formula (III) wherein R^1 is (ii) an optionally substituted C_{1-6} hydrocarbyl group include those in which the hydrocarbyl group is unsubstituted hydrocarbyl, for example unsubstituted alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *t*-butyl, 1-pentyl, 2-pentyl and 3-pentyl.

- Examples of compounds wherein R^1 is a non-aromatic carbocyclic or heterocyclic group include those wherein the carbocyclic or heterocyclic group is monocyclic and contains up to 2 heteroatoms selected from oxygen and nitrogen. Particular examples of such groups are cyclohexyl and piperidino.

Another sub-group of compounds of the formula (I) can be represented by the formula (IV):



- or salts or tautomers or N-oxides or solvates thereof;
- wherein R^1 and R^2 are as defined herein;
- an optional second bond may be present between carbon atoms numbered 1 and 2;
- one of U and T is selected from CH_2 , CHR^{13} , $CR^{11}R^{13}$, NR^{14} , $N(O)R^{15}$, O and $S(O)$; and the other of U and T is selected from NR^{14} , O, CH_2 , CHR^{11} , $C(R^{11})_2$, and $C=O$; r is 0, 1, 2, 3 or 4; t is 0, 1 or 2;
- R^{11} is selected from hydrogen, halogen (particularly fluorine), C_{1-3} alkyl (e.g. methyl) and C_{1-3} alkoxy (e.g. methoxy);
- R^{13} is selected from hydrogen, NHR^{14} , NOH , NOR^{14} and R^a-R^b ;
- R^{14} is selected from hydrogen and R^d-R^b ;
- R^d is selected from a bond, CO, $C(X^2)X^1$, SO_2 and SO_2NR^c ;

R^a , R^b and R^c are as hereinbefore defined; and

R^{15} is selected from C_{1-4} saturated hydrocarbyl optionally substituted by hydroxy, C_{1-2} alkoxy, halogen or a monocyclic 5- or 6-membered carbocyclic or heterocyclic group, provided that U and T cannot be O simultaneously.

- Examples of, and preferences, for the groups R^1 and R^2 are as set out above for compounds of the formulae (I), (Ia), (Ib) and (II) unless the context indicates otherwise.

Within formula (IV), r can be 0, 1, 2, 3 or 4. In one embodiment, r is 0. In another embodiment, r is 2, and in a further embodiment r is 4.

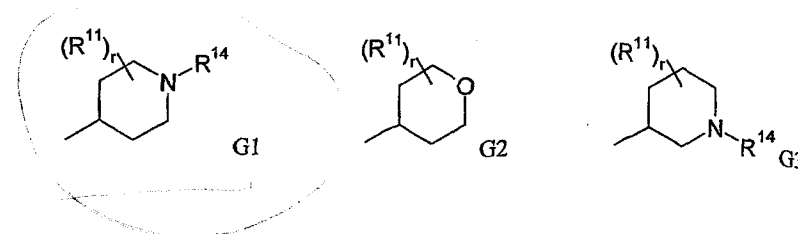
- Within formula (IV), one sub-set of preferred compounds is the set of compounds where there is only a single bond between the carbon atoms numbered 1 and 2.

However, in another sub-set of compounds, there is a double bond between the carbon atoms numbered 1 and 2.

- Another sub-set of compounds is characterised by *gem* disubstitution at the 2-carbon (when there is a single bond between carbon atoms numbers 1 and 2) and/or the 6-carbon. Preferred *gem* disubstituents include difluoro and dimethyl.

A further sub-set of compounds is characterised by the presence of an alkoxy group, for example a methoxy group at the carbon atom numbered 3, i.e. at a position α with respect to the group T.

- Within formula (IV) are compounds wherein, for example, R^3 is selected from any of the following ring systems:



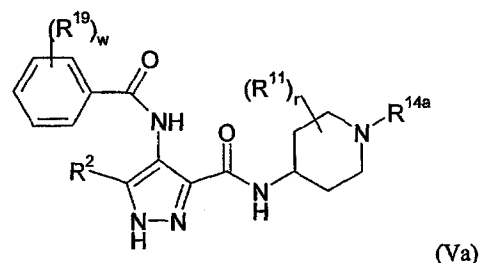
methoxyethyl), carboxy, C₁₋₄ alkoxycarbonyl (e.g. ethoxycarbonyl) and amino-C₁₋₂-alkyl (e.g. aminomethyl).

Particular examples of R¹⁴ are hydrogen; C₁₋₄ alkyl optionally substituted by fluoro or a five or six membered saturated heterocyclic group (e.g. a group selected from

- (i) methyl, ethyl, n-propyl, i-propyl, butyl, 2,2,2-trifluoroethyl and tetrahydrofuranylmethyl; and/or (ii) 2-fluoroethyl and 2,2-difluoroethyl); cyclopropylmethyl; substituted or unsubstituted pyridyl-C₁₋₂ alkyl (e.g. 2-pyridylmethyl); substituted or unsubstituted phenyl-C₁₋₂ alkyl (e.g. benzyl); C₁₋₄ alkoxycarbonyl (e.g. ethoxycarbonyl and t-butyloxycarbonyl); substituted and unsubstituted phenyl-C₁₋₂ alkoxycarbonyl (e.g. benzyloxycarbonyl); substituted and unsubstituted 5- and 6-membered heteroaryl groups such as pyridyl (e.g. 2-pyridyl and 6-chloro-2-pyridyl) and pyrimidinyl (e.g. 2-pyrimidinyl); C₁₋₂-alkoxy-C₁₋₂ alkyl (e.g. methoxymethyl and methoxyethyl); C₁₋₄ alkylsulphonyl (e.g. methanesulphonyl).

- 15 Preferred compounds include those in which (i) U is CHR¹³ (more preferably CH₂) and T is NR₁₄, and (ii) T is CHR¹³ (more preferably CH₂) and U is NR¹⁴.

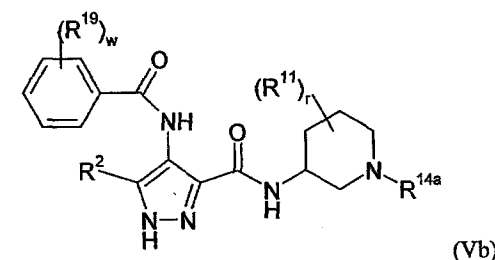
One particular preferred sub-group of compounds of the formula (IV) can be represented by the formula (Va):



- 20 or salts or tautomers or N-oxides or solvates thereof; wherein R^{14a} is selected from hydrogen, C₁₋₄ alkyl optionally substituted by fluoro (e.g. methyl, ethyl, n-propyl, i-propyl, butyl and 2,2,2-trifluoroethyl), cyclopropylmethyl, phenyl-C₁₋₂ alkyl (e.g. benzyl), C₁₋₄ alkoxycarbonyl

- (e.g. ethoxycarbonyl and t-butyloxycarbonyl), phenyl-C₁₋₂ alkoxycarbonyl (e.g. benzyloxycarbonyl), C₁₋₂-alkoxy-C₁₋₂ alkyl (e.g. methoxymethyl and methoxyethyl), and C₁₋₄ alkylsulphonyl (e.g. methanesulphonyl), wherein the phenyl moieties when present are optionally substituted by one to three substituents
- 5 selected from fluorine, chlorine, C₁₋₄ alkoxy optionally substituted by fluoro or C₁₋₂-alkoxy, and C₁₋₄ alkyl optionally substituted by fluoro or C₁₋₂-alkoxy; w is 0, 1, 2 or 3; R² is hydrogen or methyl, most preferably hydrogen; R¹¹ and r are as hereinbefore defined; and
- 10 { R¹⁹ is selected from fluorine; chlorine; C₁₋₄ alkoxy optionally substituted by fluoro or C₁₋₂-alkoxy; and C₁₋₄ alkyl optionally substituted by fluoro or C₁₋₂-alkoxy.

Another particular preferred sub-group of compounds of the formula (IV) can be represented by the formula (Vb):



- 15 or salts or tautomers or N-oxides or solvates thereof; wherein R^{14a} is selected from hydrogen, C₁₋₄ alkyl optionally substituted by fluoro (e.g. methyl, ethyl, n-propyl, i-propyl, butyl and 2,2,2-trifluoroethyl), cyclopropylmethyl, phenyl-C₁₋₂ alkyl (e.g. benzyl), C₁₋₄ alkoxycarbonyl (e.g. ethoxycarbonyl and t-butyloxycarbonyl), phenyl-C₁₋₂ alkoxycarbonyl (e.g. benzyloxycarbonyl), C₁₋₂-alkoxy-C₁₋₂ alkyl (e.g. methoxymethyl and methoxyethyl), and C₁₋₄ alkylsulphonyl (e.g. methanesulphonyl), wherein the phenyl moieties when present are optionally substituted by one to three substituents
- 20 selected from fluorine, chlorine, C₁₋₄ alkoxy optionally substituted by fluoro or C₁₋₂-alkoxy, and C₁₋₄ alkyl optionally substituted by fluoro or C₁₋₂-alkoxy; w is 0, 1, 2 or 3;
- 25

R^2 is hydrogen or methyl, most preferably hydrogen;

R^{11} and r are as hereinbefore defined; and

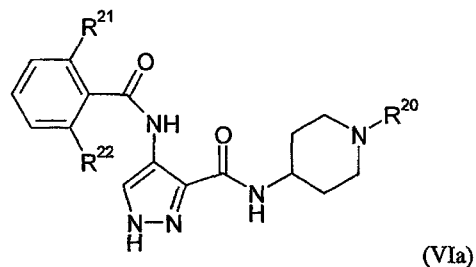
R^{19} is selected from fluorine; chlorine; C_{1-4} alkoxy optionally substituted by fluoro or C_{1-2} -alkoxy; and C_{1-4} alkyl optionally substituted by fluoro or C_{1-2} -alkoxy.

- 5 In formulae (Va) and (Vb), when w is 1, 2 or 3, it is preferred that the phenyl ring is 2-monosubstituted, 3-monosubstituted, 2,6-disubstituted, 2,3-disubstituted, 2,4-disubstituted, 2,5-disubstituted, 2,3,6-trisubstituted or 2,4,6-trisubstituted. Most preferably the phenyl ring is disubstituted at positions 2- and 6- with substituents selected from fluorine, chlorine and methoxy.

- 10 R^{11} is preferably hydrogen (or r is 0).

R^{14a} is most preferably hydrogen or methyl.

One preferred sub-group of compounds of the formula (Va) can be represented by the formula (VIa):



- 15 or salts or tautomers or N-oxides or solvates thereof;

wherein R^{20} is selected from hydrogen and methyl;

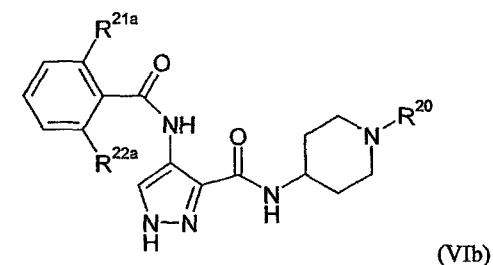
R^{21} is selected from fluorine and chlorine; and

R^{22} is selected from fluorine, chlorine and methoxy; or

one of R^{21} and R^{22} is hydrogen and the other is selected from chlorine, methoxy,

- 20 ethoxy, difluoromethoxy, trifluoromethoxy and benzyloxy.

Another preferred sub-group of compounds of the formula (Va) can be represented by the formula (VIb):



or salts or tautomers or N-oxides or solvates thereof;

wherein R^{20} is selected from hydrogen and methyl;

R^{21a} is selected from fluorine and chlorine; and

- 5 R^{22a} is selected from fluorine, chlorine and methoxy.

Particular compounds within formula (VIb) include:

4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid piperidin-4-ylamide;

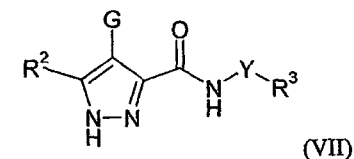
4-(2,6-difluoro-benzoylamino)-1H-pyrazole-3-carboxylic acid (1-methyl-piperidin-4-yl)-amide;

- 10 4-(2,6-dichloro-benzoylamino)-1H-pyrazole-3-carboxylic acid piperidin-4-ylamide; and

4-(2-fluoro-6-methoxy-benzoylamino)-1H-pyrazole-3-carboxylic acid piperidin-4-ylamide;

or salts or tautomers or N-oxides or solvates thereof.

- 15 A further group of compounds of the invention is represented by the formula (VII):

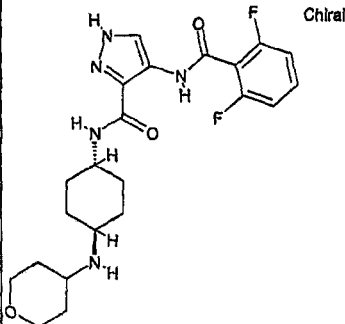
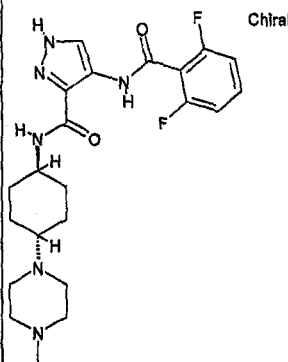
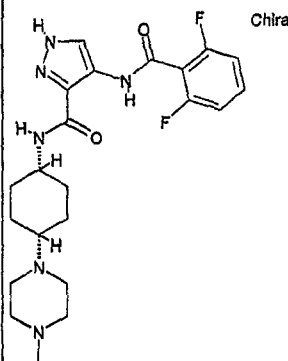
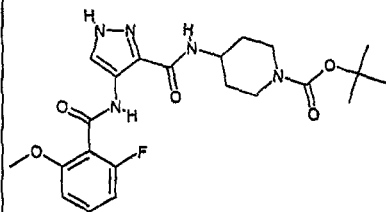


or salts or tautomers or N-oxides or solvates thereof;

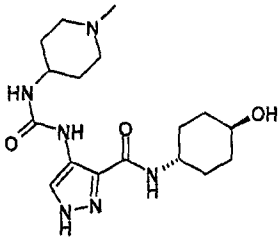
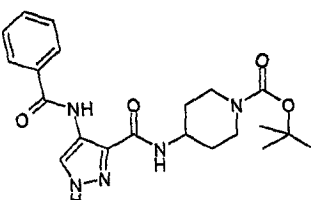
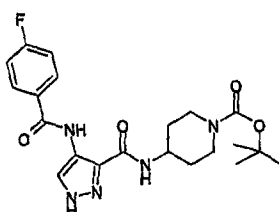
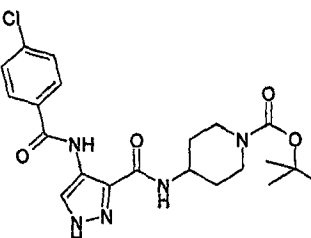
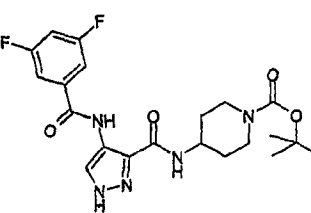
wherein R^2 , R^3 and Y are as hereinbefore defined and G is a 5- or 6-membered carbocyclic or heterocyclic ring.

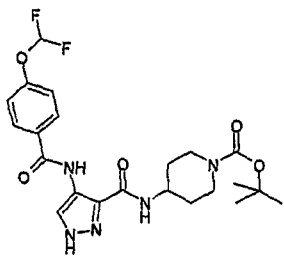
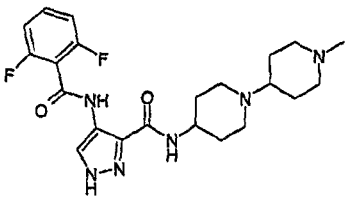
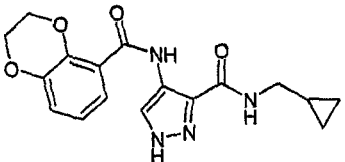
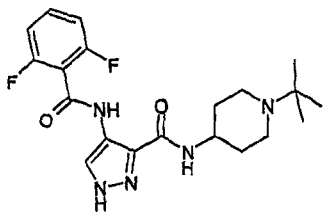
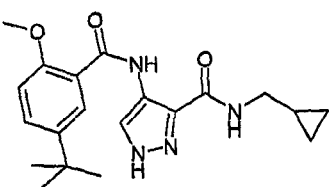
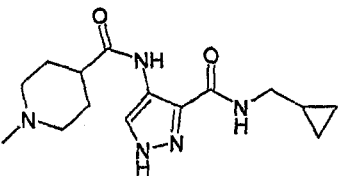
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Example No.		Method of Preparation	LCMS
116		Procedure A DMSO instead of DMF, Et ₃ N 2 equiv Starting amine prepared according to Procedure L	[M+H] ⁺ 448 R _t 1.87
117		Procedure A DMSO instead of DMF, Et ₃ N 2 equiv Starting amine prepared according to Procedure L	[M+H] ⁺ 447 R _t 1.65
118		Procedure A DMSO instead of DMF, Et ₃ N 2 equiv Starting amine prepared according to Procedure L	[M+H] ⁺ 447 R _t 1.72
119		Procedure B	[M+H] ⁺ 462 R _t 2.97

Example No.		Method of Preparation	LCMS
135		Procedure B	$[M+H]^+$ 458 R_t 2.26
136		Procedure B HOAt instead of HOBt,	$[M+H]^+$ 468 R_t 3.07
137		Procedure A Et_3N 2 equiv., HOAt instead of HOBt,	$[M+H]^+$ 379 R_t 2.6
138		Procedure B	$[M+H]^+$ 472 R_t 2.40
139		Procedure A Et_3N 2 equiv., HOAt instead of HOBt, DMSO instead of DMF	$[M+H]^+$ 364 R_t 2.1

Example No.	Structure	Method	Differences	LCMS
171		Procedure D followed by G then E		$[M+H]^+$ 365 R_t 0.34
172		B	Purified by column chromatography (pet. ether-EtOAc (1:1))	$[M+H]^+$ 414.13 R_t 3.05
173		B	Purified by column chromatography (pet. ether-EtOAc (1:1))	$[M+H]^+$ 432.12 R_t 3.12
174		B	Purified by column chromatography (pet. ether-EtOAc (1:1))	$[M+H]^+$ 448.06 R_t 3.33
175		B	Purified by column chromatography (pet. ether-EtOAc (1:1))	$[M+H]^+$ 450.08 R_t 3.29

Example No.	Structure	Method	Differences	LCMS
176		B	Purified by column chromatography (pet. ether-EtOAc (1:1))	[M+H] ⁺ 480.05 R _t 3.18
177		A Starting amine prepared according to Procedure L	HOAt instead of HOBt DMSO as solvent instead of DMF Et ₃ N 2 eq Purified by HPLC and formation of HCl salt	[M+H] ⁺ 447 R _t 2.01
178		B		[M+H] ⁺ 343.05 R _t 3.38 (polar method)
179		A Butyl-piperidin-4-ylamine prepared by Procedure N	HOAt instead of HOBt Purified by titration with MeOH	[M+H] ⁺ 406 R _t 1.85
180		B		[M+H] ⁺ 371.09 R _t 3.27 (polar method)
181		B		[M+H] ⁺ 306.06 R _t 1.53

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300

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

Bogotá, D.C., 10 de marzo de 2011

Apoderado: Jimena Escobar Uribe

ASUNTO

Radicación 07-75247

Oficio

Trámite 002

Evento 001

Actuación 430

Folios

Patente de Invención



Vía PCT fase nacional



Cap. I



Cap. II



No. Sol. Internacional

PCT/GB2006/000196

Fecha de Presentación Internal. 20/ene/2006

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descripción: Folios: 11 a 219 como se radicó inicialmente

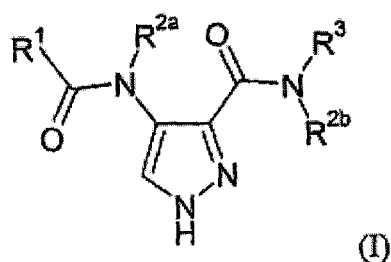
1.2. Reivindicaciones: Folios 220 a 235 Como se radicó inicialmente

1.4 Prioridad: Folios: US 60/646.217; 21/ene/2005
GB 0501480.8; 22/ene/2005
GB 0501748.8; 27/ene/2005
US 60/651.339; 09/feb/2005

1. Objeto de la invención

Título de la solicitud: DERIVADOS DE PIRAZOL PARA LA INHIBICIÓN DE LAS CDKs Y GSKs.

§ El objeto de la invención se refiere a derivados de (3-carbamoil-1H-pirazol-4-il)carbamato cubiertos bajo la fórmula Markush (I):



- Reivindicaciones 1-38, 47, 51, 55, 56: Un compuesto de la fórmula (I).
- Reivindicación 39-46, 57, 58: Procedimiento de tratamiento que consiste en administrar un compuesto a un paciente
- Reivindicaciones 48, 54: Uso
- Reivindicación 49, 50: Composiciones que los comprenden.
- Reivindicación 53: método de diagnóstico y método de tratamiento
- reivindicación 59: proceso para la obtención de un compuesto de fórmula (I).

§ El problema planteado en esta solicitud es la necesidad de compuestos útiles para inhibir o modular la actividad de las cinasas dependientes de ciclina (CDK) y cinasas de sintasa de glicógeno (GSK).

§ Para solucionar este problema técnico la solicitud en estudio proporciona compuestos derivados de (3-carbamoyl-1H-pirazol-4-yl)carbamato cubiertos bajo la fórmula Markush (I).

Se catalogó la invención, según la Clasificación Internacional de Patentes (IPC.): C07D231/14; C07D231/40; A01N43/56; A61K31/44; A61K31/4545.

2. De la solicitud de Patente

2.1. Reivindicaciones (artículo 30 D 486 de la C.A.N.)

- La reivindicación 34, no es clara, hace referencia a la descripción y en las reivindicaciones debe aparecer explícitamente la materia para la cual se solicita protección.
- La reivindicaciones 47, 51, 55, 56, son inconsistentes, puesto que el encabezado no es consecuente con el texto de la reivindicación, se encabezan como compuesto y el texto de la reivindicación hace referencia al uso; cuando allí debe aparecer la parte técnica que define un compuesto, o sea, su estructura química particular o su nombre químico.
- Las reivindicaciones 49 y 50, son materia redundante, ya que en ambas se reclama la misma materia una composición farmacéutica, dado que el objeto de esta reivindicación no es nuevo "per se" (composición que comprende compuestos de la reivindicación I), ya que es el uso tácito de los compuestos para obtener composiciones en ambos casos; el hecho que se le agregue a la reivindicación 50 un resultado por obtener los mismos los hace diferentes.

Por lo tanto las reivindicaciones no cumplen con el requisito de claridad, concisión o sustento por la descripción de acuerdo al art. 30 de la Decisión 486.

3. Excepción a la patentabilidad (artículo 20 literal d) D486 de la C.A.N.)

-Las reivindicaciones 39-46,53, 57,58 reclaman un método para el tratamiento del cuerpo humano o animal, por lo tanto están comprendidas por lo dispuesto en el artículo 20 literal d) D486 de la C.A.N.

4. Reivindicaciones relativas a un uso o a un uso distinto (artículos 14 y 21 D 486)

- Las reivindicaciones 48 y 54 reclaman los usos y de acuerdo con la legislación actual vigente, el uso no se considera para protección, como se lee en el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina "... Los Países Miembros otorgarán patentes para las invenciones sean de productos o procedimientos en todos los campos de la tecnología..."; Aquí NO se hace alusión al uso como factor patentable; los segundos usos no son patentables por aplicación del Art. 21. Asimismo, de conformidad con la sentencia del TJAC 89-AI-2000, los usos en general no son patentables.

5. Determinación del Estado de la Técnica

Considerando la fecha de prioridad reclamada de la presente solicitud de patente 21/ene/2005, se realizó la búsqueda del estado de la técnica, en bases de datos donde ésta oficina tiene acceso libre, para búsquedas de documentos relacionados con la materia que se reclama como nueva e inventiva en la presente solicitud.

Encontrándose el siguiente documento relevante:

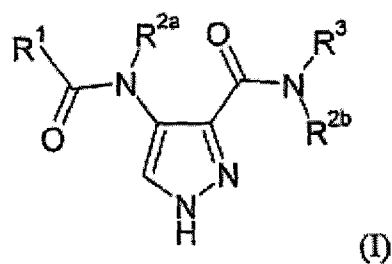
N°	Documento	Título	Fecha de Publicación*
D1*	WO2005012256	3,4-disubstituted 1H-pyrazole compounds and their use as cyclin dependent Kinases (CDK) and glycogen synthase kinase-3 (GSK-3) modulators	10/feb/2005

*Si se trata de una solicitud colombiana esta fecha corresponde también a la fecha de presentación de la solicitud colombiana aún sin haber sido publicada o sin habersele cumplido el plazo previsto en el art.40.

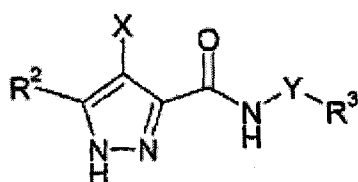
6. Análisis de patentabilidad (artículo 14 D486 de la C.A.N.)

6.1. Novedad (artículo 16 D486 de la C.A.N.)

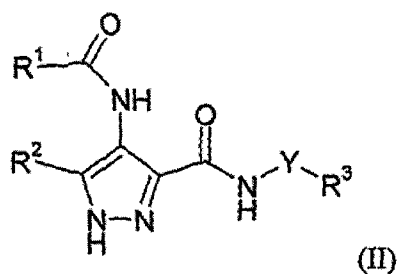
-La solicitud en estudio reclama los derivados de (3-carbamoyl-1H-pirazol-4-yl)carbamato cubiertos bajo la fórmula Markush (I):



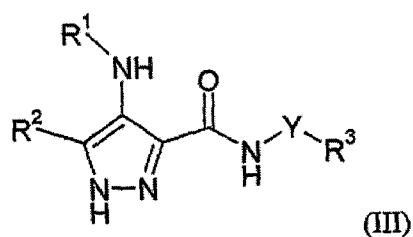
§ La anterioridad D1 enseña derivados 1H-pirazol-3,4-disustituido, como (3 carbamoil-1H-pirazol-4-il)carbamato de fórmula:



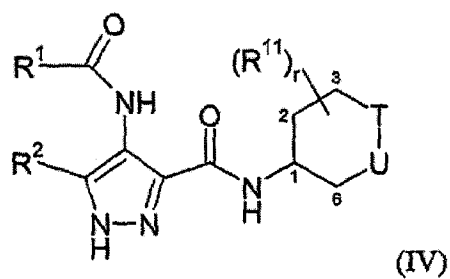
Véase en todo D1, especialmente en como sigue: las pags.37-46, tabla 1, pags. 51-59, tabla 2;



Véase en las págs. 66-70;

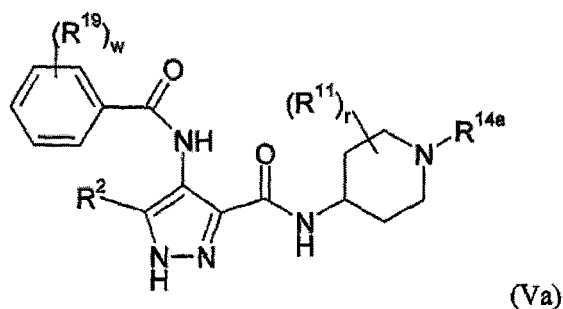


véase en las págs. 71-72;

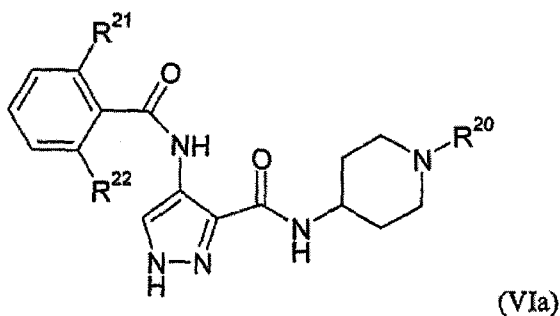


véase en las págs.72-76;

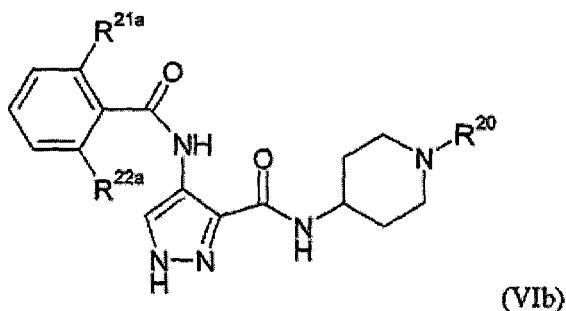
281
304



véase en las págs..76-77;



Véase en la pág. 78:



Véase en la pag. 79.

Véase además las reivindicaciones.

Tal como se puede ver, la materia reclamada en la solicitud en estudio está comprendida en la anterioridad, por lo tanto la solicitud no cumple con lo exigido en el

Si existen oposiciones por parte de terceros, demostrar cómo los fundamentos de éstas afectan la Novedad es decir cómo los objetos se consideran idénticos.

7. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D1	WO2005012256	1-59	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente

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comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha
17 8 MAR. 2011

CONCEPTO TECNICO No. 923	EXAMINADOR TECNICO Cód N°202012
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