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N-(3-(3-SUSTITUIDAS-PIRAZOLO (1,5-a)PIRIMIDIN-7-IL)-FENIL)-

SULFONAMIDAS Y COMPOSICIONES Y METODOS RELACIONADOS

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10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$463.000
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica
- ☒ Poderes, si fuere el caso **Fotocopia Autenticada**
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros - Tarjeta de Propietarios

2

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente,

NOMBRE: CARLOS H. PALACIO EASTMAN

FIRMA:


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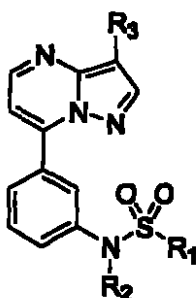
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(54) Title: N-[3-(3-SUBSTITUTED-PYRAZOLO[1,5-a]PYRIMIDIN-7-YL)PHENYL]-SULFONAMIDES, AND COMPOSITIONS, AND METHODS RELATED THERETO



(I)

(57) Abstract: The present invention relates to compounds of Formula (I); wherein R₁, R₂ and R₃ are as defined in the claims. The compounds have specific affinity for the GABA_A receptor and are therefore useful in the treatment and prevention of diseases modulated by the α₁- and α₂-GABA_A receptors.

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**N-[3-(3-SUBSTITUTED-PYRAZOLO[1,5-a]PYRIMIDIN-7-YL)PHENYL]-
SULFONAMIDES, AND COMPOSITIONS, AND METHODS RELATED THERETO**

5 **Technical field**

This invention is directed to agents with affinity for GABA_A receptor, more specifically to pyrazolo[1,5-a]pyrimidines.

10

Background of the invention

GABA_A receptor (γ -aminobutyric acid_A) is a pentameric protein which forms a membrane ion channel. GABA_A receptor is implicated in the regulation of sedation, anxiety, muscle tone, epileptogenic activity and memory functions. These actions are due to defined subunits of GABA_A receptor, particularly the α_1 - and α_2 -subunits.

20 Sedation is modulated by the α_1 -subunit. Zolpidem is characterized by a high affinity for the α_1 -receptors and its sedative and hypnotic action is mediated by these receptors *in vivo*. Similarly, the hypnotic action of zaleplon is also mediated by the α_1 -receptors.

25

The anxiolytic action of diazepam is mediated by the enhancement of GABAergic transmission in a population of neurons expressing the α_2 -receptors. This indicates that the α_2 -receptors are highly specific targets for the treatment of anxiety.

30

Muscle relaxation in diazepam is mainly mediated by α_2 -receptors, since these receptors exhibit a highly specific expression in spinal cord.

5 The anticonvulsant effect of diazepam is partly due to α_1 -receptors. In diazepam, a memory-impairing compound, anterograde amnesia is mediated by α_1 -receptors.

10 GABA_A receptor and its α_1 - and α_2 -subunits have been widely reviewed by H. Möhler et al. (J. Pharmacol. Exp. Ther., 300, 2-8, 2002); H. Möhler et al. (Curr. Opin. Pharmacol., 1, 22-25, 2001); U. Rudolph et al. (Nature, 401, 796-800, 1999); and D.J. Nutt et al. (Br. J. Psychiatry, 179, 390-396, 2001).

15 Diazepam and other classical benzodiazepines are extensively used as anxiolytic agents, hypnotic agents, anticonvulsants and muscle relaxants. Their side effects include anterograde amnesia, decrease in motor activity and
20 potentiation of ethanol effects.

In this context, the compounds of this invention are ligands of α_1 - and α_2 -GABA_A receptor for their clinical application in sleep disorders, preferably insomnia,
25 anxiety and epilepsy.

Insomnia is a highly prevalent disease. Its chronicity affects 10% of the population and 30% when transitory insomnia is computed as well. Insomnia describes the
30 trouble in getting to sleep or staying asleep and is associated with next-day hangover effects such as weariness, lack of energy, low concentration and

irritability. The social and health impact of this complaint is important and results in evident socioeconomic repercussions.

5 Pharmacological therapy in the management of insomnia firstly included barbiturates and chloral hydrate, but these drugs elicit numerous known adverse effects, for example, overdose toxicity, metabolic induction, and enhanced dependence and tolerance. In addition, they affect
10 the architecture of sleep by decreasing above all the duration and the number of REM sleep stages. Later, benzodiazepines meant an important therapeutic advance because of their lower toxicity, but they still showed serious problems of dependence, muscle relaxation, amnesia
15 and rebound insomnia following discontinuation of medication.

The latest known therapeutic approach has been the introduction of non-benzodiazepine hypnotics, such as
20 pyrrolo[3,4-b]pyrazines (zopiclone), imidazo[1,2-a]pyridines (zolpidem) and, finally, pyrazolo[1,5-a]pyrimidines (zaleplon). Later, two new pyrazolo[1,5-a]pyrimidines, indiplon and ocinaplon, have entered into development, the latter with rather anxiolytic action. All
25 these compounds show a rapid sleep induction and have less next-day hangover effects, lower potential for abuse and lower risk of rebound insomnia than benzodiazepines. The mechanism of action of these compounds is the allosteric activation of GABA_A receptor through its binding to
30 benzodiazepine binding site (C. F. P. George, The Lancet, 358, 1623-1626, 2001). While benzodiazepines are unspecific ligands at GABA_A receptor binding site, zolpidem and zaleplon show a greater selectivity for α_1 -subunit.

Notwithstanding that, these drugs still affect the architecture of sleep and may induce dependence in long-term treatments.

5 In US patent documents No. 4,626,538 (zaleplon), No. 4,654,347, 6,399,621 (indiplon) and European Patent No. 129,847 (ocinaplon) hypnotic pyrazolo[1,5-a]pyrimidines are disclosed.

10 Research for new active compounds in the management of insomnia answers an underlying health need, because even recently introduced hypnotics still affect the architecture of sleep and may induce dependence in long-term treatments.

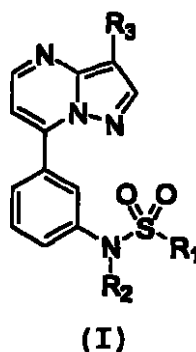
15 It is therefore desirable to focus on the development of new hypnotic agents with a lower risk of side effects.

Thus, the present invention is directed to new N-[3-(3-substituted-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-
20 sulfonamides which are active versus GABA_A and, particularly, versus its α_1 - and α_2 -subunits. Consequently, the compounds of this invention are useful in the treatment and prevention of all those diseases mediated by GABA_A receptor α_1 - and α_2 -subunits. Non-limitative examples of
25 such diseases are sleep disorders, preferably insomnia, anxiety and epilepsy. Non-limitative examples of the relevant indications of the compounds of this invention are all those diseases or conditions, such as insomnia or anesthesia, in which an induction of sleep, an induction of
30 sedation or an induction of muscle relaxation are needed.

g 8

Detailed description of the invention

The present invention relates to novel N-[3-(3-substituted-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-sulfonamides of formula (I)



and their pharmaceutically acceptable salts;

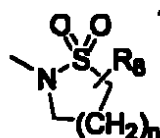
wherein

R_1 is selected from the group consisting of alkyl(C_1-C_6), alkenyl(C_2-C_6), ω,ω,ω -trifluoroalkyl(C_1-C_6), cycloalkyl(C_3-C_6), cycloalkyl(C_3-C_6)alkyl(C_1-C_6), -O-alkyl(C_1-C_6), -NH-alkyl(C_1-C_6), -N(dialkyl(C_1-C_6)), alkyl(C_1-C_6)-O-alkyl(C_1-C_6), alkyl(C_1-C_6)-NH-alkyl(C_1-C_6), alkyl(C_1-C_6)-N(dialkyl(C_1-C_6)), phenyl, monosubstituted phenyl, disubstituted phenyl, phenylalkyl(C_1-C_6), phenylalkenyl(C_2-C_6), furyl, substituted furyl, isoxazolyl, substituted isoxazolyl, pyrazolyl, substituted pyrazolyl, thienyl, substituted thienyl, thiazolyl, substituted thiazolyl, pyridyl and substituted pyridyl;

R_2 is selected from the group consisting of hydrogen, alkyl(C_1-C_6), alkenyl(C_2-C_6), alkynyl(C_2-C_6) and cycloalkyl(C_3-C_6);

or else

R_1 and R_2 form a cycle having the structure:



5 wherein n is an integer 1, 2 or 3 inclusive;

R₃ is selected from the group consisting of hydrogen, halogen, alkyl(C₁-C₆), cycloalkyl(C₃-C₆), alkenyl(C₂-C₅), alkynyl(C₂-C₆), -O-alkyl(C₁-C₆), halo-alkyl(C₁-C₆), -CN, -SO₂-R₄, -NH-R₄, -NR₄R₅, -COR₆, -CO-NHR₆, -COOR₆, -C(NR₇)R₆, phenyl, substituted phenyl, heteroaryl and substituted heteroaryl;

R₄ and R₅ are independently selected from the group consisting of alkyl(C₁-C₆), cycloalkyl(C₃-C₆), aryl and heteroaryl;

15 R₆ is selected from the group consisting of hydrogen, alkyl(C₁-C₆), alkenyl(C₂-C₆), alkynyl(C₂-C₆), cycloalkyl(C₃-C₆), phenyl, substituted phenyl, furyl, substituted furyl, thienyl, substituted thienyl, thiazolyl, substituted thiazolyl, pyridyl and substituted pyridyl;

20 R₇ is selected from the group consisting of alkyl(C₁-C₆), cycloalkyl(C₃-C₆), -OH, -O-alkyl(C₁-C₆), alkyl(C₁-C₆)-O-alkyl(C₁-C₆), alkyl(C₁-C₆)-NH-alkyl(C₁-C₆), alkyl(C₁-C₆)-N(dialkyl(C₁-C₆)), phenyl, monosubstituted phenyl, furyl, thienyl, thiazolyl and pyridyl; and

25 R₈ is selected from the group consisting of hydrogen, alkyl(C₁-C₆), cycloalkyl(C₃-C₆), aryl and substituted or unsubstituted heteroaryl;

with the proviso that:

R₁ may simultaneously not be p-tolyl and R₂ methyl and R₃ benzoyl; and

30 R₁ may simultaneously not be p-tolyl and R₂ ethyl and R₃ furyl-2-carbonyl.

9

US Patent No. 4.654.347 (Example 80) discloses N-[3-(3-benzoyl-pyrazolo[1,5-a]pyrimidin-7-yl)phenyl]-N,4-dimethyl-benzenesulfonamide and European Patent No. 129.847 (Example 166) discloses N-ethyl-N-[3-[3-(2-furylcarbonyl) -pyrazolo[1,5-a]pyrimidin-7-yl]phenyl]-4-methyl-benzene-sulfonamide. These compounds are merely recited in the above patents as synthetic intermediates, and they are not considered pharmacologically active substances. This fact, therefore, does not suggest that analog compounds, like those in the instant invention, may be therapeutically interesting, which finding has unexpectedly been discovered by the applicants. These compounds, which are comprised in the general formula (I), have purposely been thus excluded from the scope of this invention.

R_1 is preferably selected from alkyl(C_1-C_6); ω,ω,ω -trifluoroalkyl(C_1-C_6); phenyl; phenyl substituted with 1 or 2 groups which are independently selected from halogen (in particular fluoro and chloro), cyano, NO_2 , Oalkyl(C_1-C_6) and alkyl(C_1-C_6); phenylalkenyl(C_2-C_6); cycloalkyl(C_3-C_6); cycloalkyl(C_3-C_6)alkyl(C_1-C_6); phenylalkyl(C_1-C_6); alkenyl(C_2-C_6); isoxazolyl which may be substituted with 1 or 2 alkyl(C_1-C_6); furyl which may be substituted with 1 or 2 alkyl(C_1-C_6); furyl which may be substituted with 1 alkyl(C_1-C_6) and 1 trifluoromethyl; thiazolyl which may be substituted with 1 or 2 alkyl(C_1-C_6); pyrazolyl which may be substituted with 1, 2 or 3 alkyl(C_1-C_6); thienyl which may be substituted with 1 or 2 alkyl(C_1-C_6) and pyridyl which may be substituted with 1 or 2 4-morpholinyl groups; or R_1 and R_2 together form the above mentioned cycle wherein n and R_3 are as defined above.

R^2 is preferably selected from H, alkyl(C_1-C_6), cycloalkyl(C_3-C_6) and alkynyl(C_2-C_6), or R_2 forms together with R_1 the above mentioned cycle wherein n and R_8 are as defined above.

5 R_3 is preferably selected from H, CN and COR_6 wherein R_6 is selected from phenyl which may be substituted with 1 or 2 groups which are independently selected from halogen (in particular fluoro or chloro), alkyl(C_1-C_6) and Oalkyl(C_1-C_6); thienyl; pyridyl and oxadiazolyl which may be
10 substituted with alkyl(C_1-C_6).

A preferred embodiment relates to the compounds of formula I wherein R_3 is cyano, R_1 is selected from alkyl(C_1-C_6), phenyl and phenyl substituted with an Oalkyl(C_1-C_6) group,
15 and R_2 is selected from alkyl(C_1-C_6), cycloalkyl(C_3-C_6) and alkynyl(C_2-C_6).

A further preferred embodiment relates to compounds of formula I, wherein R_3 is thiophene carbonyl, in particular
20 thiophene-2-carbonyl, R_1 is selected from alkyl(C_1-C_6); phenylalkenyl(C_2-C_6); ω,ω,ω -trifluoroalkyl(C_1-C_6); phenyl; phenyl substituted with 1 or 2 groups which are independently selected from halogen (in particular fluoro and chloro), cyano, Oalkyl(C_1-C_6) and nitro; phenylalkyl(C_1-C_6);
25 cycloalkyl(C_3-C_6); alkenyl(C_2-C_6); cycloalkyl(C_3-C_6)alkyl(C_1-C_6); isoxazolyl substituted with 1 or 2 alkyl(C_1-C_6); furyl substituted with 1 or 2 groups independently selected from alkyl(C_1-C_6) and w,w,w -trifluoroalkyl (C_1-C_6); thiazolyl substituted with 1 or 2 alkyl(C_1-C_6); pyridyl
30 which is substituted with a 4-morpholinyl group; thienyl; and pyrazolyl substituted with 1, 2 or 3 alkyl(C_1-C_6), and R_2 is selected from H, alkyl(C_1-C_6), cycloalkyl(C_3-C_6) and alkynyl(C_2-C_6).

2X10

5 A further preferred embodiment relates to compounds of formula I, wherein R_3 is selected from benzoyl, wherein the phenyl group may be substituted with halogen (in particular fluoro or chloro), alkyl(C_1-C_6) and Oalkyl(C_1-C_6); oxadiazolyl which is substituted with alkyl(C_1-C_6) and pyridylcarbonyl; R_1 is alkyl(C_1-C_6) and R_2 is H, alkyl(C_1-C_6) or alkynyl(C_2-C_6).

10 Preferably, the present invention relates to new N-[3-(3-substituted-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-sulfonamides of formula (I) wherein R_1 is selected from the group consisting of methyl, ethyl, n-propyl, i-propyl, n-butyl, 2-phenylethenyl, 2,2,2-trifluoroethyl, phenyl, 2-
15 clorophenyl, 3-clorophenyl, 4-clorophenyl, 2,4-diclorophenyl, 3,4-dichlorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-methoxyphenyl, 3-nitrophenyl, 4-nitrophenyl, 2-thienyl, 5-methyl-4-isoxazolyl, 5-methyl-2-trifluoromethyl-3-furyl, 4-(4-morpholinyl)-3-pyridyl,
20 2,4-dimethyl-5-thiazolyl, cyclopropyl, benzyl, vinyl, 3,5-dimethyl-4-isoxazolyl, 1,3,5-trimethyl-4-pyrazolyl and cyclopentylmethyl; R_2 is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, cyclopropyl and 2-propynyl, or R_1 and R_2 form in
25 conjunction with the $-N-SO_2-$ group an isothiazolidine-1,1-dioxide ring, in such a way that R_1 and R_2 form together a 1,3-propylene group, and R_3 is selected from a cyano group, a benzoyl group, a 4-fluorobenzoyl group, a 4-methylbenzoyl group, a 4-methoxybenzoyl group, a 5-methyl-1,2,4-oxadiazol-3-yl group, a pyridyl-2-carbonyl group, a
30 pyridyl-4-carbonyl group and a thiophene-2-carbonyl group.

"Heteroaryl" means 5- or 6-membered aromatic heterocyclic groups containing 1, 2 or 3 heteroatoms which are independently from each other selected from N, O and S. Examples for heteroaryl groups are pyridyl, pyrimidinyl, triazinyl, pyrrolyl, thienyl, furyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl.

"Aryl" means preferably phenyl or naphthyl.

"Halogen" or "halo" means F, Cl, Br or I, preferably F or Cl.

"Cycloalkyl(C₃-C₆)" preferably means cyclopropyl, cyclopentyl or cyclohexyl.

"Substituted" (including mono- and di- substituted) means that the group in question carries 1, 2 or 3 substituents which are independently from each other selected from alkyl(C₁-C₆), Oalkyl(C₁-C₆), halogen, CN and NO₂. In case of heteroaryl groups the substituent may also be attached to a hetero nitrogen atom.

Alkyl groups (also in -Oalkyl, -NHalkyl etc.) include straight chain and branched groups and preferably have 1 to 4 carbon atoms.

The term "pharmaceutically acceptable salt" used herein encompasses any salt formed from organic and inorganic acids, such as hydrobromic, hydrochloric, phosphoric, nitric, sulfuric, acetic, adipic, aspartic, benzenesulfonic, benzoic, citric, ethanesulfonic, formic, fumaric, glutamic, lactic, maleic, malic, malonic,

mandelic, methanesulfonic, 1,5-naphthalendisulfonic, oxalic, pivalic, propionic, p-toluenesulfonic, succinic, tartaric acids and the like.

5 The preferred compounds of the present invention are shown below:

N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-methanesulfonamide;

10 N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-methanesulfonamide;

N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-benzenesulfonamide;

N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-benzenesulfonamide;

15 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

20 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-benzenesulfonamide;

N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-benzenesulfonamide;

N-prop-2-ynyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

25 N-propyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

30 N-prop-2-ynyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

- N-butyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
7-(3-(2-isothiazolidinyl-1,1-dioxide)-phenyl)-3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidine;
- 5 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide;
N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide;
- 10 N-propyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide;
N-butyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide;
- N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-prop-2-ynyl-methanesulfonamide;
- 15 N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-propyl-ethanesulfonamide;
N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-ethanesulfonamide;
- N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-prop-2-ynyl-propane-2-sulfonamide;
- 20 N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-ethanesulfonamide;
N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-butyl-ethanesulfonamide;
- 25 7-(3-(2-isothiazolidinyl-1,1-dioxide)-phenyl)-3-cyano-pyrazolo[1,5-a]pyrimidine;
N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-2-propanesulfonamide;
- 30 N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-2-propanesulfonamide;
N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-butyl-2-propanesulfonamide;

- 12
- N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-propyl-2-propanesulfonamide;
- N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-prop-2-ynyl-ethanesulfonamide;
- 5 N-methyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
- N-ethyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
- 10 N-prop-2-ynyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
- N-methyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
- N-ethyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
- 15 N-prop-2-ynyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
- N-methyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
- N-ethyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
- 20 N-methyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
- N-ethyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
- 25 N-prop-2-ynyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
- N-prop-2-ynyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
- 30 N-methyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
- N-ethyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-ethyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

5 N-prop-2-ynyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-prop-2-ynyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

10 N-methyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-ethyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

15 N-ethyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-prop-2-ynyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

20 N-prop-2-ynyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-ethyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

25 N-methyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-ethyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

30 N-prop-2-ynyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-prop-2-ynyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

- N-methyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
- N-ethyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
- 5 N-methyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
- N-ethyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
- N-prop-2-ynyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
- 10 N-prop-2-ynyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
- N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-phenylethanesulfonamide;
- 15 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,2,2-trifluoroethane-sulfonamide;
- N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-chlorobenzenesulfonamide;
- N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-3-chlorobenzenesulfonamide;
- 20 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-4-chlorobenzenesulfonamide;
- N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,4-dichlorobenzene-sulfonamide;
- 25 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-3,4-dichlorobenzene-sulfonamide;
- N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-cyanobenzenesulfonamide;
- N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-3-cyanobenzenesulfonamide;
- 30 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-4-cyanobenzenesulfonamide;

- N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-3-nitrobenzenesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-4-nitrobenzenesulfonamide;
5 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-thiophenesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-5-methyl-4-isoxazolyl-sulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-trifluoromethyl-5-methyl-3-furylsulfonamide;
10 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-6-(morpholin-4-yl)-3-pyridylsulfonamide;
15 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,4-dimethyl-5-thiazolyl-sulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-cyclopropylsulfonamide;
20 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-benzylsulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-vinylsulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-3,5-dimethyl-4-isoxazolyl-sulfonamide;
25 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-1,3,5-trimethyl-4-pyrazolyl-sulfonamide;
30 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-propanesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-butanesulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-cyclopentylmethane-sulfonamide;
N-{3-[3-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide; and
5 N-ethyl-N-{3-[3-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide.

Another embodiment of the present invention is to provide a process for preparing the compounds of formula (I) and
10 their pharmaceutically acceptable salts.

Another embodiment of the present invention is to provide a method for treating or preventing diseases associated with GABA_A receptor modulation in a mammal which comprises
15 administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing diseases associated with α_1 -GABA_A receptor modulation in a mammal which comprises
20 administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing diseases associated with α_2 -GABA_A receptor modulation in a mammal which comprises
25 administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.
30

Another embodiment of the present invention is to provide a method for treating or preventing anxiety in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing epilepsy in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing sleep disorders in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for treating or preventing insomnia in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for inducing sedation-hypnosis in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

Another embodiment of the present invention is to provide a method for inducing anesthesia in a mammal which comprises administering to said mammal an effective amount of a

15

compound of formula (I) or a pharmaceutically acceptable salt thereof.

5 Another embodiment of the present invention is to provide a method for modulating the necessary time to induce sleep and its duration in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

10 Another embodiment of the present invention is to provide a method for inducing muscle relaxation in a mammal which comprises administering to said mammal an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

15 Another embodiment of the present invention is to provide a pharmaceutical composition containing a compound of formula (I) or a pharmaceutically acceptable salt thereof in association with therapeutically inert carriers.

20 The compositions include those suitable for oral, rectal and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route will depend on the nature and severity of the condition being treated. The most preferred route of the present invention is the oral route. The compositions may be conveniently presented in unit dosage form, and prepared by any of the methods well known in the art of pharmacy.

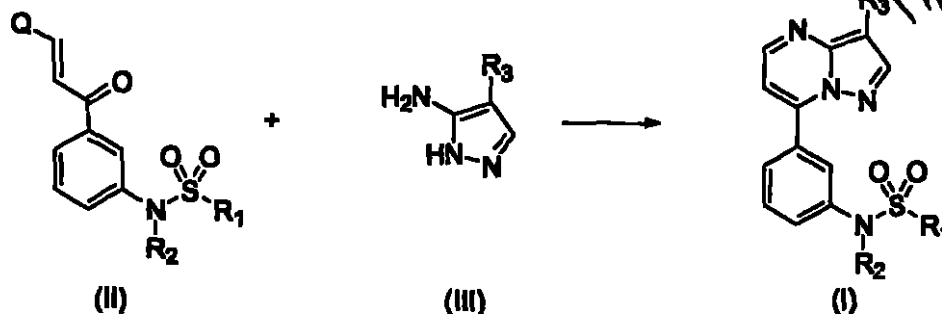
25 30 The active compound can be combined with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of

forms depending on the form of the preparation desired for administration, e.g. oral or parenteral (including intravenous injections or infusions). In preparing the compositions for oral dosage form any of the usual pharmaceutical media may be employed. Usual pharmaceutical media include, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents, and the like in the case of oral liquid preparations (such as for example, suspensions, solutions, emulsions and elixirs); aerosols; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like, in the case of oral solid preparations (such as for example, powders, capsules, and tablets) with the oral solid preparations being preferred over the oral liquid preparations.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

A suitable dosage range for use is from about 0.01 mg to about 100,00 mg total daily dose, given as a once daily administration or in divided doses if required.

The compounds of general formula (I) may be prepared according to the reaction shown in Scheme 1.

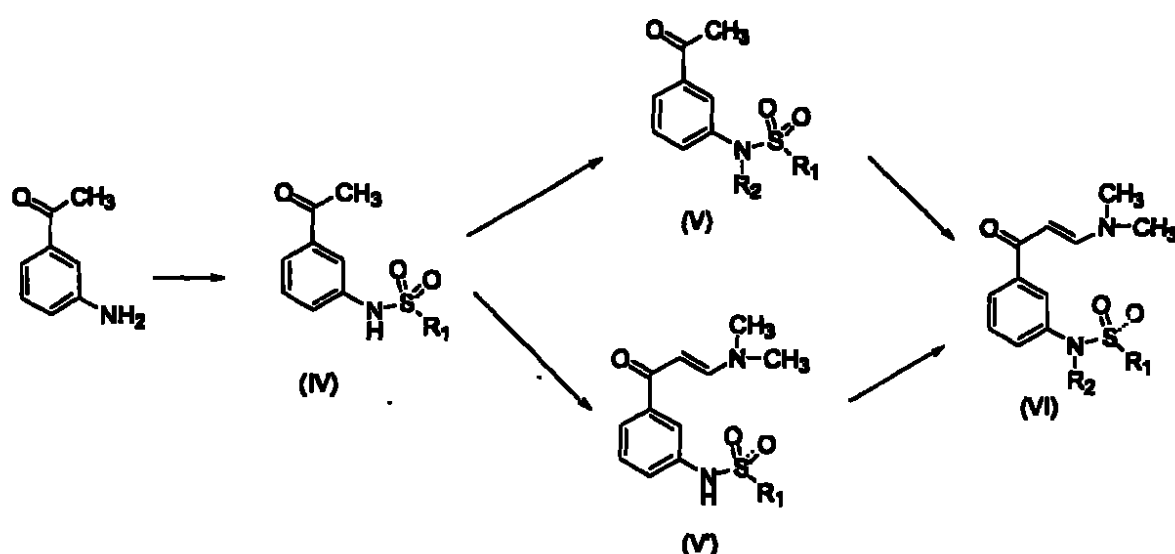


Scheme 1

5 R_1 , R_2 and R_3 are as described above and Q is an appropriate leaving group consisting of $N(\text{dialkyl}(C_1-C_6))$, alkylthio(C_1-C_6) and alkoxy(C_1-C_6). Preferably Q is selected from the group consisting of dimethylamino, methylthio or methoxy.

10 The reaction of aminopyrazole of general formula (III) with appropriately substituted 1-aryl-2-propen-1-one (II) is carried out in an inert polar protic or aprotic solvent such as glacial acetic acid, ethanol, methanol, dimethylformamide or dimethylsulfoxide at a temperature
 15 ranging from 50° to 130°C . After elapsing several hours (reaction time), the solvent is removed and the residue obtained is partitioned between an aqueous solution of sodium bicarbonate and dichloromethane. The crude resulting from evaporating the organic layer to dryness may be
 20 purified by one of the following methods: (a) silica gel chromatography using ethyl acetate or dichloromethane /methanol as eluent; or (b) crystallization in a suitable solvent (ethyl acetate, ethanol, methanol, etc.).

25 The intermediate of formula (II) when Q is dimethylamino [intermediate (VI)] can be obtained following the reaction sequence shown in Scheme 2



Scheme 2

5

wherein R_1 and R_2 are as described above.

10

The sulfonamides of formula (IV) are prepared according to the method described by R. H. Uloth et al (J. Med. Chem. 9, 88-96, 1966).

15

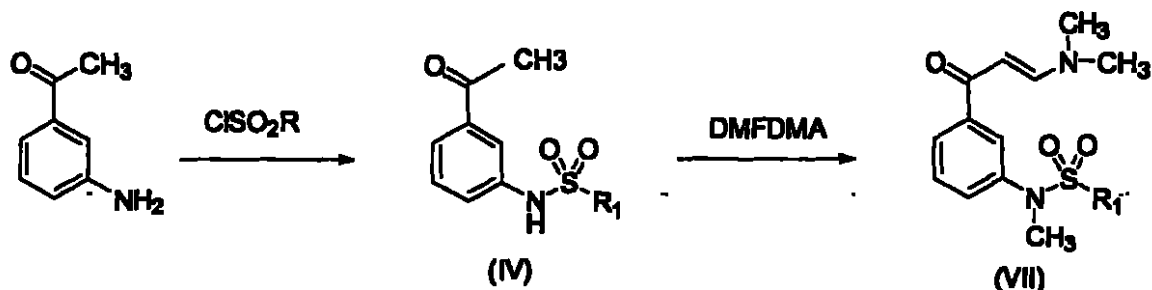
The alkylation of the sulfonamides (IV) leading to the intermediates of formula (V) is performed, in accordance with methods well known by experts in Organic Chemistry, via formation of an anion and subsequent reaction with an alkyl halide.

20

The enaminones of formula (VI) are prepared according to general synthetic procedures of enamines described by J. M. Domagala et al (J. Heterocyclic Chem., 26(4), 1147-58, 1989); and K. Sawada et al (Chem. Pharm. Bull., 49(7), 799-813, 2001) by reacting an acetophenone with N,N-dimethylformamide dimethylacetal (DMFDMA) or Brederick's reagent (tert-butoxybis(dimethylamino)methane).

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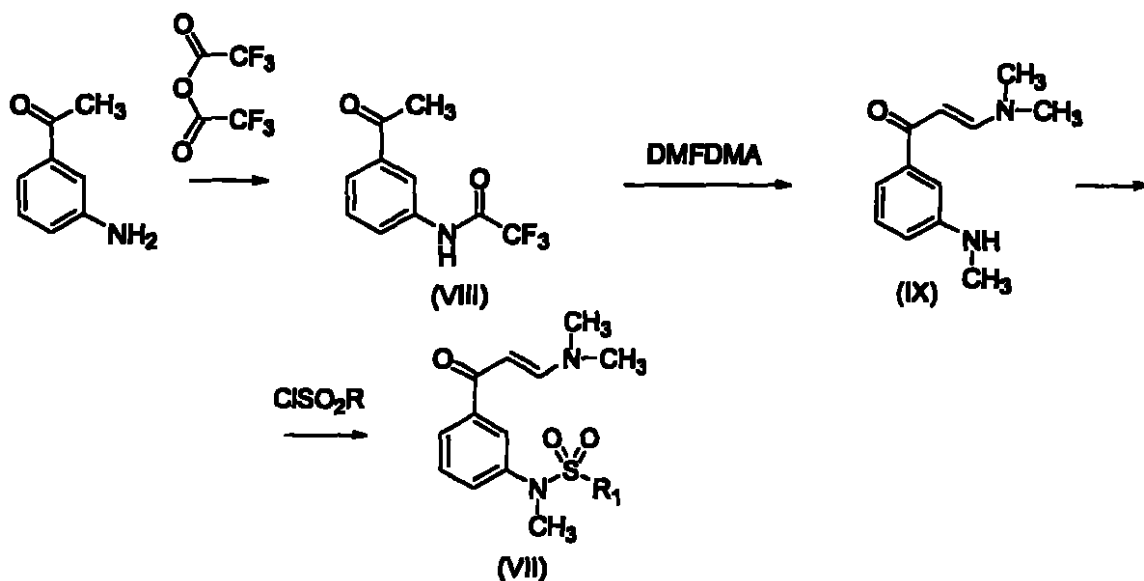
The intermediates of formula (II), when Q is dimethylamino and R₂ is methyl (VII), can alternatively be prepared according to Scheme 3.



Scheme 3

The conversion of (IV) into (VII) leads to the formation of the enaminone and, simultaneously, the formation of the N-methyl-sulfonamide as a result of the use of the properties of the N,N-dimethylformamide dimethyl acetal as a methylating agent.

Intermediate (VII) can also be prepared according to Scheme 4.



Scheme 4

The advantage of this process is based on the fact that the formation of the sulfonamide takes place in the last state of process. As a result, the total number of reaction steps is reduced in the preparation of large series of products. Moreover, as shown in the scheme, the conversion of (VIII) into (IX) leads to three following reactions in a one-pot process: (a) formation of the anaminone; (b) methylation of the trifluoroacetamide; and (c) deacylation yielding the N-methylated amine. The subsequent reaction of (IX) with the corresponding sulfonic acid chloride leads to obtaining intermediates (VII).

The preparation of intermediates (VII) by reaction between intermediates (IV) and N,N-dimethylformamide dimethyl acetal has not ever disclosed in the chemical literature and is another embodiment of the present invention.

Similarly, the preparation of intermediates (VII) by reaction between N-(3-acetylphenyl)-2,2,2-trifluoroacetamide (VIII) and N,N-dimethylformamide dimethyl acetal, followed by the formation of the sulfonamide by reaction with the corresponding sulfonic acid chloride have not disclosed either in the chemical literature and is another embodiment of the present invention.

From the compounds of general formula (I) it is possible to obtain their pharmaceutically acceptable salts by treatment with the corresponding acids.

The applicants have discovered that the compounds of the present invention have a high affinity for α_1 - and α_2 -GABA_A receptors as shown in Tables 1 and 2. These in vitro

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results are consistent with those *in vivo* results obtained in sedation-hypnosis tests (Table 3).

5 In accordance with the results obtained, certain compounds of the present invention have surprisingly evidenced pharmacological activity both *in vitro* and *in vivo*, which has been similar to or higher than that of prior-art compounds. All these results support their use in diseases
10 or conditions modulated by α_1 - and α_2 -GABA_A receptors, such as insomnia or anesthesia, in which an induction of sleep, an induction of sedation or an induction of muscle relaxation are needed.

15 The pharmacological activity of the compounds of the present invention has been determined as shown below.

Ligand-binding assays. Determination of the affinity of test compounds for α_1 - and α_2 -GABA_A receptor.

20 Male Sprague-Dawley rats weighing 200-250 g at the time of experiment were used. After decapitation of the animal, the cerebellum (tissue that mostly contains α_1 -GABA_A receptor) and spinal cord (tissue that mostly contains α_2 -GABA_A receptor) were removed. The membranes were prepared
25 according to the method by J. Lameh et al. (Prog. Neuro-Psychopharmacol. Biol. Psychiatry, 24, 979-991, 2000). Once the tissues weighed, they were suspended in 50 mM Tris·HCl (pH 7.7), 1:40 (v/v), homogenized and then centrifuged at 20000 g for 10 min at 7°C. The resulting pellet was
30 resuspended under the same conditions and centrifuged again. The pellet was finally resuspended on a minimum volume and kept at -80°C overnight. On the next day, the

process was repeated until the final pellet was resuspended at a ratio of 1:10 (v/v).

Affinity was determined by competitive tests using

radiolabeled flumazenil as ligand. The tests were performed

5 according to the methods described by S. Arbilla et al.

(Eur. J. Pharmacol., 130, 257-263, 1986); and Y. Wu et al.

(Eur. J. Pharmacol., 278, 125-132, 1995). The membranes

containing the study receptors, flumazenil (radiolabeling

at a final concentration of 1 nM) and ascending

10 concentrations of test compounds (in a total volume of 500

µl in 50 mM [pH 7.4] Tris·HCl buffer) were incubated.

Simultaneously, the membranes were only incubated with the

radiolabeled flumazenil (total binding, 100%) and in the

presence of an elevated concentration of unradiolabeled

15 flumazenil (non-specific binding, % estimation of

radiolabeled ligand). The reactions started on adding the

radiolabeled ligand followed by incubation for 60 minutes

at 0°C. At the end of the incubation period, the tubes were

filtered using a Brandel Mod. M-48R harvester and then

20 washed three times with cold test buffer. The harvester was

fitted with a GF/B filter that retained the membranes

containing the receptors and the radiolabeled ligand which

had been bound to the receptors. Then the filters were

removed and left till dry. Once dried, the filters were

25 cut, placed in vials with scintillation liquid and left

under stirring overnight. The next day the filters were

counted using a Packard Mod. Tricarb scintillation counter.

For analysis of the results the percentage of specific

binding for every concentration of test compound was

30 calculated as follows:

$$\% \text{ specific binding} = (X-N/T-N) \times 100$$

19

where,

X: amount of bound ligand for every concentration of compound.

5 T: total binding, maximum amount bound to the radiolabeled ligand.

N: non-specific binding, amount of radiolabeled ligand bound in a non-specific way irrespective of the receptor used.

10 Every concentrations of compound were tested in duplicate and their mean values were used to determine the experimental values of % specific binding versus the concentration of compound. The values thus attained were fitted to a equation for competitive assays (SigmaPlot, SPSS Inc.) and the IC₅₀ values (concentration of compound
15 able to inhibit by 50% the specific binding). Inhibition constants (K_i) were calculated from the IC₅₀ values according to Cheng-Prusoff's formula (Y. Cheng y W. H. Prusoff, Biochem. Pharmacol., 22(23), 3099-3108, 1973). The
20 affinity data for subunit α_2 are alternatively expressed as % inhibition at the concentrations of 10⁻⁵ M and 10⁻⁷ M. The results of these tests are given in Tables 1 and 2.

Table 1. Affinity for α_1 -GABA_A receptor

Compound	Ki (nM)
Example 2	74.5
Example 3	7.4
Example 5	13.4
Example 6	3.0
Example 16	0.7
Example 17	28.0
Example 18	5.9
Example 19	0.5
Example 20	12.5
Example 22	20.9
Example 23	26.7

Example 24	30.7
Example 25	26.6
Example 27	28.2
Example 29	53.2
Example 30	52.1
Example 33	608.7
Example 34	33.2
Example 35	88.9
Example 37	577.8
Example 38	119.4
Example 39	37.2
Example 40	7.3
Example 46	41.0
Example 51	38.7
Example 52	48.1
Example 53	33.2
Example 58	47.9
Example 63	62.1
Example 64	32.9
Example 68	8.9
Example 69	16.6
Example 70	6.2
Example 72	14.6
Example 76	201.2
Example 77	35.6
Example 78	2031.0
Example 79	499.0
Example 82	63.6
Example 83	42.0
Example 84	28.9
Example 87	1.9
Example 91	2.8
Example 92	0.4
Example 94	0.5
Zaleplon	198.9

Table 2. Affinity for α_2 -GABA_A receptor

Compound	K _i (nM)
Example 2	831.3
Example 3	36.7
Example 5	290.2

X 20

Example 6	34.9	
Zaleplon	1302.5	
Compound	% Inhibition (10^{-5} M)	% Inhibition (10^{-7} M)
Example 16	100.2	87.2
Example 17	74.5	0
Example 18	93.7	20.7
Example 19	94.4	45.2
Example 20	97.7	40.3
Example 22	98.2	24.2
Example 23	93.8	45.5
Example 24	83.0	10.4
Example 25	78.9	9.1
Example 27	85.2	2.9
Example 29	92.7	13.4
Example 30	73.3	0
Example 33	45.2	0
Example 34	87.6	6.9
Example 35	86.5	24.5
Example 37	40.2	0
Example 38	77.6	17.4
Example 39	96.6	23.3
Example 40	99.5	47.3
Example 46	97.6	11.9
Example 51	94.7	16.8
Example 52	61.2	0
Example 53	89.8	1.0
Example 58	93.8	24.0
Example 63	91.3	0
Example 64	61.5	20.9
Example 68	92.7	31.6
Example 69	99.0	36.7
Example 70	99.9	63.4

Example 72	98.6	44.9
Example 76	41.7	0
Example 77	88.5	13.8
Example 78	36.2	0
Example 79	52.9	0
Example 82	31.8	0
Example 83	94.4	39.1
Example 84	89.5	0
Example 87	97.6	65.1
Example 91	84.1	4.8
Example 92	95.7	36.5
Example 94	99.5	41.2
Zaleplon	78.4	--

In vivo determination of predictive sedative-hypnotic action.

5 The *in vivo* effects of these compounds were assessed by a predictive sedation-hypnosis test in mice (D. J. Sanger et al., Eur. J. Pharmacol., 313, 35-42, 1996; and G. Griebel et al., Psychopharmacology, 146, 205-213, 1999).

10 Groups of 5-8 male CD1 mice, weighing 22-26 g at the time of test, were used. The test compounds were administered in single equimolecular intraperitoneal doses, suspended in 0.25% agar with one drop of Tween in a volume of 10 ml/kg. Control animals received the vehicle alone. Using an Actisystem DAS16 (Panlab, S.L., Spain) the crossings
15 (number of counts) were recorded for each mouse at 5-min intervals during a period of 30 minutes after dosing. The inhibition percentage of crossings of treated animals versus control animals (the first 5 min were discarded) was calculated. The results of this test are given in Table 3.

Table 3. Determination of sedation-hypnosis in mice

Compound	% Motor Activity Inhibition
Example 2	71.39
Example 3	93.58
Example 5	80.91
Example 6	66.55
Example 16	95.36
Example 17	94.21
Example 18	93.39
Example 19	89.88
Example 20	95.23
Example 22	91.39
Example 23	94.57
Example 24	94.01
Example 25	92.79
Example 27	93.12
Example 29	93.73
Example 30	94.86
Example 33	77.58
Example 34	92.58
Example 35	92.55
Example 37	92.13
Example 38	94.85
Example 39	95.28
Example 40	94.32
Example 46	93.98
Example 51	90.04
Example 52	92.83
Example 53	94.89
Example 58	93.31
Example 63	95.32

Example 64	90.32
Example 68	87.78
Example 69	96.90
Example 70	94.54
Example 72	93.78
Example 76	78.36
Example 77	70.12
Example 78	36.12
Example 79	51.50
Example 82	39.87
Example 83	53.38
Example 84	68.98
Example 87	74.88
Example 91	72.85
Example 92	74.36
Example 94	88.69
Zaleplon	47.17

The following non-limiting examples illustrate the scope of the present invention.

5 **Example 1:** N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-methanesulfonamide

1.58 g (6.96 mmol) of N-(3-acetyl-phenyl)-N-methyl-methanesulfonamide were dissolved in 15 ml of N,N-dimethylformamide dimethylacetal and the resultant solution
10 was refluxed for 18 hours. The excess of volatile reagent was removed by reduced pressure distillation to yield a crude which was chromatographed over silica gel using a gradient of ethyl acetate/methanol as eluent. 1.12 g of N-
15 [3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl

methanesulfonamide as a yellowish-white solid were obtained (yield 88.6%).

¹H NMR(400 MHz, DMSO-d₆): δ 2.91 (3H, s), 2.94 (3H, s), 3.14 (3H, s), 3.26 (3H, s), 5.79 (1H, d, J= 12.4 Hz), 7.44 (1H, t, J= 7.6 Hz), 7.49-7.52 1H, m), 7.71 (1H, d, J= 12.4 Hz), 7.78-7.81 (2H, m).

MS (ES) m/z = 283 (MH⁺)

HPLC = 99.2%

Example 2: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-methanesulfonamide

A mixture of 0.1 g (0.93 mmol) of 4-cyano-2H-pyrazol-3-ylamine and 0.26 g (0.93 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-methanesulfonamide in 10 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 217 mg of N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-methanesulfonamide as a yellow solid (yield 71%; m.p.= 193-195 °C).

¹H NMR(400 MHz, DMSO-d₆): δ 3.01 (3H, s), 3.30 (3H, s), 7.60 (1H, d, J= 4.8 Hz), 7.65-7.67 (2H, m), 8.00-8.02 (1H, m), 8.09 (1H, s), 8.85 (1H, s), 8.91 (1H, d, J= 4.8 Hz).

MS (ES) m/z = 328 (MH⁺)

HPLC = 95.9%

Example 3: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

A mixture of 0.1 g (0.52 mmol) of (5-amino-1H-pyrazol-4-yl)-thiophene-2-yl-methanone and 0.146 g (0.93 mmol) of N-{3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl}-N-methyl-methanesulfonamide (obtained as described in Example 2) in 10 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 178 mg N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide as a yellow solid (yield 83%; m.p. = 169-170°C).

¹H NMR(400 MHz, DMSO-d₆): δ 3.02 (3H, s), 3.32 (3H, s), 7.29 (1H, t, J= 6 Hz), 7.54 (1H, d, J= 4.4 Hz), 7.62-7.67 (2H, m), 8.02-8.04 (2H, m), 8.11 (1H, s), 8.20 (1H, d, J= 6 Hz), 8.80 (1H, s), 8.89 (1H, d, J= 4.4 Hz).

MS (ES) m/z = 413 (MH⁺)

HPLC = 99.2%

Example 4: N-[3-[3-(dimethylamino)-1-oxo-2-propenyl] phenyl]-N-ethyl-methanesulfonamide

1.1 g (4.56 mmol) of N-(3-acetyl-phenyl)-N-ethyl-methanesulfonamide were dissolved in 10 ml of N,N-dimethylformamide dimethylacetal and the resultant solution was refluxed for 18 hours. The excess of volatile reagent was removed by reduced pressure distillation to yield a crude which was chromatographed over silica gel using a gradient of ethyl acetate/methanol as eluent. 1.2 g of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-methanesulfonamide as a yellowish-white solid were obtained (yield 88.6%)

¹H NMR(400 MHz, CDCl₃): δ 1.23 (3H, t, J= 7.2 Hz), 2.88 (3H, s), 2.94 (3H, s), 3.16 (3H, s), 3.76 (2H, q, J= 7.2 Hz), 5.66 (1H, d, J= 12 Hz), 7.41-7.44 (2H, m), 7.79 (1H, d, J= 12 Hz), 7.80-7.84 (2H, m).

HPLC = 95.6%

Example 5: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-methanesulfonamide

A mixture of 0.196 g (1.82 mmol) of 4-cyano-2H-pyrazol-3-ylamine and 0.54 g (1.82 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-methanesulfonamide in 10 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 324 mg of N-[3-(3-cyano-pyrazolo[1,5-

alpyrimidin-7-yl)-phenyl]-N-ethyl-methanesulfonamide as a yellow solid (yield 52.4%).

¹H NMR(400 MHz, CDCl₃): δ 1.21 (3H, t, J= 7.2 Hz), 2.95 (3H, s), 3.81 (2H, q, J= 6.8 Hz), 7.21 (1H, d, J= 4.4 Hz), 7.58-7.60 (1H, m), 7.64 (1H, t, J= 7.6 Hz), 7.98 (1H, d, J= 7.2 Hz), 8.06 (1H, s), 8.41 (1H, s), 8.78 (1H, d, J= 4 Hz).

MS (ES) m/z = 342 (MH⁺)

HPLC = 98.9%

Example 6: N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

A mixture of 0.36 g (1.86 mmol) of 5-amino-1H-pyrazol-4-yl)-thiophene-2-yl-methanone and 0.55 g (1.86 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-methane

sulfonamide in 10 ml of glacial acetic acid was refluxed for 8 hours. Thereafter, the reaction mixture was cooled and the precipitate formed, which was filtered, was washed first with acetic acid, then with saturated sodium bicarbonate solution and finally with water. 472 mg of N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methane-sulfonamide were obtained as a yellow solid (yield 59.6%).

¹H NMR(400 MHz, CDCl₃): δ 1.23 (3H, t, J= 7.6 Hz), 2.97 (3H, s), 3.82 (2H, q, J= 6.8 Hz), 7.17 (1H, d, J= 4.4 Hz), 7.18-7.20 (1H, m), 7.57-7.60 (2H, m), 7.62 (1H, t, J= 7.2 Hz), 7.69 1H, dd, J= 4.8 y 1.2 Hz), 7.99-8.02 (1H, m), 8.07-8.1 (3H, m), 8.69 (1H, s), 8.80 (1H, d, J= 4.4 Hz).

MS (ES) m/z = 427 (MH⁺).

24

HPLC = 98.3%

Example 7: N-[3-[3-(dimethylamino)-1-oxo-2-propenyl] phenyl]-N-methyl-benzenesulfonamide

5

1.25 g (4.32 mmol) of N-(3-acetyl-phenyl)-N-methyl-benzenesulfonamide were dissolved in 10 ml of N,N-dimethylformamide dimethylacetal and the resultant solution was refluxed for 18 hours. The excess of volatile reagent was removed by reduced pressure distillation to yield a crude which was chromatographed over silica gel using a gradient of ethyl acetate/methanol as eluent. 1.25 g of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-benzenesulfonamide as a yellowish-white solid were obtained (yield 84%).

10

15

^1H NMR (400 MHz, CDCl_3): δ 2.92 (3H, s), 3.15 (3H, s), 3.19 (3H, s), 5.58 (1H, d, $J = 12$ Hz), 7.21-7.23 (1H, m), 7.33 (1H, t, $J = 8$ Hz), 7.41-7.46 (2H, m), 7.52-7.58 (4H, m), 7.76 (1H, d, $J = 12$ Hz), 7.77-7.80 (1H, m).

20

HPLC = 100%

Example 8: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-benzenesulfonamide

25

A mixture of 0.134 g (1.24 mmol) of 4-cyano-2H-pyrazol-3-ylamine and 0.43 g (1.24 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-benzenesulfonamide in 10 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous

30

layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 205 mg of N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-benzenesulfonamide as a yellow solid (yield 42%).

^1H NMR(400 MHz, CDCl_3): δ 3.23 (3H, s,) 7.13 (1H, d, $J=$ 4.8 Hz), 7.25-7.30 (1H, m), 7.45-7.63 (6H, m), 7.83 (1H, s), 7.93-7.97 (1H, m), 8.37 (1H, s), 8.75 (1H, d, $J=$ 4.4 Hz).

MS (ES) m/z = 390 (MH $^+$)

HPLC = 99.0%

Example 9: N-methyl-N-(3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl)-benzenesulfonamide

A mixture of 0.43 g (2.23 mmol) of (5-amino-1H-pyrazol-4-yl)-thiophene-2-yl-methanone and 0.8 g (2.23 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-methane-sulfonamide in 10 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 872 g of N-methyl-N-(3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]

pyrimidin-7-yl]-phenyl]-benzenesulfonamide as a yellow solid (yield 82.3%).

¹H NMR(400 MHz, CDCl₃): δ 3.24 (3H, s), 7.07 (1H, d, J= 4.4 Hz), 7.19 (1H, t, J= 4 Hz), 7.28-7.31 (1H, m), 7.46-7.62 (6H, m), 7.7 (1H, d, J= 5.2 Hz), 7.82 (1H, t, J= 2 Hz), 7.97 (1H, d, J= 6.8 Hz), 8.09 (1H, d, J= 3.6 Hz), 8.66 (1H, s), 8.79 (1H, d, J= 4.4 Hz).

MS (ES) m/z = 475 (MH⁺)

HPLC = 97.9%

Example 10: N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-benzenesulfonamide

1.05 g (3.46 mmol) of N-(3-acetyl-phenyl)-N-ethyl-benzenesulfonamide were dissolved in 10 ml of N,N-dimethylformamide dimethylacetal and the resultant solution was refluxed for 18 hours. The excess of volatile reagent was removed by reduced pressure distillation to yield a crude which was chromatographed over silica gel using a gradient of ethyl acetate/methanol as eluent. 1.2 g of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-benzenesulfonamide as a yellowish-white solid were obtained (yield 96%).

¹H NMR(400 MHz, CDCl₃): δ 1.06 (3H, t, J= 7.2 Hz), 2.92 (3H, s), 3.15 (3H, s), 3.62 (2H, q, J= 7.6 Hz), 5.56 (1H, d, J= 12.4 Hz), 7.14-7.17 (1H, m), 7.35 (1H, t, J= 7.6 Hz), 7.42-7.49 (3H, m), 7.52-7.60 (3H, m), 7.76 (1H, d, J=12.4 Hz), 7.81 (1H, d, J= 8 Hz).

HPLC = 100%

Example 11: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-benzenesulfonamide

A mixture of 0.15 g (1.38 mmol) of 4-cyano-2H-pyrazol-3-ylamine and 0.50 g (1.38 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-benzenesulfonamide in 10 ml of glacial acetic acid was refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 260 mg of N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-benzenesulfonamide as a yellow solid (yield 47%).

¹H NMR(400 MHz, CDCl₃): δ 1.14 (3H, t, J= 6.8 Hz), 3.66 (2H, q, J= 7.2 Hz), 7.12 (1H, d, J= 4.8 Hz), 7.26 (1H, d, J= 7.6 Hz), 7.46-7.65 (6H, m), 7.76 (1H, s), 8.02 (1H, d, J= 7.6 Hz), 8.38 (1H, s), 8.76 (1H, d, J= 4.4 Hz).

MS (ES) m/z = 404 (MH⁺)

HPLC = 98.9%

Example 12: N-ethyl-N-(3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl)-benzenesulfonamide

A mixture of 0.33 g (1.70 mmol) of (5-amino-1H-pyrazol-4-yl)-thiophene-2-yl-methanone and 0.61 g (1.70 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-benzenesulfonamide in 10 ml of glacial acetic acid was

refluxed for 8 hours and then the solvent was removed by reduced pressure distillation. To the resulting residue were added 10 ml of dichloromethane and 10 ml of saturated sodium bicarbonate solution. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporated to dryness to yield an oil which, in the presence of ethyl acetate, gave 535 mg of N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-benzenesulfonamide as a yellow solid (yield 64.4%).

¹H NMR(400 MHz, CDCl₃): δ 1.15 (3H, t, J= 7.6 Hz), 3.67 (2H, q, J= 7.6 Hz), 7.07 (1H, d, J= 4.4 Hz), 7.18-7.21 (1H, m), 7.27-7.30 (1H, m), 7.51 (2H, t, J= 7.6 Hz), 7.56 (1H, t, J= 7.6 Hz), 7.60-7.67 (4H, m), 7.69 (1H, dd, J= 5.2 Hz y J= 1.2 Hz), 7.75 (1H, t, J= 2 Hz), 8.06 (1H, d, J= 7.6 Hz), 8.09 (1H, d, J= 3.6 Hz), 8.67 (1H, s), 8.79 (1H, d, J= 4.4 Hz).

MS (ES) m/z = 489 (MH⁺)

HPLC = 97.9%

Example 13: General procedure for the preparation of N-methyl-enamine-sulfonamides of general formula (VI) following Scheme 2

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-ethanesulfonamide

2 g (8.8 mmol) of N-(3-acetyl-phenyl)-ethanesulfonamide were dissolved in 15 ml of N,N-dimethylformamide dimethyl acetal

and heated at 150°C for 12 h. The solvent was removed by reduced pressure distillation to yield a crude which was chromatographed (silica gel) using ethyl acetate/methanol as eluent. 1.4 g (yield= 56%) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-ethanesulfonamide were obtained.

0.25 g (0.89 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-ethanesulfonamide were dissolved in 6 ml of dry N,N-dimethylformamide. To the solution formed at 0°C and under inert atmosphere, 0.043 g (1.08 mmol) of sodium hydride were added. After stirring for 30 minutes, 0.15 g (0.98 mmol) of ethyl iodide were added and stirring was maintained at room temperature for 5 h. To the reaction mixture 1 ml of water and then 20 ml of 0.5M NaOH were added. The product was separated by extraction with 3x25 ml of dichloromethane, and the organic layers were washed with 25 ml of water, dried over anhydrous sodium sulfate, filtered off and evaporated to dryness by reduced pressure distillation. 0.25 g (yield= 90%) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-ethanesulfonamide were obtained as an oil.

¹H NMR (400 MHz, CDCl₃): δ 1.12 (3H, t, J= 6.8 Hz), 1.37 (3H, t, J= 7.6 Hz), 2.94 (3H, s), 3.01 (2H, q, J= 7.6 Hz), 3.15 (3H, s), 4.79 (2H, q, J= 8.2 Hz), 5.66 (1H, d, J= 12.4 Hz), 7.39-7.46 (2H, m), 7.77-7.84 (3H, m)
HPLC = 99%

As described in the above general procedure, the following compounds were prepared:

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-ethyl-isopropanesulfonamide

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¹H NMR (400 MHz, CDCl₃): δ 1.12 (3H, t, J= 7.2 Hz), 1.37 (6H, d, J= 6.8 Hz), 2.95 (3H, s), 3.18 (3H, s), 3.18-3.25 (1H, m), 3.82 (2H, q, J= 7.6 Hz), 5.67 (1H, d, J= 12.4 Hz), 7.39-7.49 (2H, m), 7.78-7.81 (2H, m), 7.85-7.87 (1H, m)

5 HPLC = 99.4%

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-propyl-methanesulfonamide

10 ¹H NMR (400 MHz, DMSO-d₆): δ 0.83 (3H, t, J= 7.6 Hz), 1.31-1.36 (2H, m), 2.49 (3H, s), 2.91 (3H, s), 3.14 (3H, s), 3.61 (2H, t, J= 7.2 Hz), 7.78 (1H, d, J= 12 Hz), 7.42-7.51 (2H, m), 7.71 (1H, d, J= 12.4 Hz), 7.77-7.78 (1H, m), 7.82-7.85 (1H, m)

15 HPLC = 88.8%

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-propyl-ethanesulfonamide

20 ¹H NMR (400 MHz, CDCl₃): δ 0.89 (3H, t, J= 7.6 Hz), 1.37 (3H, t, J= 7.6 Hz), 1.42-1.51 (2H, m), 2.71 (1H, s), 2.94 (3H, s), 3.02 (2H, q, J= 7.6 Hz), 3.16 (3H, s, J= 12.4 Hz), 3.69 (2H, t, J= 7.2 Hz), 7.39-7.47 (2H, m), 7.78-7.85 (3H, m)

25 HPLC = 98%

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-propyl-isopropanesulfonamide

30 ¹H NMR (400 MHz, CDCl₃): δ 0.88 (3H, t, J= 7.2 Hz), 1.37 (6H, d, J= 6.8 Hz), 1.45-1.51 (2H, m), 2.94 (3H, s), 3.17 (3H, s), 3.17-3.24 (1H, m), 3.73 (2H, t, J= 7.6 Hz), 5.67

(1H, d, J= 12.8 Hz), 7.41 (1H, t, J= 8 Hz), 7.48-7.51 (1H, m), 7.77-7.87 (3H, m)

HPLC = 99.6%

- 5 N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-butyl-methanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 0.81 (3H, t, J= 7.6 Hz), 1.25-1.31 (4H, m), 2.92 (3H, s), 3.14 (3H, s), 3.64 (2H, t, J= 6.8 Hz), 5.78 (1H, d, J= 12 Hz), 7.44-7.50 (2H, m), 7.71 (1H, d, J= 12 Hz), 7.76-7.77 (1H, m), 7.82-7.85 (1H, m)

HPLC = 98%

- 15 N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-butyl-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 0.86 (3H, t, J= 7.6 Hz), 1.3-1.46 (7H, m), 2.94 (3H, s), 3.01 (2H, q, J= 7.2 Hz), 3.17 (3H, s), 3.73 (2H, t, J= 7.6 Hz), 5.63 (1H, d), 7.39-7.47 (2H, m), 7.78-7.85 (3H, m)

HPLC = 98.1%

- 25 N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-butyl-isopropanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 0.86 (3H, t, J= 7.6 Hz), 1.28-1.34 (2H, m), 1.36 (6H, d, J= 7.2 Hz), 1.41-1.45 (2H, m), 2.94 (3H, s), 3.16-3.24 (4H, m), 3.76 (2H, t, J= 7.2 Hz), 5.67 (1H, d, J= 12.4 Hz), 7.41 (1H, t, J= 8 Hz), 7.47-7.51 (1H, m), 7.78-7.82 (2H, m), 7.86-7.88 (1H, m)

HPLC = 99.4%

24

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-propargyl-methanesulfonamide

5 ^1H NMR (400 MHz, CDCl_3): δ 2.5 (1H, t, $J = 2.8$ Hz), 2.94 (3H, s), 3.05 (3H, s), 3.17 (3H, s), 4.46 (2H, s), 5.67 (1H, d, $J = 12.4$ Hz), 7.44 (1H, t, $J = 8$ Hz), 7.63-7.66 (1H, m), 7.81 (1H, m, $J = 12$ Hz), 7.84-7.87 (1H, m), 8.09 (1H, t, $J = 2$ Hz)

HPLC = 98.8%

10

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-propargyl-ethanesulfonamide

15 ^1H NMR (400 MHz, CDCl_3): δ 1.39 (3H, t, $J = 7.2$ Hz), 2.4 (1H, t, $J = 2.8$ Hz), 2.94 (3H, s), 3.14-3.22 (5H, m), 4.47 (2H, d, $J = 2.4$ Hz), 5.66 (1H, d, $J = 12.4$ Hz), 7.42-7.44 (2H, m), 7.61-7.64 (1H, m), 7.78-7.85 (3H, m), 8.05 (1H, t, $J = 2$ Hz)

MS (ES) $m/z = 321$ (MH $^+$)

20

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-propargyl-isopropanesulfonamide

25 ^1H NMR (400 MHz, CDCl_3): δ 1.4 (6H, d, $J = 6.4$ Hz), 2.37 (1H, t, $J = 2.4$ Hz), 2.94 (3H, s), 3.17 (3H, s), 3.34-3.41 (1H, m), 4.49 (2H, d, $J = 2.8$ Hz), 5.66 (1H, d, $J = 12.4$ Hz), 7.40-7.44 (1H, m), 7.59-7.62 (1H, m), 7.78-7.87 (2H, m), 7.99-8.00 (1H, m)

HPLC = 81%

30

Example 14: General procedure for the preparation of N-methyl-enamine-sulfonamides of general formula (VII) following Scheme 3

5 N-(3-acetylphenyl)-1-propane-sulfonamide

1 g (7.4 mmol) of 3-aminoacetophenone were dissolved in 35 ml of dry dichloromethane. To the resultant solution cooled at 0°C 0.89 ml (11.09 mmol) of anhydrous pyridine and 1.26 g (8.87 mmol) of 1-propanesulfonic acid chloride were added. After stirring the reaction mixture for 20 h at room temperature and under inert atmosphere, 15 ml of water were added. The two layers were separated, and the aqueous layer was washed with 2x15 ml of dichloromethane. The organic layers were washed with 30 ml of water and dried over anhydrous sodium sulfate. The dichloromethane layer was evaporated to dryness to yield a yellow solid, 1.8 g (yield= 100%) of N-(3-acetylphenyl)-1-propane-sulfonamide which was directly used for the following reaction.

20

N-[3-{3-(dimethylamino)-1-oxo-2-propenyl}phenyl]-N-methyl-1-propanesulfonamide

1 g (4.14 mmol) of N-(3-acetylphenyl)-1-propane-sulfonamide were dissolved in 10 ml of N,N-dimethylformamide. To the resultant solution 2.77 ml (20.74 mmol) of N,N-dimethylformamide dimethyl acetal were added and heated at 150°C for 2 h. The solvent was removed by reduced pressure distillation to yield an oil, which was treated with a mixture of ethyl acetate-ethyl ether. A small quantity of a solid precipitated which was discarded. The filtrate was evaporated to dryness, dissolved in dichloromethane, and the organic layer was washed with 4x50 ml of water and

25

30

evaporated to dryness. 1.23 g (yield = 96%) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-1-propane-sulfonamide were obtained.

5 ¹H NMR (400 MHz, CDCl₃): δ 0.99 (3H, t, J= 7.6 Hz), 1.75-1.90 (2H, m), 2.91-2.97 (5H, m), 3.15 (3H, a), 3.35 (3H, s), 5.66 (1H, d, J= 12.5 Hz), 7.36-7.52 (2H, m), 7.73-7.88 (3H, m)

10 As described in the above general procedure, the following compounds were prepared:

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-butanesulfonamide

15 ¹H NMR (400 MHz, CDCl₃): δ 0.92 (3H, t, J= 7.4 Hz), 1.35-1.5 (2H, m), 1.75-1.87 (2H, m), 2.97-3.03 (5H, m), 3.18 (3H, a), 3.39 (3H, s), 5.7 (1H, d, J= 12.2 Hz), 7.39-7.46 (1H, m), 7.52-7.56 (1H, m), 7.77-7.87 (1H, m), 7.83 (1H, d, J = 12.2 Hz), 7.9-7.91 (1H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-cyclopentylmethanesulfonamide

25 ¹H NMR (400 MHz, CDCl₃): δ 1.22-1.3 (2H, m), 1.55-1.63 (4H, m), 1.91-1.98 (2H, m), 2.27-2.4 (1H, m), 2.86-2.93 (5H, m), 3.15 (3H, a), 3.34 (3H, s), 5.67 (1H, d, J= 12.5 Hz), 7.37-7.52 (2H, m), 7.44-7.98 (3H, m)

30 **Example 15:** General procedure for the preparation of N-methyl-enamine-sulfonamides of general formula (VII) following Scheme 4

N-(3-acetylphenyl)-2,2,2-trifluoroacetamide

5 g (37 mmol) of 3-aminoacetophenone were dissolved in 30 ml of anhydrous dichloromethane. To the resultant solution 3.15 ml (38.84 mmol) of anhydrous pyridine and 5.5 ml (38.84 mmol) of trifluoroacetic anhydride were added at 0°C. The reaction mixture was stirred for 30 minutes at the same temperature and poured onto 100 ml of water-ice. 100 ml of a saturated solution of sodium chloride were added and extracted with 2x70 ml of dichloromethane and 3x50 ml of ethyl acetate. The organic layers were washed with water, dried over anhydrous sodium sulfate and evaporated to dryness by reduced pressure distillation. 8.7 g (yield=100%) as a solid of N-(3-acetylphenyl)-2,2,2-trifluoroacetamide were obtained.

¹H NMR (400 MHz, CDCl₃): δ 2.64 (3H, s), 7.53 (1H, t, J=7.6 Hz), 7.82 (1H, d, J=7.6 Hz), 8.15 (1H, d, J=8.2 Hz), 8.25 (1H, s), 9.12 (1H, a)

3-(dimethylamino)-1-[3-(methylamino)phenyl]prop-2-en-1-one

8.37 g (36.21 mmol) de N-(3-acetylphenyl)-2,2,2-trifluoroacetamide were dissolved in 80 ml of N,N-dimethyl formamide. To the resultant solution 24.23 ml (181.02 mmol) of N,N-dimethylformamide dimethyl acetal were added and heated at 150°C for 2 h. The solvent was removed by reduced pressure distillation to yield an oil which was treated with 50 ml of water and extract with 3x100 ml of dichloromethane. The organic layers were washed with 2x200 ml of a saturated solution of sodium chloride, dried over anhydrous sodium sulfate and evaporated to dryness by reduced pressure distillation. A solid was obtained, which precipitated from

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a mixture of ethanol-ethyl ether to give 4.1 g (yield=55%)
of 3-(dimethylamino)-1-[3-(methylamino)phenyl]prop-2-en-1-
one.

5 ¹H NMR (400 MHz, CDCl₃): δ 2.85 (3H, s), 2.87 (3H, s), 3.11
(3H, s), 3.85 (1H, a), 5.68 (1H, d, J= 12.2 Hz), 6.67-6.72
(1H, m), 7.16-7.24 (3H, m), 7.77 (1H, d, J= 12.2 Hz)

10 N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-2-
phenyl-ethylenesulfonamide

0.4 g (1.96 mmol) of 3-(dimethylamino)-1-[3-
(methylamino)phenyl]prop-2-en-1-one were dissolved in 15 ml
of dry dichloromethane. To the resultant solution 0.24 ml
15 (2.01 mmol) of anhydrous pyridine and 0.48 g (2.37 mmol) of
2-phenyl-ethene-sulfonic acid chloride were added. After
stirring the reaction mixture for 17 h at room temperature
and under inert atmosphere, 15 ml of water were added. The
two layers were separated, and the aqueous layer was washed
20 with 2x15 ml of dichloromethane. The organic layers were
washed with 30 ml of water and dried over anhydrous sodium
sulfate. The dichloromethane layer was evaporated to
dryness to yield a crude which was chromatographed (silica
gel) using dichloromethane-methanol as eluent. 0.53 (yield=
25 73%) of a solid, N-[3-[3-(dimethylamino)-1-oxo-2-
propenyl]phenyl]-N-methyl-2-phenyl-ethylene-sulfonamide,
were obtained

30 ¹H NMR (400 MHz, CDCl₃): δ 2.9 (3H, a), 3.16 (3H, a), 3.31
(3H, s), 5.65 (1H, d, J= 12.5 Hz), 6.7 (1H, d, J= 15.5 Hz),
7.38-7.5 (8H, m), 7.77-7.85 (3H, m)

As described in the above general procedure the following compounds were prepared:

5 N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-3-chlorobenzenesulfonamide

^1H NMR (400 MHz, CDCl_3): δ 2.93 (3H, a), 3.16 (3H, a), 3.22 (3H, s), 5.6 (1H, d), 7.23-7.27 (1H, m), 7.35-7.41 (3H, m), 7.52-7.58 (3H, m), 7.76 (1H, s), 7.79-7.83 (1H, m)

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N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-4-chlorobenzenesulfonamide

15 ^1H NMR (400 MHz, CDCl_3): δ 2.94 (3H, a), 3.18 (3H, a), 3.2 (3H, a), 5.59 (1H, d, $J=12.2$ Hz), 7.23-7.29 (1H, m), 7.34-7.55 (6H, m), 7.77-7.83 (2H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-2-chlorobenzenesulfonamide

20

^1H NMR (400 MHz, CDCl_3): δ 2.73 (3H, a), 2.96 (3H, a), 3.24 (3H, s), 5.6 (1H, d, $J=12.5$ Hz), 7.06-7.14 (3H, m), 7.21-7.32 (2H, m), 7.5-7.6 (3H, m), 7.68 (1H, dd), $J=7.9$ Hz, $J=1.5$ Hz)

25

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-2,2,2-trifluoroethanesulfonamide

30 ^1H NMR (400 MHz, CDCl_3): δ 2.95 (3H, a), 3.18 (3H, s), 3.42 (3H, s), 3.73 (2H, c, $J=9.1$ Hz), 5.66 (1H, d, $J=12.2$ Hz), 7.42-7.53 (2H, m), 7.8 (1H, s), 7.83-7.89 (2H, m)

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N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-
2,4-dichlorobenzenesulfonamide

5 ¹H NMR (400 MHz, CDCl₃): δ 2.96 (3H, a), 3.19 (3H, s), 3.46
(3H, s), 5.6 (1H, d, J= 12.2 Hz), 7.27 (1H, d, J= 2.1 Hz),
7.31 (1H, d, J= 1.8 Hz), 7.34-7.38 (1H, m), 7.53 (1H, d, J=
2.1 Hz), 7.71-7.84 (4H, m)

10 N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-
3,4-dichlorobenzenesulfonamide

15 ¹H NMR (400 MHz, CDCl₃): δ 2.86 (3H, s), 3.09 (3H, s), 3.15
(3H, s), 5.52 (1H, d, J= 12.2 Hz), 7.16-7.23 (1H, m), 7.26
(1H, d, J= 2.1 Hz), 7.32 (1H, t, J= 7.9 Hz), 7.45 (1H, d,
J= 8.5 Hz), 7.49 (1H, m), 7.61 (1H, d, J= 2.1 Hz)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-
2-cyanobenzenesulfonamide

20 ¹H NMR (400 MHz, CDCl₃): δ 2.97 (3H, a), 3.19 (3H, a), 3.43
(3H, s), 5.64 (1H, d, J= 12.2 Hz), 7.35 (1H, m), 7.41 (1H,
t, J= 7.9 Hz), 7.6-7.89 (7H, m)

25 N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-
3-cyanobenzenesulfonamide

30 ¹H NMR (400 MHz, CDCl₃): δ 2.94 (3H, a), 3.16 (3H, a), 3.23
(3H, s), 5.62 (1H, d, J= 12.2 Hz), 7.24-7.29 (1H, m), 7.39
(1H, t, J= 7.6 Hz), 7.5 (1H, m), 7.55-7.62 (1H, m), 7.69-
7.86 (5H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-
4-cyanobenzenesulfonamide

5 ¹H NMR (400 MHz, CDCl₃): δ 2.94 (3H, a), 3.17 (3H, a), 3.22 (3H, s), 5.6 (1H, d, J= 12.2 Hz), 7.24-7.3 (1H, m), 7.39 (1H, t, J= 7.9 Hz), 7.51 (1H, m), 7.64-7.7 (2H, m), 7.73-7.82 (4H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-3-nitrobenzenesulfonamide

10 ¹H NMR (400 MHz, CDCl₃): δ 2.93 (3H, a), 3.16 (3H, a), 3.26 (3H, s), 5.6 (1H, d, J= 12.2 Hz), 7.27-7.32 (2H, m), 7.39 (1H, t, J= 7.9 Hz), 7.48 (1H, m), 7.62-7.82 (4H, m), 8.4-8.44 (1H, m)

15 N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-4-nitrobenzenesulfonamide

20 ¹H NMR (400 MHz, CDCl₃): δ 2.92 (3H, a), 3.17 (3H, a), 3.25 (3H, s), 5.6 (1H, d, J= 12.5 Hz), 7.25-7.29 (1H, m), 7.39 (1H, t, J= 7.9 Hz), 7.53 (1H, m), 7.73 (2H, d, J= 9 Hz), 8.4-8.44 (1H, m), 7.77-7.84 (2H, m), 8.3 (2H, d, J= 9 Hz)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-2-thiophenesulfonamide

25

¹H NMR (400 MHz, CDCl₃): δ 2.85 (3H, a), 3.07 (3H, a), 3.19 (3H, s), 5.54 (1H, d, J= 12.5 Hz), 6.99 (1H, dd, J= 4.8 Hz), 7.19-7.32 (3H, m), 7.48-7.53 (2H, m), 7.67-7.74 (2H, m)

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N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-5-methyl-4-isoxazolesulfonamide

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¹H NMR (400 MHz, CDCl₃): δ 2.13 (3H, s), 2.88 (3H, a), 3.11 (3H, s), 3.19 (3H, m), 5.53 (1H, d, J= 12.5 Hz), 7.21-7.28 (1H, m), 7.35 (1H, t, J= 7.9 Hz), 7.56-7.81 (3H, m), 8.15 (1H, m)

5

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-2-trifluoromethyl-5-methyl-3-furansulfonamide

¹H NMR (400 MHz, CDCl₃): δ 2.13 (3H, s), 2.94 (3H, a), 3.27 (3H, s), 5.61 (1H, d, J= 12.2 Hz), 6.8 (1H, m), 7.3-7.44 (2H, m), 7.66 (1H, t), 7.79-7.86 (2H, m)

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N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-6-(morpholin-4-yl)-3-pyridinesulfonamide

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¹H NMR (400 MHz, CDCl₃): δ 2.88 (3H, a), 3.13 (3H, s), 3.54-3.58 (4H, m), 3.71-3.75 (4H, m), 5.59 (1H, d, J= 12.5 Hz), 6.43 (1H, dd, J= 9.1 Hz), 7.21-7.3 (2H, m), 7.35 (1H, dd, J= 9.1 Hz), 7.58-7.6 (1H, m), 7.69-7.74 (2H, m), 8.3 (1H, dd, J= 2.6 y 0.8 Hz)

20

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-2,4-dimethyl-5-thiazolesulfonamide

25

¹H NMR (400 MHz, CDCl₃): δ 2.06 (3H, s), 2.6 (3H, s), 2.88 (3H, a), 3.1 (3H, a), 3.23 (3H, s), 5.56 (1H, dd, J= 12.2 Hz), 7.23-7.38 (2H, m), 7.7-7.8 (3H, m)

30

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-cyclopropanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.03-1.12 (1H, m), 1.23-1.32 (1H, m), 1.5-1.54 (1H, m), 2.26-2.37 (1H, m), 2.88 (3H, a),

3.09 (3H, a), 3.16-3.28 (1H, m), 3.31 (3H, s), 5.62 (1H, d, J= 12.2 Hz), 7.3-7.37 (1H, m), 7.44-7.48 (1H, m), 7.7-7.77 (2H, m), 7.87-7.88 (1H, m)

5 N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-benzylsulfonamide

¹H NMR (400 MHz, CDCl₃): δ 3.05 (3H, a), 3.25 (6H, s), 4.37 (2H, s), 5.76 (1H, d, J= 12.2 Hz), 7.44-7.51 (7H, m), 7.83-
10 7.93 (3H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl-vinylsulfonamide

15 ¹H NMR (400 MHz, CDCl₃): δ 2.92 (3H, a), 3.14 (3H, a), 5.66 (1H, d, J= 12.2 Hz), 5.97 (1H, dd), 6.13 (1H, dd), 6.39 (1H, dd), 7.31-7.47 (2H, m), 7.7-7.75 (2H, m), 7.87 (1H, d, J= 12.2 Hz)

20 N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl 3,5-dimethyl-4-isoxazolesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 2.03 (3H, s), 2.27 (3H, s), 2.94 (3H, a), 3.16 (3H, a), 3.27 (3H, s), 5.58 (1H, d, J= 12.2
25 Hz), 7.31-7.43 (2H, m), 7.66 (1H, m), 7.77-7.85 (2H, m)

N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-methyl 1,3,5-trimethyl-4-pyrazolesulfonamide

30 ¹H NMR (400 MHz, CDCl₃): δ 1.96 (3H, s), 2.84 (3H, a), 3.16 (3H, a), 3.2 (3H, a), 3.68 (3H, s), 5.63 (1H, d, J= 12.5 Hz), 7.34-7.37 (2H, m), 7.63 (1H, m), 7.76-7.82 (2H, m)

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Example 16: General procedure for the preparation of pyrazolo[1,5-a]pyrimidines of general formula (I) following Scheme 1

N-prop-2-ynyl-N-(3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl)-methanesulfonamide

0.1 g (0.33 mmol) of 4-thiophene-2-carbonyl-2H-pyrazol-3-ylamine and 0.063 g (0.33 mmol) of N-[3-[3-(dimethylamino)-1-oxo-2-propenyl]phenyl]-N-prop-2-ynyl-methanesulfonamide were dissolved in 10 ml of glacial acetic acid. After refluxing for 8 hours, the solvent was removed by reduced pressure distillation. To the resultant residue 10 ml of dichloromethane and 10 ml of a saturated solution of sodium bicarbonate were added. The two layers were separated, and the aqueous layer was washed with 10 ml of dichloromethane. The organic layers were washed with 10 ml of water and dried over magnesium sulfate. The dichloromethane layer was evaporate to dryness to yield an oil which, in the presence of ethyl acetate gave a yellow solid, 111 mg (yield= 78%) N-prop-2-ynyl-N-(3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl)-methanesulfonamide.

^1H NMR (400 MHz, CDCl_3): δ 2.54 (1H, s), 3.12 (3H, s), 4.54 (2H, s), 7.15 (1H, d, $J = 4$ Hz), 7.19-7.21 (1H, m), 7.65 (1H, t, $J = 7.6$ Hz), 7.69-7.71 (1H, m), 7.84-7.87 (1H, m), 8.03-8.06 (1H, m), 8.08-8.10 (1H, m), 8.31 (1H, t, $J = 2$ Hz), 8.71 (1H, s), 8.82 (1H, d, $J = 4.4$ Hz)

MS (ES) $m/z = 437$ (MH $^+$)

HPLC = 100%

As described in the general procedure of Example 16, the following exemplified compounds were prepared:

Example 17: N-propyl-N-(3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl)-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 0.94 (3H, t, J= 7.6 Hz), 1.42 (3H, t, J= 7.6 Hz), 1.54-1.63 (2H, m), 3.08-3.31 (2H, m), 3.75 (2H, t, J= 7.2 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.19-7.21 (1H, m), 7.59-7.65 (2H, m), 7.69-7.71 (1H, m), 7.99-8.02 (1H, m), 8.09-8.11 (2H, m, J= 2 Hz), 8.71 (1H, s), 8.82 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 455 (MH⁺)

HPLC = 97.86%

Example 18: N-ethyl-N-(3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl)-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.22 (3H, t, J= 6.8 Hz), 1.43 (3H, t, J= 7.6 Hz), 3.11 (2H, c, J= 7.6 Hz), 3.85 (2H, c, J= 6.8 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.19-7.21 (1H, m, J= 4.4 Hz), 7.58-7.66 (2H, m), 7.69-7.71 (1H, m), 7.99-8.02 (1H, m), 8.09-8.11 (2H, m), 8.71 (1H, s), 8.82 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 441 (MH⁺)

HPLC = 97.73%

Example 19: N-prop-2-ynyl-N-(3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl)-2-propanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.44 (6H, d, J= 6.4 Hz), 2.42 (1H, m), 3.44-3.51 (1H, m), 4.56 (1H, s), 7.15 (1H, d, J= 4

Hz), 7.19-7.20 (1H, m), 7.65 (1H, t, J= 8 Hz), 7.69-7.71 (1H, m), 7.76-7.79 (1H, m), 8.02-8.05 (1H, m).8.09-8.11 (1H, m).8.24-8.25 (1H, m).8.7 (1H, s).8.82 (1H, d, J= 4.4 Hz)

5 MS (ES) m/z = 465 (MH+)
HPLC = 100%

Example 20: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

10

¹H NMR (400 MHz, CDCl₃): δ 1.41 (3H, t, J= 7.2 Hz), 3.12 (2H, c, J= 7.6 Hz), 3.45 (3H, s), 7.15 (1H, d, J= 4.4 Hz), 7.19-7.23 (1H, m, J= 4.4 Hz), 7.61-7.63 (2H, m), 7.69-7.71 (1H, m), 7.92-7.95 (1H, m), 8.09-8.11 (1H, m), 8.13-8.14 (1H, m).8.71 (1H, s).8.82 (1H, d, J= 4.4 Hz)

15

MS (ES) m/z = 427 (MH+)
HPLC = 84.2%

Example 21: N-butyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

20

¹H NMR (400 MHz, CDCl₃): δ 0.91 (3H, t, J= 7.2 Hz), 1.36-1.44 (5H, m), 1.52-1.57 (2H, m), 3.1 (2H, c, J= 7.6 Hz), 3.78 (2H, t, J= 7.2 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.20-7.25 (1H, m), 7.61-7.63 (2H, m), 7.69-7.71 (1H, m), 7.99-8.02 (1H, m).8.09-8.11 (2H, m).8.71 (1H, s).8.82 (1H, d, J= 4.4 Hz)

25

MS (ES) m/z = 469 (MH+)
HPLC = 99.06%

30

Example 22: 7-(3-(2-isothiazolidinyl-1,1-dioxide)-phenyl)-3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidine

¹H NMR (400 MHz, CDCl₃): δ 2.57-2.61 (2H, m), 3.43 (2H, t, J= 7.6 Hz), 3.87 (2H, t, J= 6.4 Hz), 7.14 (1H, d, J= 4 Hz), 7.19 (1H, t), 7.46-7.50 (1H, m), 7.58 (1H, t), 7.68-7.69 (1H, d, J= 4 Hz), 7.78-7.79 (1H, d), 7.9 (1H, s).8.09 (1H, d, J= 3.2 Hz).8.69 (1H, s).8.79 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 425 (MH+)
HPLC = 97.1%

Example 23: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propane-sulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.4 (6H, d, J= 6.8 Hz), 3.36-3.41 (1H, m), 3.47 (3H, s), 7.15 (1H, d, J= 4.4 Hz), 7.18-7.21 (1H, m), 7.58-7.64 (2H, m), 7.69-7.71 (1H, m), 7.89-7.93 (1H, m), 8.09-8.10 (1H, m), 8.14-8.16 (1H, m).8.7 (1H, s).8.81 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 441 (MH+)
HPLC = 96.35%

Example 24: N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propane-sulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.21 (3H, t, J= 6.8 Hz), 1.41 (6H, d, J= 6.4 Hz), 3.28-3.32 (1H, m), 3.87 (2H, c, J= 7.2 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.18-7.21 (1H, m), 7.61-7.62 (2H, m), 7.69-7.71 (1H, m), 7.9-8.1 (1H, m), 8.09-8.12 (1H, m).8.7 (1H, s).8.81 (1H, d, J= 4.4 Hz).
MS (ES) m/z = 455 (MH+)
HPLC = 88.35%

28/35

Example 25: N-propyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propane-sulfonamide

5 ¹H NMR (400 MHz, CDCl₃): δ 0.93 (3H, t, J= 7.2 Hz), 1.41 (6H, d, J= 6.8 Hz), 1.57 (2H, q, J= 7.2 Hz), 3.3 (1H, m, J= 6.8 Hz), 3.77 (2H, t, J= 7.2 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.19-7.21 (1H, m), 7.61-7.63 (2H, m), 7.69-7.71 (1H, m), 7.99-8.11 (1H, m), 8.09-8.13 (2H, m), 8.7 (1H, s), 8.81 (1H, d, J= 4.4 Hz)

10 MS (ES) m/z = 469 (MH⁺)
HPLC = 97%

Example 26: N-butyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propane-sulfonamide

15

¹H NMR (400 MHz, CDCl₃): δ 0.9 (3H, t, J= 7.2 Hz), 1.36 (2H, q, J= 8 Hz), 1.41 (6H, d, J= 6.8 Hz), 1.51-1.55 (2H, m), 3.29 (1H, m, J= 6.4 Hz), 8.81 (2H, t, J= 6.8 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.19-7.21 (1H, m), 7.62-7.63 (2H, m), 7.70-7.71 (1H, m), 7.99-8.01 (1H, m), 8.10-8.14 (2H, m), 8.7 (1H, s), 8.82 (1H, d, J= 4.4 Hz)

20 MS (ES) m/z = 483 (MH⁺)
HPLC = 100%

25

Example 27: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-prop-2-ynyl-methanesulfonamide

30 ¹H NMR (400 MHz, CDCl₃): δ 2.53 (1, s), 3.1 (3H, s), 4.53 (2H, s), 7.19 (1H, d, J= 4.4 Hz), 7.65 (1H, t, J= 7.6 Hz), 7.85-7.88 (1H, m, J= 4.4 Hz), 8.0-8.29 (1H, m), 8.27-8.28 (1H, m), 8.42 (1H, s), 8.79 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 352 (MH⁺)

HPLC = 95.78%

5 **Example 28:** N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-propyl-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 0.93 (3H, t, J= 7.6 Hz), 1.41 (3H, t, J= 7.2 Hz), 1.54-1.59 (2H, m), 3.01 (2H, q, J= 7.2 Hz), 3.74 (2H, t, J= 7.2 Hz), 7.2 (1H, d, J= 4.4 Hz), 7.59-7.65 (2H, m), 7.96-7.99 (1H, m), 8.07-8.08 (1H, m), 8.41 (1H, s), 8.78 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 370 (MH⁺)

HPLC = 98%

15 **Example 29:** N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-ethanesulfonamide

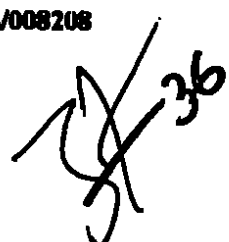
¹H NMR (400 MHz, CDCl₃): δ 1.21 (3H, t, J= 7.2 Hz), 1.42 (3H, t, J= 7.6 Hz), 3.09 (2H, q, J= 7.6 Hz), 3.84 (2H, q, J= 7.2 Hz), 7.2 (1H, d, J= 4 Hz), 7.58-7.65 (2H, m), 7.97-7.99 (1H, m), 8.07 (1H, t, J= 1.6 Hz), 8.42 (1H, s), 8.78 (1H, d, J= 4.8 Hz)

MS (ES) m/z = 356 (MH⁺)

HPLC = 99%

25 **Example 30:** N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-prop-2-ynyl-propane-2-sulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.43 (6H, d, J= 7.2 Hz), 2.41-2.42 (1H, m), 3.43-3.50 (1H, m), 3.54 (2H, s), 7.2 (1H, d, J= 4 Hz), 7.63 (1H, t, J= 7.6 Hz), 7.77-7.80 (1H, m), 7.99-8.02 (1H, m), 8.21-8.22 (1H, m), 8.42 (1H, s), 8.78 (1H, d, J= 4.4 Hz)



MS (ES) m/z = 380 (MH⁺)

HPLC = 97.46%

5 **Example 31:** N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.4 (3H, t, J= 7.2 Hz), 3.11 (2H, q, J= 7.2 Hz), 3.43 (3H, s), 7.19 (1H, d, J= 4.4 Hz), 7.60-7.63 (2H, m), 7.89-7.92 (1H, m), 8.11 (1H, a), 8.42 (1H, s), 8.78 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 342 (MH⁺)

HPLC = 91%

15 **Example 32:** N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-butyl-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.43 (3H, t, J= 7.2 Hz), 2.49 (1H, t, J= 2.4 Hz), 3.26 (2H, q, J= 7.2 Hz), 4.54 (2H, d, J= 2.4 Hz), 7.2 (1H, d, J= 4 Hz), 7.64 (1H, t, J= 8 Hz), 7.82-7.85 (1H, m), 8.00-8.03 (1H, m), 8.25 (1H, t, J= 2 Hz), 8.42 (1H, s), 8.79 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 366 (MH⁺)

HPLC = 98%

25 **Example 33:** 7-(3-(2-isothiazolidinyl-1,1-dioxide)-phenyl)-3-cyano-pyrazolo[1,5-a]pyrimidine

¹H NMR (400 MHz, DMSO-d₆): δ 2.47-2.51 (2H, m), 3.61 (2H, t, J= 7.6 Hz), 3.87 (2H, t, J= 6.8 Hz), 7.52-7.56 (1H, m), 7.6 (1H, d, J= 4.8 Hz), 7.66 (1H, t), 7.8-7.85 (2H, m), 8.88 (1H, s), 8.95 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 340 (MH⁺)

HPLC = 91.47%

Example 34: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-2-propanesulfonamide

5 ¹H NMR (400 MHz, CDCl₃): δ 1.39 (6H, d, J= 6.8 Hz), 3.38 (1H, m), 3.45 (3H, s), 7.19 (1H, d, J= 4 Hz), 7.56-7.66 (2H, m), 7.87-7.90 (1H, m), 8.125 (1H, t, J= 2 Hz), 8.41 (1H, s), 8.78 (1H, d, J= 4 Hz)
MS (ES) m/z = 356 (MH+)
10 HPLC = 91%

Example 35: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-2-propanesulfonamide

15 ¹H NMR (400 MHz, CDCl₃): δ 1.95 (3H, t, J= 7.2 Hz), 1.41 (6H, d, J= 6.8 Hz), 3.28 (1H, m), 3.86 (2H, q, J= 7.2 Hz), 7.2 (1H, d, J= 4.4 Hz), 7.61-7.62 (2H, m), 7.96-7.99 (1H, m), 8.08-8.09 (1H, m), 8.41 (1H, s), 8.78 (1H, d, J= 4 Hz)
MS (ES) m/z = 370 (MH+)
20 HPLC = 98%

Example 36: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-butyl-2-propanesulfonamide

25 ¹H NMR (400 MHz, CDCl₃): δ 0.89 (3H, t, J= 7.2 Hz), 1.32-1.36 (2H, m), 1.53-1.56 (6H, d, J= 6.8 Hz), 1.49-1.51 (2H, m), 3.27 (1H, m), 3.79 (2H, t, J= 7.6 Hz), 7.2 (1H, d, J= 4.4 Hz), 7.61-7.63 (2H, m), 7.95-7.98 (1H, m), 8.1 (1H, a), 8.41 (1H, s), 8.78 (1H, d, J= 4 Hz)
30 MS (ES) m/z = 398 (MH+)
HPLC = 95%

2/3

Example 37: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-propyl-2-propanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 0.92 (3H, t, J= 7.2 Hz), 1.4 (6H, d, J= 6.8 Hz), 1.53-1.56 (2H, m), 3.27 (1H, m), 3.76 (2H, t, J= 7.6 Hz), 7.2 (1H, d, J= 4.4 Hz), 7.61-7.63 (2H, m), 7.96-7.98 (1H, m), 8.1 (1H, a), 8.41 (1H, s), 8.78 (1H, d, J= 4 Hz)

MS (ES) m/z = 384 (MH⁺)

HPLC = 98.05%

Example 38: N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-prop-2-ynyl-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 7.2 (3H, t, J= 7.6 Hz), 2.48 (1H, s), 3.25 (2H, c, J= 7.2 Hz), 4.54 (2H, s), 7.2 (1H, d, J= 4 Hz), 7.64 (1H, t, J= 8.4 Hz), 7.82-7.85 (1H, m), 7.99-8.03 (1H, m), 8.26-8.26 (1H, m), 8.42 (1H, s), 8.79 (1H, d, J= 4.1 Hz)

MS (ES) m/z = 366 (MH⁺)

HPLC = 97.7%

Example 39: N-methyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 2.92 (3H, s), 3.41 (3H, s), 7.17 (1H, d, J= 4.4 Hz), 7.48-7.51 (1H, m), 7.62-7.63 (2H, m), 7.90-7.94 (2H, m), 8.16-8.16 (1H, m), 8.24 (1H, d, J= 6.8 Hz), 8.73-8.75 (1H, m), 8.90 (1H, d, J= 4.4 Hz), 9.36 (1H, s)

MS (ES) m/z = 408 (MH⁺)

HPLC = 99%

Example 40: N-ethyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.22 (3H, t, J= 7.2 Hz), 2.97 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.18 (1H, d, J= 4 Hz), 7.48-7.51 (1H, m), 7.59-7.67 (2H, m), 7.90-7.94 (1H, m), 7.98-8.00 (1H, m), 8.15 (1H, s), 8.24 (1H, d, J= 7.6 Hz), 8.75 (1H, d, J= 4.8 Hz), 8.9 (1H, d, J= 4.4 Hz), 9.36 (1H, s)

MS (ES) m/z = 422 (MH⁺)

HPLC = 100%

Example 41: N-prop-2-ynyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

15

¹H NMR (400 MHz, CDCl₃): δ 2.52-2.53 (1H, m), 3.12 (3H, s), 4.53-4.54 (2H, m), 7.17 (1H, d, J= 4.4 Hz), 7.48-7.52 (1H, m), 7.65 (2H, t, J= 8 Hz), 7.82-7.85 (1H, m), 7.92 (1H, t, J= 0.8 Hz), 8.03-8.06 (1H, m), 8.24 (1H, d, J= 8.4 Hz), 8.35 (1H, s), 8.75 (1H, d, J= 5.6 Hz), 8.9 (1H, d, J= 5.6 Hz), 9.37 (1H, s)

20

MS (ES) m/z = 432 (MH⁺)

HPLC = 96%

Example 42: N-methyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

25

¹H NMR (400 MHz, CDCl₃): δ 1.4 (3H, t, J= 7.6 Hz), 3.12 (2H, q, J= 7.6 Hz), 3.44 (3H, s), 7.17 (1H, d, J= 4.4 Hz), 7.48-7.51 (1H, m), 7.61-7.64 (2H, m), 7.88-7.93 (2H, m), 8.16 (1H, t, J= 2 Hz), 8.24 (1H, d, J= 8.4 Hz), 8.74-8.75 (1H, m), 8.89 (1H, d, J= 5.2 Hz), 9.36 (1H, s)

30

MS (ES) m/z = 422 (MH⁺)

2/1 38

HPLC = 100%

Example 43: N-ethyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo
[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

5

¹H NMR (400 MHz, CDCl₃): δ 1.35 (3H, t, J= 7.2 Hz), 1.33
(3H, t, J= 7.2 Hz), 3.05 (2H, q, J= 7.2 Hz), 3.77 (2H, q,
J= 7.2 Hz), 7.14 (1H, d, J= 4.8 Hz), 7.40-7.43 (1H, m),
7.54-7.56 (2H, m), 7.82-7.85 (1H, m), 7.92-7.93 (1H, m),
8.1 (1H, s), 8.13 (1H, d, J= 8 Hz), 8.66 (1H, d, J= 4.4
Hz), 8.81 (1H, d, J= 4.4 Hz), 9.28 (1H, s)

10

MS (ES) m/z = 436 (MH⁺)

HPLC = 95%

15

Example 44: N-prop-2-ynyl-N-{3-[3-(pyridin-2-carbonyl)-
pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.42 (3H, t, J= 7.2 Hz), 2.47
(1H,), 3.26 (2H, q, J= 7.2 Hz), 4.54 (2H, d, J= 2.4 Hz),
7.17 (1H, d, J= 4.8 Hz), 7.48-7.51 (1H, m), 7.63 (1H, t, J=
7.6 Hz, 7.8-7.82 (1H, m), 7.89-7.93 (1H, m), 8.02-8.05 (1H,
m), 8.23 (1H, d, J= 8 Hz), 8.3 (1H, t, J= 2 Hz), 8.73-8.75
(1H, m), 8.89 (1H, d, J= 5.2 Hz), 9.36 (1H, s)

20

MS (ES) m/z = 446 (MH⁺)

25

HPLC = 98%

Example 45: N-methyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo
[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 2.92 (3H, s), 3.41 (3H, s), 7.2
(1H, d, J= 4.4 Hz), 7.26-7.64 (2H, m), 7.71-7.73 (2H, m),
7.93-7.96 (1H, m), 8.127-8.129 (1H, m), 8.57 (1H, s), 8.81-
8.83 (3H, m)

30

MS (ES) m/z = 408 (MH⁺)

HPLC = 95%

5 **Example 46:** N-ethyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo
[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.22 (3H, t, J= 7.2 Hz), 2.96
(3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.22 (1H, d, J= 4.4 Hz),
(1H, m), 5.73 (2H, d, J= 5.6 Hz), 8.01 (1H, d, J= 7.6 Hz),
10 8.1 (1H, t, J= 2 Hz), 8.57 (1H, s), 8.82-8.84 (3H, m)

MS (ES) m/z = 422 (MH⁺)

HPLC = 89%

15 **Example 47:** N-methyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo
[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.39 (3H, t, J= 7.2 Hz), 3.11
(2H, q, J= 7.2 Hz), 3.44 (3H, s), 7.2 (1H, d, J= 4.8 Hz),
7.62-7.63 (2H, m), 7.71-7.72 (2H, m), 7.92-7.94 (1H, m),
20 8.13-8.14 (1H, m), 8.57 (1H, s), 8.81-8.83 (3H, m)

MS (ES) m/z = 422 (MH⁺)

HPLC = 94%

25 **Example 48:** N-ethyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo
[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.13 (3H, t, J= 7.2 Hz), 1.318
(3H, t, J= 7.2 Hz), 3.04 (2H, q, J= 7.2 Hz), 3.77 (2H, q,
J= 7.2 Hz), 7.18 (1H, d, J= 4.8 Hz), 7.52-7.58 (2H, m),
30 7.61-7.94 (2H, m), 8.05 (1H, s), 8.47 (1H, s), 8.71-8.73
(3H, m)

MS (ES) m/z = 436 (MH⁺)

HPLC = 89%

39

Example 49: N-prop-2-ynyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.22 (3H, t, J= 7.2 Hz), 2.96 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.22 (1H, d, J= 4.4 Hz), 7.58-7.60 (1H, m), 7.66 (1H, t, J= 8 Hz), 7.71-7.73 (2H, m), 8.01 (1H, d, J= 7.6 Hz), 8.1 (1H, t, J= 2 Hz), 8.57 (1H, s), 8.82-8.84 (3H, m)

MS (ES) m/z = 422 (MH⁺)

HPLC = 89%

Example 50: N-prop-2-ynyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 2.53 (1H, t, J= 2 Hz), 3.11 (3H, s), 4.54 (2H, d, J= 2.4 Hz), 7.2 (1H, d, J= 4.4 Hz), 7.66 (1H, t, J= 7.6 Hz), 7.72-7.73 (2H, m), 7.86-7.89 (1H, m), 8.03-8.05 (1H, m), 8.31 (1H, t, J= 2 Hz), 8.56 (1H, s), 8.82-8.84 (3H, m)

MS (ES) m/z = 432 (MH⁺)

HPLC = 93%

Example 51: N-methyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 2.93 (3H, s), 3.42 (3H, s), 7.15-7.20 (3H, m), 7.61-7.63 (2H, m), 7.94-7.99 (3H, m), 8.12-8.13 (1H, m), 8.55 (1H, s), 8.78 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 425 (MH⁺)

HPLC = 98%

Example 52: N-ethyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.23 (3H, t, J= 7.2 Hz), 2.97 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.16-7.20 (3H, m), 7.56-7.60 (1H, m), 7.65 (1H, t, J= 8 Hz), 7.96-8.02 (3H, m), 8.1 (1H, t, J= 2 Hz), 8.55 (1H, s), 8.79 (1H, d, J= 4.4 Hz)

5 MS (ES) m/z = 439 (MH⁺)

HPLC = 98%

Example 53: N-methyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

10

¹H NMR (400 MHz, CDCl₃): δ 1.38 (3H, t, J= 7.2 Hz), 3.11 (2H, q, J= 7.2 Hz), 3.42 (3H, s), 7.13-7.17 (3H, m), 7.59-7.61 (2H, m), 7.90-7.97 (3H, m, J= 8 Hz), 8.13 (1H, a), 8.53 (1H, s), 8.76 (1H, d, J= 4.4 Hz)

15 MS (ES) m/z = 439 (MH⁺)

HPLC = 94%

Example 54: N-ethyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

20

¹H NMR (400 MHz, CDCl₃): δ 1.21 (3H, t, J= 7.2 Hz), 1.41 (3H, t, J= 7.2 Hz), 3.1 (2H, q, J= 7.2 Hz), 3.84 (2H, q, J= 7.2 Hz), 7.14-7.18 (3H, m), 7.58 (2H, m), 7.94-8.01 (3H, m), 8.1 (1H, a), 8.54 (1H, s), 8.77 (1H, d, J= 4.4 Hz)

25 MS (ES) m/z = 453 (MH⁺)

HPLC = 99%

Example 55: N-prop-2-ynyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

30

¹H NMR (400 MHz, CDCl₃): δ 1.43 (3H, t, J= 7.2 Hz), 2.48 (1H, t, J= 2.4 Hz), 3.27 (2H, q, J= 7.2 Hz), 4.54 (2H, d,

40

J= 2.4 Hz), 7.15-7.2 (3H, m), 7.64 (1H, t, J= 8 Hz), 7.81-7.84 (1H, m), 7.96-8.04 (3H, m), 8.28 (1H, a), 8.56 (1H, s), 8.79 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 463 (MH⁺)

5 HPLC = 96%

Example 56: N-prop-2-ynyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

10

¹H NMR (400 MHz, CDCl₃): δ 2.54 (1H, t, J= 2 Hz), 3.1 (3H, s), 4.52 (2H, d, J= 2 Hz), 7.14-7.18 (3H, m), 7.64 (1H, t, J= 7.6 Hz), 7.83-7.86 (1H, m), 7.94-7.96 (2H, m), 8.02-8.04 (1H, m), 8.3 (1H, t, J= 2 Hz), 8.54 (1H, s), 8.77 (1H, d, J= 4 Hz)

15

MS (ES) m/z = 449 (MH⁺)

HPLC = 96%

Example 57: N-methyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

20

¹H NMR (400 MHz, CDCl₃): δ 2.93 (3H, s), 3.42 (3H, s), 3.9 (3H, s), 6.97-7.01 (2H, m), 7.12 (1H, d, J= 4.4 Hz), 7.61-7.65 (2H, m), 7.94-7.99 (3H, m), 8.13 (1H, a), 8.55 (1H, s), 8.78 (1H, d, J= 3.6 Hz)

25

MS (ES) m/z = 437 (MH⁺)

HPLC = 99%

Example 58: N-ethyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

30

¹H NMR (400 MHz, CDCl₃): δ 1.23 (3H, t, J= 7.2 Hz), 2.97 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 3.9 (3H, s), 6.98-7.00

(2H, m), 7.14 (1H, d, J= 4 Hz), 7.59-7.60 (1H, m), 7.65 (1H, t, J= 8 Hz), 7.96-8.03 (3H, m), 8.1 (1H, t, J= 2 Hz), 8.55 (1H, s), 8.78 (1H, d, J= 4 Hz)

MS (ES) m/z = 451 (MH+)

5

HPLC = 98%

Example 59: N-methyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-ethane-sulfonamide

10

¹H NMR (400 MHz, CDCl₃): δ 1.41 (3H, t, J= 7.2 Hz), 3.13 (2H, q, J= 7.2 Hz), 3.45 (3H, s), 3.9 (3H, s), 6.98-7.00 (2H, m), 7.12 (1H, d, J= 4.4 Hz), 7.61-7.63 (2H, m), 7.93-7.98 (3H, m), 8.14 (1H, t, J= 1.2 Hz), 8.55 (1H, s), 8.78 (1H, d, J= 4 Hz)

15

MS (ES) m/z = 451 (MH+)

HPLC = 97%

Example 60: N-ethyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

20

¹H NMR (400 MHz, CDCl₃): δ 1.23 (3H, t, J= 7.2 Hz), 1.43 (3H, t, J= 7.2 Hz), 3.12 (2H, q, J= 7.2 Hz), 3.86 (2H, q, J= 7.2 Hz), 3.91 (3H, s), 6.98-7.00 (2H, m), 7.14 (1H, d, J= 4 Hz), 7.6-7.65 (2H, m), 7.96-8.02 (3H, m), 8.11 (1H, t, J= 1.6 Hz), 8.55 (1H, s), 8.78 (1H, d, J= 4 Hz)

25

MS (ES) m/z = 465 (MH+)

HPLC = 98%

Example 61: N-prop-2-ynyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

30

¹H NMR (400 MHz, CDCl₃): δ 1.43 (3H, t, J= 7.2 Hz), 2.48 (1H, t, J= 2.4 Hz), 3.27 (2H, q, J= 7.2 Hz), 3.9 (3H, s),

4.55 (2H, d, J= 2.4 Hz), 6.98-7.00 (2H, m), 7.13 (1H, d, J= 4.4 Hz), 7.64 (1H, t, J= 8 Hz), 7.80-7.83 (1H, m), 7.96-7.98 (2H, m), 8.03-8.05 (1H, m), 8.28 (1H, a), 8.55 (1H, s), 8.78 (1H, d, J= 3.6 Hz)

5 MS (ES) m/z = 475 (MH+)

HPLC = 97%

Example 62: N-prop-2-ynyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

10

¹H NMR (400 MHz, CDCl₃): δ 2.53 (1H, t, J= 2 Hz), 3.11 (3H, s), 3.87 (3H, s), 4.53 (2H, d, J= 2 Hz), 6.98 (2H, d, J= 8.8 Hz), 7.12 (1H, d, J= 4.4 Hz), 7.63 (1H, t, J= 7.6 Hz), 7.82-7.84 (1H, m), 7.95 (2H, d, J= 8.8 Hz), 8.03 (1H, d, J= 7.6 Hz), 8.31 (1H, t, J= 2 Hz), 8.54 (1H, s), 8.76 (1H, d, J= 4.4 Hz)

15

MS (ES) m/z = 461 (MH+)

HPLC = 100%

20 **Example 63:** N-methyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 2.5 (3H, s), 2.97 (3H, s), 3.46 (3H, s), 7.18 (1H, d, J= 4.4 Hz), 7.34 (2H, d, J= 8.4 Hz), 7.65-7.67 (2H, m), 7.89 (2H, d, J= 8 Hz), 7.98-8.00 (1H, m), 8.17 (1H, s), 8.58 (1H, s), 8.83 (1H, d, J= 4.4 Hz)

25

MS (ES) m/z = 421 (MH+)

HPLC = 99%

30 **Example 64:** N-ethyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.23 (3H, t, J= 7.2 Hz), 2.45 (3H, s), 2.96 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.15 (1H, d, J= 4.4 Hz), 7.29-7.3 (2H, m), 7.58-7.64 (2H, m), 7.83-7.85 (2H, m), 7.99-8.02 (1H, m), 8.1 (1H, t, J= 2 Hz), 8.53 (1H, s), 8.79 (1H, d, J= 4.8 Hz)

MS (ES) m/z = 435 (MH⁺)

HPLC = 96%

Example 65: N-methyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.41 (3H, t, J= 7.2 Hz), 2.46 (3H, s), 3.12 (2H, q, J= 7.2 Hz), 3.44 (3H, s), 7.13 (1H, d, J= 4 Hz), 7.31 (2H, d, J= 8.4 Hz), 7.61-7.63 (2H, m), 7.85-7.87 (2H, m), 7.92-7.93 (1H, m), 8.13-8.14 (1H, m), 8.54 (1H, s), 8.79 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 435 (MH⁺)

HPLC = 98%

Example 66: N-ethyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.22 (3H, t, J= 7.2 Hz), 1.42 (3H, t, J= 7.2 Hz), 2.46 (3H, s), 3.11 (2H, q, J= 7.2 Hz), 3.85 (2H, q, J= 7.2 Hz), 7.15 (1H, d, J= 4.4 Hz), 7.31 (2H, d, J= 8.2 Hz), 7.60-7.66 (2H, m), 7.84-7.86 (2H, m), 8 (1H, d, J= 7.6 Hz), 8.11 (1H, t, J= 1.6 Hz), 8.54 (1H, s), 8.8 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 449 (MH⁺)

HPLC = 100%

Example 67: N-prop-2-ynyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

42

¹H NMR (400 MHz, CDCl₃): δ 1.43 (3H, t, J= 7.2 Hz), 2.46 (3H, s), 2.48 (1H, t, J= 2.4 Hz), 3.27 (2H, q, J= 7.2 Hz), 4.54 (2H, d, J= 2.4 Hz), 7.14 (1H, d, J= 4 Hz), 7.31 (2H, d, J= 8 Hz), 7.63 (1H, t, J= 8 Hz), 7.81-7.86 (3H, m), 8.03 (1H, d, J= 8 Hz), 8.28 (1H, t, J= 2 Hz), 8.54 (1H, s), 8.8 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 459 (MH+)
HPLC = 98%

10

Example 68: N-prop-2-ynyl-N-(3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl)-methanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 2.46 (3H, s), 2.53 (1H, t, J= 2.4 Hz), 3.11 (3H, s), 4.54 (2H, d, J= 2.4 Hz), 7.14 (1H, d, J= 4 Hz), 7.3 (2H, d, J= 8 Hz), 7.64 (1H, t, J= 8 Hz), 7.83-7.86 (3H, m), 8.03-8.05 (1H, m), 8.31 (1H, t, J= 2 Hz), 8.54 (1H, s), 8.8 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 445 (MH+)
HPLC = 98%

20

Example 69: N-methyl-N-(3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl)-methanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 2.93 (3H, s), 3.42 (3H, s), 7.15 (1H, d, J= 4.4 Hz), 7.49-7.52 (2H, m), 7.58-7.63 (3H, m), 7.92-7.94 (3H, m), 8.13 (1H, a), 8.54 (1H, s), 8.81 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 407 (MH+)
HPLC = 96%

30

Example 70: N-ethyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.22 (3H, t, J= 7.2 Hz), 2.97
5 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.17 (1H, d, J= 4.4 Hz),
7.49-7.52 (2H, m), 7.56-7.67 (3H, m), 7.91-7.94 (2H, m),
7.80-8.02 (1H, m), 8.11 (1H, t, J= 2 Hz), 8.53 (1H, s),
8.82 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 421 (MH+)
10 HPLC = 98%

Example 71: N-methyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.39 (3H, t, J= 7.2 Hz), 3.11
15 (2H, q, J= 7.2 Hz), 3.43 (3H, s), 7.15 (1H, a), 7.47-7.61
(5H, m), 7.91 (3H, d, J= 7.6 Hz), 8.14 (1H, s), 8.52 (1H,
s), 8.79 (1H, a)
MS (ES) m/z = 421 (MH+)
20 HPLC = 98%

Example 72: N-ethyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.23 (3H, t, J= 7.2 Hz), 1.42
25 (3H, t, J= 7.2 Hz), 1.56 (3H, s), 3.11 (2H, q, J= 7.2 Hz),
3.85 (2H, q, J= 7.2 Hz), 7.17 (1H, d, J= 4.4 Hz), 7.49-7.53
(2H, m), 7.58-7.66 (3H, m), 7.92-7.94 (2H, m), 8.01 (1H, d,
J= 7.6 Hz), 8.11 (1H, t, J= 1.6 Hz), 8.54 (1H, s), 8.82
30 (1H, d, J= 4.8 Hz)
MS (ES) m/z = 435 (MH+)
HPLC = 100%

Example 73: N-prop-2-ynyl-N-{3-[3-(benzoyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.43 (3H, t, J= 7.2 Hz), 2.48 (1H, t, J= 2.8 Hz), 3.27 (2H, q, J= 7.2 Hz), 4.54 (2H, d, J= 2.8 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.49-7.52 (2H, m), 7.58-7.66 (2H, m), 7.82 (1H, d, J= 8 Hz), 7.93 (2H, d, J= 6.8 Hz), 8.04 (1H, d, J= 8 Hz), 8.29 (1H, a), 8.54 (1H, s), 8.81 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 445 (MH⁺)

HPLC = 97%

Example 74: N-prop-2-ynyl-N-{3-[3-(benzoyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 2.53 (1H, t, J= 2.4 Hz), 3.12 (3H, s), 4.54 (2H, d, J= 2.4 Hz), 7.16 (1H, d, J= 4.8 Hz), 7.49-7.53 (2H, m), 7.58-7.60 (1H, m), 7.65 (1H, t, J= 8 Hz), 7.84-7.86 (1H, m), 7.92-7.94 (2H, m), 8.04 (1H, d, J= 8 Hz), 8.32 (1H, t, J= 2 Hz), 8.54 (1H, s), 8.82 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 431 (MH⁺)

HPLC = 97%

Example 75: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-2-phenylethene-sulfonamide

¹H NMR (400 MHz, CDCl₃): δ 3.35 (3H, s), 6.78 (1H, d, J= 15.5 Hz), 7.13 (1H, d, J= 4.6 Hz), 7.21 (1H, dd), 7.48-7.52 (6H, m), 7.6-7.63 (2H, m), 7.71 (1H, dd), 7.92-7.96 (1H, m), 8.06 (1H, dd), 8.13 (1H, m), 8.53 (1H, m), 8.8 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 501 (MH⁺)

HPLC = 96.98%

Example 76: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-
pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-2,2,2-
trifluoroethane-sulfonamide

¹H NMR (400 MHz, CDCl₃): δ 3.48 (3H, s), 3.87 (2H, c, J= 9.1 Hz), 7.16 (1H, d, J= 4.6 Hz), 7.21 (1H, dd), 7.65-7.67 (1H, m), 7.68 (1H, s), 7.72 (1H, dd), 7.98-8.02 (1H, m), 8.09 (1H, dd), 8.2 (1H, m), 8.7 (1H, s), 8.84 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 481 (MH⁺)

HPLC = 99.05%

Example 77: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-
pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-2-chlorobenzene-
sulfonamide

¹H NMR (400 MHz, CDCl₃): δ 3.47 (3H, s), 7.06 (1H, d, J= 4.6 Hz), 7.19-7.23 (1H, m), 7.32-7.39 (1H, m), 7.46-7.57 (4H, m), 7.7-7.72 (1H, m), 7.92-8 (3H, m), 8.09-8.11 (1H, m), 8.67 (1H, s), 8.8 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 510 (MH⁺)

HPLC = 99.81%

Example 78: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-
pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-3-
chlorobenzenesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 3.27 (3H, s), 7.11 (1H, d, J= 4.6 Hz), 7.19-7.61 (7H, m), 7.7-7.72 (1H, m), 7.85 (1H, m), 7.97-8.01 (1H, m), 8.09-8.11 (1H, m), 8.68 (1H, s), 8.81 (1H, d, J= 4.6 Hz)

44

MS (ES) m/z = 510 (MH⁺)

HPLC = 97.44%

5 **Example 79:** N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo [1,5-a]pyrimidin-7-yl]-phenyl}-4-chlorobenzenesulfonamide

10 ¹H NMR (400 MHz, CDCl₃): δ 3.25 (3H, s), 7.1 (1H, d, J= 4.6 Hz), 7.2-7.24 (1H, m), 7.33-7.37 (1H, m), 7.46-7.6 (5H, m), 7.72 (1H, dd), 7.85-7.87 (1H, m), 7.95-8 (1H, m), 8.09-8.11 (1H, m), 8.69 (1H, s). 8.82 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 510 (MH⁺)

HPLC = 99.69%

15 **Example 80:** N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,4-dichlorobenzene-sulfonamide

20 ¹H NMR (400 MHz, CDCl₃): δ 3.46 (3H, s), 7.08 (1H, d, J= 4.6 Hz), 7.21 (1H, dd), 7.33 (1H, dd), 7.46-7.59 (3H, m), 7.71 (1H, dd), 7.87-7.98 (3H, m), 8.09 (1H, dd), 8.67 (1H, s), 8.81 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 543 (MH⁺)

HPLC = 98.04%

25 **Example 81:** N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-3,4-dichlorobenzene-sulfonamide

30 ¹H NMR (400 MHz, CDCl₃): δ 3.27 (3H, s), 7.11 (1H, d, J= 4.6 Hz), 7.21 (1H, dd), 7.37-7.47 (2H, m), 7.56-7.62 (2H, m), 7.7-7.72 (2H, m), 7.86-7.88 (1H, m), 7.94-7.99 (1H, m), 8.09 (1H, dd), 8.67 (1H, s). 8.81 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 543 (MH⁺)

HPLC = 98.03%

5 **Example 82:** N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-cyanobenzene-sulfonamide

¹H NMR (400 MHz, CDCl₃): δ 3.41 (3H, s), 7.15 (1H, d, J= 4.6 Hz), 7.2 (1H, dd), 7.34-7.39 (1H, m), 7.53-7.59 (1H, m), 7.69-7.77 (3H, m), 7.83-7.87 (1H, m), 7.91-8.01 (3H, m), 8.1 (1H, dd), 8.63 (1H, s), 8.79 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 500 (MH⁺)

HPLC = 99.32%

15 **Example 83:** N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-3-cyanobenzene-sulfonamide

20 ¹H NMR (400 MHz, CDCl₃): δ 3.28 (3H, s), 7.13 (1H, d, J= 4.6 Hz), 7.19-7.22 (1H, m), 7.33-7.36 (1H, m), 7.56-7.72 (3H, m), 7.83-7.97 (5H, m), 8.09 (1H, d, J= 3.6 Hz), 8.66 (1H, s), 8.81 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 500 (MH⁺)

HPLC = 96.69%

25 **Example 84:** N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-4-cyanobenzene-sulfonamide

30 ¹H NMR (400 MHz, CDCl₃): δ 3.28 (3H, s), 7.12 (1H, d, J= 4.2 Hz), 7.2-7.32 (3H, m), 7.58 (1H, t, J= 8 Hz), 7.71-7.83 (4H, m), 7.91 (1H, a), 7.99 (1H, d, J= 7.6 Hz), 8.09 (1H, d, J= 3.3 Hz), 8.68 (1H, s), 8.83 (1H, d, J= 3.9 Hz)

~~45~~ 45

MS (ES) m/z = 500 (MH⁺)

HPLC = 97.9%

5 **Example 85:** N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-3-nitrobenzene-sulfonamide

¹H NMR (400 MHz, CDCl₃): δ 3.3 (3H, s), 7.12 (1H, d, J= 4.6 Hz), 7.22 (1H, dd), 7.38-7.43 (1H, m), 7.6 (1H, t, J= 7.9 Hz), 7.7-7.77 (2H, m), 7.86-7.97 (3H, m), 8.09 (1H, dd), 8.4-8.5 (2H, m), 8.6 (1H, s), 8.8 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 520 (MH⁺)

HPLC = 99.14%

15 **Example 86:** N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-4-nitrobenzene-sulfonamide

¹H NMR (400 MHz, CDCl₃): δ 3.3 (3H, s), 7.13 (1H, d, J= 4.6 Hz), 7.23 (1H, dd, J= 4.8 - 0.9 Hz), 7.32-7.37 (1H, m), 7.6 (1H, t, J= 7.9 Hz), 7.73 (1H, dd, J= 4.8 - 3.6 Hz), 7.82 (2H, d, J= 9.1 Hz), 7.9 (1H, m), 7.95-7.99 (1H, m), 8.07 (1H, dd), 8.36 (2H, d, J= 9.1 Hz), 8.66 (1H, s), 8.83 (1H, d, J= 4.6 Hz)

25 MS (ES) m/z = 520 (MH⁺)

HPLC = 96.18%

30 **Example 87:** N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-thiophene-sulfonamide

¹H NMR (400 MHz, CDCl₃): δ 3.35 (3H, s), 7.13-7.18 (2H, d), 7.23-7.31 (1H, m), 7.39-7.46 (2H, m), 7.58-7.68 (2H, m),

7.74-7.77 (1H, m), 7.93 (1H, d, $J = 1.5$ Hz), 8.06 (1H, dd, $J = 7.9 - 1.2$ Hz), 8.14 (1H, m), 8.72 (1H, s). 8.85 (1H, d, $J = 4.3$ Hz)

MS (ES) $m/z = 481$ (MH⁺)

5 HPLC = 98.82%

Example 88: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-5-methyl-4-isoxazolylsulfonamide

10

¹H NMR (400 MHz, CDCl₃): δ 2.3 (3H, s), 3.29 (3H, s), 7.11 (1H, d, $J = 4.2$ Hz), 7.21 (1H, dd, $J = 5.2 - 3.9$ Hz), 7.51-7.55 (1H, m), 7.63 (1H, t, $J = 7.9$ Hz), 7.71 (1H, dd, $J = 5.2 - 1.2$ Hz), 7.91-7.94 (2H, m), 8.07 (1H, dd), 8.32 (1H, d, $J = 0.6$ Hz). 8.7 (1H, s). 8.82 (1H, d, $J = 4.2$ Hz)

15

MS (ES) $m/z = 480$ (MH⁺)

HPLC = 96.78%

Example 89: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-trifluoromethyl-5-methyl-3-furylsulfonamide

20

¹H NMR (400 MHz, CDCl₃): δ 2.23 (3H, s), 3.3 (3H, s), 7.11 (1H, d, $J = 4.6$ Hz), 7.2-7.24 (1H, m), 7.52-7.66 (2H, m), 7.72 (1H, dd, $J = 4.9 - 1.2$ Hz), 7.91-7.95 (2H, m), 8.07 (1H, dd), 8.67 (1H, s), 8.82 (1H, d, $J = 4.2$ Hz)

25

MS (ES) $m/z = 547$ (MH⁺)

HPLC = 98.88%

Example 90: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-6-(morpholin-4-yl)-3-pyridylsulfonamide

30

¹H NMR (400 MHz, CDCl₃): δ 3.24 (3H, s), 3.62-3.67 (4H, m), 3.78-3.82 (4H, m), 6.55 (1H, d, J= 9.1 Hz), 7.14 (1H, d, J= 4.2 Hz), 7.21 (1H, dd, J= 4.9 - 3.6 Hz), 7.36-7.4 (1H, m), 7.53-7.6 (2H, m), 7.72 (1H, dd, J= 4.9 - 1.2 Hz), 7.93-8.01 (2H, m), 8.1-8.12 (1H, m), 8.39 (1H, d, J= 2.4 Hz), 8.69 (1H, s), 8.81 (1H, d, J= 4.6 Hz)
MS (ES) m/z = 561 (MH+)
HPLC = 98.7%

Example 91: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,4-dimethyl-5-thiazolylsulfonamide

¹H NMR (400 MHz, CDCl₃): δ 2.22 (3H, s), 2.69 (3H, s), 3.35 (3H, s), 7.11 (1H, d, J= 4.6 Hz), 7.2 (1H, dd), 7.43-7.47 (1H, m), 7.59 (1H, m), 7.71 (1H, dd), 7.93-7.94 (1H, m), 7.97-8.02 (1H, m), 8.09 (1H, dd, J= 3.7 - 1.1 Hz), 8.68 (1H, s), 8.81 (1H, d, J= 4.6 Hz)
MS (ES) m/z = 510 (MH+)
HPLC = 99.18%

Example 92: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-cyclopropyl-sulfonamide

¹H NMR (400 MHz, CDCl₃): δ 0.95-1.06 (2H, m), 1.09-1.18 (2H, m), 2.4-2.51 (1H, m), 3.44 (3H, s), 7.16 (1H, d, J= 4.6 Hz), 7.19-7.23 (1H, m), 7.58-7.73 (3H, m), 7.96 (1H, m), 8.11 (1H, m), 8.16 (1H, m), 8.71 (1H, s), 8.82 (1H, d, J= 4.2 Hz)
MS (ES) m/z = 439 (MH+)
HPLC = 96.7%

Example 93: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-benzylsulfonamide

¹H NMR (400 MHz, CDCl₃): δ 3.21 (3H, s), 4.39 (2H, s), 7.1 (1H, d, J= 4.6 Hz), 7.2-7.24 (1H, m), 7.33-7.47 (6H, m), 7.54-7.6 (1H, m), 7.71 (1H, d, J= 4.9 Hz), 7.87-7.92 (2H, m), 8.12 (1H, d, J= 3.3 Hz), 8.74 (1H, s), 8.83 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 489 (MH⁺)

HPLC = 97.95%

Example 94: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-vinylsulfonamide

¹H NMR (400 MHz, CDCl₃): δ 3.32 (3H, s), 6.08 (1H, d, J= 9.7 Hz), 6.26 (1H, d, J= 16.4 Hz), 6.51 (1H, dd, J= 16.4 - 9.7 Hz), 7.15 (1H, d, J= 4.2 Hz), 7.2 (1H, dd, J= 4.8 - 3.9 Hz), 7.53-7.64 (2H, m), 7.7 (1H, dd, J= 4.8 - 1.2 Hz), 7.94-7.98 (1H, m), 8.06-8.11 (2H, m)

MS (ES) m/z = 425 (MH⁺)

HPLC = 97.53%

Example 95: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-3,5-dimethyl-4-isoxazolylsulfonamide

¹H NMR (400 MHz, CDCl₃): δ 2.12 (3H, s), 2.33 (3H, s), 3.31 (3H, s), 7.1 (1H, d, J= 4.5 Hz), 7.19-7.23 (1H, m), 7.52-7.66 (2H, m), 7.71 (1H, d, J= 5.5 Hz), 7.93-7.96 (2H, m), 8.07 (1H, d, J= 3.6 Hz), 8.69 (1H, s), 8.82 (1H, d, J= 4.2 Hz)

MS (ES) m/z = 494 (MH⁺)

HPLC = 99.17%

~~20~~ 47

Example 96: N-methyl-N-(3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl)-1,3,5-trimethyl-4-pyrazolylsulfonamide

¹H NMR (400 MHz, CDCl₃): δ 2.09 (3H, s), 2.1 (3H, s), 3.24 (3H, s), 3.7 (3H, s), 7.1 (1H, d, J= 4.2 Hz), 7.2 (1H, dd, J= 4.8 - 3.6 Hz), 7.45-7.59 (2H, m), 7.71 (1H, dd), 7.9-7.98 (2H, m), 8.09-8.11 (1H, m), 8.67 (1H, s), 8.8 (1H, d, J= 4.2 Hz)

MS (ES) m/z = 507 (MH⁺)

HPLC = 94.68%

Example 97: N-methyl-N-(3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl)-propanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.06 (3H, t, J= 7.5 Hz), 1.92-1.97 (2H, m), 3.02-3.08 (2H, m), 3.43 (3H, s), 7.16 (1H, d, J= 4.2 Hz), 7.19-7.23 (1H, m), 7.62-7.64 (2H, m), 7.72 (1H, m), 7.93-7.97 (1H, m), 8.11-8.14 (2H, m), 8.71 (1H, s), 8.83 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 441 (MH⁺)

HPLC = 97.75%

Example 98: N-methyl-N-(3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl)-butanesulfonamide

¹H NMR (400 MHz, CDCl₃): δ 0.93 (3H, t, J= 7.5 Hz), 1.44 (2H, m), 1.77-1.89 (2H, m), 3.04-3.11 (2H, m), 3.43 (3H, s), 7.16 (1H, d, J= 4.6 Hz), 7.2 (1H, dd, J= 5.2 - 3.9 Hz), 7.61-7.64 (2H, m), 7.71 (1H, dd, J= 5.2 - 1.2 Hz), 7.91-7.96 (1H, m), 8.1 (1H, dd, J= 3.9 - 1.2 Hz), 8.14 (1H, m), 8.7 (1H, s), 8.82 (1H, d, J= 4.3 Hz)

MS (ES) m/z = 455 (MH⁺)

HPLC = 98.54%

Example 99: N-methyl-N-{3-[3-(thiophene-2-carbonyl)-
pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-cyclopentylmethane-
sulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.23-1.34 (2H, m), 1.56-1.66
(4H, m), 1.95-2.03 (2H, m), 2.32-2.44 (1H, m), 3.08 (2H, d,
J= 7 Hz), 3.42 (3H, s), 7.16 (1H, d, J= 4.2 Hz), 7.2 (1H,
dd, J= 4.9 - 3.9 Hz), 7.61-7.63 (2H, m), 7.71 (1H, dd, J=
4.9 - 1.2 Hz), 7.91-7.96 (1H, m), 8.09-8.14 (2H, m), 8.7 (1H,
s), 8.82 (1H, d, J= 4.2 Hz)

MS (ES) m/z = 481 (MH⁺)

HPLC = 96.43%

Example 100: N-{3-[3-(5-methyl-[1,2,4]oxadiazol-3-yl)-
pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methane-sulfonamide

¹H NMR (400 MHz, CDCl₃): δ 2.71 (3H, s), 3.12 (3H, s), 7.08
(1H, d, J= 4.4 Hz), 7.1 (1H, a), 7.43-7.46 (1H, m), 7.57
(1H, t, J= 7.6 Hz), 7.80-7.83 (1H, m), 7.95 (1H, t, J= 2
Hz), 8.69 (1H, s), 8.8 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 371 (MH⁺)

HPLC = 94%

Example 101: N-ethyl-N-{3-[3-(5-methyl-[1,2,4]oxadiazol-3-
yl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methane-
sulfonamide

¹H NMR (400 MHz, CDCl₃): δ 1.21 (3H, t, J= 7.2 Hz), 2.69
(3H, s), 2.95 (3H, s), 3.81 (2H, q, J= 7.2 Hz), 7.1 (1H, d,
J= 4.8 Hz), 7.56-7.58 (1H, m), 7.64 (1H, t, J= 8 Hz), 8.04

(1H, d, J= 8 Hz), 8.09 (1H, t, J= 2 Hz), 8.69 (1H, s), 8.817
(1H, d, J= 4.8 Hz)

MS (ES) m/z = 399 (MH⁺)

HPLC = 94%

5

Example 102: 5 mg tablets

Compound of Example 2	5.0 mg
Colloidal silicon dioxide	0.6 mg
Croscarmellose sodium	12.0 mg
Talc	4.0 mg
Magnesium stearate	1.5 mg
Polysorbate 80	1.0 mg
Lactose	75.0 mg
Hydroxypropyl methylcellulose	3.0 mg
Polyethylene glycol 4000	0.5 mg
Titanium dioxide E171	1.5 mg
Microcrystalline cellulose q.s. to	125.0 mg

Example 103: 10 mg capsules

10

Compound of Example 2	10.0 mg
Colloidal silicon dioxide	0.6 mg
Crospovidone	12.0 mg
Talc	4.0 mg
Magnesium stearate	1.5 mg
Lauryl sulfate sodium	1.5 mg
Lactose	77.0 mg
Gelatin	28.5 mg
Titanium dioxide E171	1.5 mg
Indigotin E132	0.02 mg
Microcrystalline cellulose q.s. to	155.0 mg

Example 104: oral drops

Compound of Example 2	0.5	g
Propylene glycol	10.0	g
Glycerin	5.0	g
Saccharin sodium	0.1	g
Polysorbate 80	1.0	g
Lemon flavor	0.2	g
Ethanol	25.0	mL
Purified water q.s. to	100.0	mL

Example 105: 2.5 mg tablets

5

Compound of Example 16	2.5	mg
Colloidal silicon dioxide	0.6	mg
Croscarmellose sodium	12.0	mg
Talc	4.0	mg
Magnesium stearate	1.5	mg
Polysorbate 80	1.0	mg
Lactose	75.0	mg
Hydroxypropyl methylcellulose	3.0	mg
Polyethylene glycol 4000	0.5	mg
Titanium dioxide E171	1.5	mg
Microcrystalline cellulose q.s. to	125.0	mg

Example 106: 5 mg capsules

Compound of Example 16	5.0	mg
Colloidal silicon dioxide	0.6	mg
Crospovidone	12.0	mg
Talc	4.0	mg
Magnesium stearate	1.5	mg
Lauryl sulfate sodium	1.5	mg
Lactose	77.0	mg

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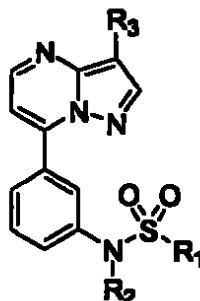
Gelatin	28.5	mg
Titanium dioxide E171	1.5	mg
Indigotin E132	0.02	mg
Microcrystalline q.s.to	155.0	mg

Example 107: Oral drops

Compound of Example 16	0.25	g
Propylene glycol	10.0	g
Glycerin	5.0	g
Saccharin sodium	0.1	g
Polysorbate 80	1.0	g
Lemon flavor	0.2	g
Ethanol	25.0	mL
Purified q.s. to	100.0	mL

CLAIMS

1) - A compound of formula (I):



(I)

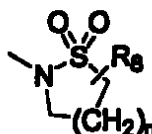
as well as pharmaceutically acceptable salts thereof;
wherein

R₁ is selected from the group consisting of alkyl(C₁-C₆),
alkenyl(C₂-C₆), ω,ω,ω-trifluoroalkyl(C₁-C₆), cycloalkyl(C₃-
C₆), cycloalkyl(C₃-C₆)alkyl(C₁-C₆), -O-alkyl(C₁-C₆), -NH-
alkyl(C₁-C₆), -N(dialkyl(C₁-C₆)), alkyl(C₁-C₆)-O-alkyl(C₁-
C₆), alkyl(C₁-C₆)-NH-alkyl(C₁-C₆), alkyl(C₁-C₆)-N(dialkyl(C₁-
C₆)), phenyl, monosubstituted phenyl, disubstituted phenyl,
phenylalkyl(C₁-C₆), phenylalkenyl(C₂-C₆), furyl, substituted
furyl, isoxazolyl, substituted isoxazolyl, pyrazolyl,
substituted pyrazolyl, thienyl, substituted thienyl,
thiazolyl, substituted thiazolyl, pyridyl and substituted
pyridyl;

R₂ is selected from the group consisting of hydrogen,
alkyl(C₁-C₆), alkenyl(C₂-C₆), alkynyl(C₂-C₆) and
cycloalkyl(C₃-C₆);

or else

R₁ and R₂ form a cycle having the structure:



wherein n is an integer 1, 2 or 3;

150

5 R_3 is selected from the group consisting of hydrogen, halogen, alkyl(C_1-C_6), cycloalkyl(C_3-C_6), alkenyl(C_2-C_6), alkynyl(C_2-C_6), -O-alkyl(C_1-C_6), halo-alkyl(C_1-C_6), -CN, - SO_2-R_4 , -NH- R_4 , -NR $_4$ R $_5$, -COR $_6$, -CO-NHR $_6$, -COOR $_6$, -C(NR $_7$)R $_6$, phenyl, substituted phenyl, heteroaryl and substituted heteroaryl;

R_4 and R_5 are independently selected from the group consisting of alkyl(C_1-C_6), cycloalkyl(C_3-C_6), aryl and heteroaryl;

10 R_6 is selected from the group consisting of hydrogen, alkyl(C_1-C_6), alkenyl(C_2-C_6), alkynyl(C_2-C_6), cycloalkyl(C_3-C_6), phenyl, substituted phenyl, furyl, substituted furyl, thienyl, substituted thienyl, thiazolyl, substituted thiazolyl, pyridyl and substituted pyridyl;

15 R_7 is selected from the group consisting of alkyl(C_1-C_6), cycloalkyl(C_3-C_6), -OH, -O-alkyl(C_1-C_6), alkyl(C_1-C_6)-O-alkyl(C_1-C_6), alkyl(C_1-C_6)-NH-alkyl(C_1-C_6), alkyl(C_1-C_6)-N(dialkyl(C_1-C_6)), phenyl, monosubstituted phenyl, furyl, thienyl, thiazolyl and pyridyl; and

20 R_8 is selected from the group consisting of hydrogen, alkyl(C_1-C_6), cycloalkyl(C_3-C_6), aryl and substituted or unsubstituted heteroaryl;

with the proviso that simultaneously:

R_1 may not be p-tolyl and R_2 methyl and R_3 benzoyl; and

25 R_1 may not be p-tolyl and R_2 ethyl and R_3 furyl-2-carbonyl.

2) - A compound according to claim 1, wherein R_1 and R_2 are independently as defined in formula (I) and R_3 is a cyano group.

30

3) - A compound according to claim 2, wherein R_1 is selected from the group consisting of methyl, ethyl, n-propyl, i-propyl, n-butyl, phenyl and 4-methoxyphenyl; and

R₂ is selected from the group consisting of methyl, ethyl, n-propyl, i-propyl, n-butyl, cyclopropyl and 2-propynyl.

5 4) - A compound according to claim 2, wherein R₁ and R₂ jointly form a 1,3-propylene group.

5) - A compound according to claim 1, wherein R₁ and R₂ are independently as defined in formula (I) and R₃ is a thiophene-2-carbonyl group.

10

6) - A compound according to claim 5, wherein R₁ is selected from the group consisting of methyl, ethyl, n-propyl, i-propyl, n-butyl, 2-phenylethenyl, 2,2,2-trifluoroethyl, phenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-methoxyphenyl, 3-nitrophenyl, 4-nitrophenyl, 2-thienyl, 5-methyl-4-isoxazolyl, 5-methyl-2-trifluoromethyl-3-furyl, 4-(4-morpholinyl)-3-pyridyl, 2,4-dimethyl-5-thiazolyl, cyclopropyl, benzyl, vinyl, 3,5-dimethyl-4-isoxazolyl, 1,3,5-trimethyl-4-pyrazolyl and cyclopentylmethyl; and R₂ is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, i-propyl, n-butyl, cyclopropyl and 2-propynyl.

25

7) - A compound according to claim 5 wherein R₁ and R₂ jointly form a 1,3-propylene group.

8) - A compound according to claim 1, wherein R₁ and R₂ are independently as defined in formula (I) and R₃ is a benzoyl group.

30

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9) - A compound according to claim 8 wherein R_1 is selected from the group consisting of methyl and ethyl; and R_2 is selected from the group consisting of methyl, ethyl and 2-propinyl.

5

10) - A compound according to claim 1, wherein R_1 and R_2 are independently as defined in formula (I) and R_3 is a 4-fluorobenzoyl group.

10

11) - A compound according to claim 10 wherein R_1 is selected from the group consisting of methyl and ethyl; and R_2 is selected from the group consisting of methyl, ethyl and 2-propinyl.

15

12) - A compound according to claim 1, wherein R_1 and R_2 are independently as defined in formula (I) and R_3 is a 4-methylbenzoyl group.

20

13) - A compound according to claim 12 wherein R_1 is selected from the group consisting of methyl and ethyl; and R_2 is selected from the group consisting of methyl, ethyl and 2-propinyl.

25

14) - A compound according to claim 1, wherein R_1 and R_2 are independently as defined in formula (I) and R_3 is a 4-methoxybenzoyl group.

30

15) - A compound according to claim 14 wherein R_1 is selected from the group consisting of methyl and ethyl; and R_2 is selected from the group consisting of methyl, ethyl and 2-propinyl.

16) - A compound according to claim 1, wherein R_1 and R_2 are independently as defined in formula (I) and R_3 is a 5-methyl-1,2,4,-oxadiazol-3-yl group.

5 17) - A compound according to claim 16 wherein R_1 is methyl and R_2 is selected from the group consisting of hydrogen and ethyl.

10 18) - A compound according to claim 1, wherein R_1 and R_2 are independently as defined in formula (I) and R_3 is a pyridyl-2-carbonyl group.

15 19) - A compound according to claim 18 wherein R_1 is selected from the group consisting of methyl and ethyl; and R_2 is selected from the group consisting of methyl, ethyl and 2-propinyl.

20 20) - A compound according to claim 1, wherein R_1 and R_2 are independently as defined in formula (I) and R_3 is a pyridyl-4-carbonyl group.

25 21) - A compound according to claim 20 wherein R_1 is selected from the group consisting of methyl and ethyl; and R_2 is selected from the group consisting of methyl, ethyl and 2-propinyl.

30 22) - A compound according to claims 2 and 3, wherein said compound is selected from the group consisting of:
N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-methanesulfonamide;
N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-methanesulfonamide;

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- N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-benzenesulfonamide;
- N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-benzenesulfonamide;
- 5 N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-prop-2-ynyl-methanesulfonamide;
- N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-propyl-ethanesulfonamide;
- 10 N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-ethanesulfonamide;
- N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-prop-2-ynyl-propane-2-sulfonamide;
- N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-ethanesulfonamide;
- 15 N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-butyl-ethanesulfonamide;
- N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-methyl-2-propanesulfonamide;
- 20 N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-ethyl-2-propanesulfonamide;
- N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-butyl-2-propanesulfonamide;
- N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-propyl-2-propanesulfonamide; and
- 25 N-[3-(3-cyano-pyrazolo[1,5-a]pyrimidin-7-yl)-phenyl]-N-prop-2-ynyl-ethanesulfonamide.

23) - A compound according to claim 4 wherein said compound is 7-(3-(2-isothiazolydiny1-1,1-dioxide)-phenyl)-3-cyano-pyrazolo[1,5-a]pyrimidine.

30

24) - A compound according to claims 5 and 6, wherein said compound is selected from the group consisting of:

- N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
5 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-benzenesulfonamide;
N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-benzenesulfonamide;
N-prop-2-ynyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
10 N-propyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
15 N-prop-2-ynyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
N-butyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
20 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide;
N-ethyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide;
25 N-propyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide;
N-butyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-propanesulfonamide;
N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2-phenylethanesulfonamide;
30 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-2,2,2-trifluoroethanesulfonamide;

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N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-2-chlorobenzenesulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-3-chlorobenzenesulfonamide;

5 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-4-chlorobenzenesulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-2,4-dichlorobenzenesulfonamide;

10 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-3,4-dichlorobenzenesulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-2-cyano-benzenesulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-3-cyano-benzenesulfonamide;

15 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-4-cyano-benzenesulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-3-nitro-benzenesulfonamide;

20 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-4-nitro-benzenesulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]
a]pyrimidin-7-yl]-phenyl}-2-thiophenesulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-5-methyl-4-isoxazolyl-sulfonamide;

25 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-2-trifluoromethyl-5-methyl-3-furyl-
sulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-6-(morpholin-4-yl)-3-pyridyl-
30 sulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-2,4-dimethyl-5-thiazolyl-
sulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-cyclopropylsulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-benzylsulfonamide;

5 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-vinylsulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-3,5-dimethyl-4-isoxazolyl-sulfonamide;

10 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-1,3,5-trimethyl-4-pyrazolyl-sulfonamide;

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-propanesulfonamide;

15 N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-butanesulfonamide; and

N-methyl-N-{3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-cyclopentylmethanesulfonamide.

20 25) - A compound according to claim 7 wherein said compound is 7-(3-(2-isothiazolyldinyl-1,1-dioxide)-phenyl)-3-(thiophene-2-carbonyl)-pyrazolo[1,5-a]pyrimidine.

25 26) - A compound according to claims 8 and 9 wherein said compound is selected from the group consisting of:

N-methyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-ethyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

30 N-methyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-ethyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

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N-prop-2-ynyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide; and
N-prop-2-ynyl-N-{3-[3-(benzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide.

5

27) - A compound according to claims 10 and 11 wherein said compound is selected from the group consisting of:

N-methyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

10 N-ethyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

15 N-ethyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-prop-2-ynyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide; and
N-prop-2-ynyl-N-{3-[3-(fluorobenzene-4-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide.

20

28) - A compound according to claims 12 and 13 wherein said compound is selected from the group consisting of:

N-methyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

25 N-ethyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

30 N-ethyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-prop-2-ynyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide; and

N-prop-2-ynyl-N-{3-[3-(4-methylbenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide.

- 29) - A compound according to claims 14 and 15 wherein
5 said compound is selected from the group consisting of:
N-methyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
N-ethyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
10 N-methyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
N-ethyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide;
N-prop-2-ynyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-ethanesulfonamide; and
15 N-prop-2-ynyl-N-{3-[3-(4-methoxybenzoyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide.

- 30) - A compound according to claims 16 and 17 wherein
20 said compound is selected from the group consisting of:
N-{3-[3-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide; and
N-ethyl-N-{3-[3-(5-methyl-[1,2,4]oxadiazol-3-yl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide.

- 25 31) - A compound according to claims 18 and 19 wherein
said compound is selected from the group consisting of:
N-methyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
30 N-ethyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;
N-prop-2-ynyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-methyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-ethyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-ethanesulfonamide; and

5 N-prop-2-ynyl-N-{3-[3-(pyridin-2-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-ethanesulfonamide.

32) - A compound according to claims 20 and 21 wherein
said compound is selected from the group consisting of:

10 N-methyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-methanesulfonamide;

N-ethyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-methanesulfonamide;

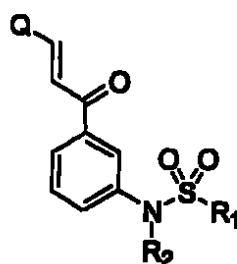
15 N-methyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-ethyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-ethanesulfonamide;

N-prop-2-ynyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-ethanesulfonamide; and

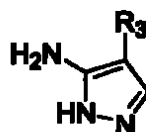
20 N-prop-2-ynyl-N-{3-[3-(pyridin-4-carbonyl)-pyrazolo[1,5-a]
pyrimidin-7-yl]-phenyl}-methanesulfonamide.

33) - A process for preparing a compound of formula
(I) or a pharmaceutically acceptable salt thereof,
25 according to claim 1, comprising reacting intermediate
(II):



(II)

wherein R_1 and R_2 are as defined in (I) and Q is an appropriate leaving group selected from the group consisting of N(dialkyl(C_1-C_6)), alkylthio(C_1-C_6) and alkoxy(C_1-C_6), with intermediate (III):



(III)

wherein R_3 is as defined in (I) and alternatively, treatment of the compounds of claim 1, in the form of free base, with an acid to form a salt thereof.

34) - A process according to claim 33, comprising utilizing the intermediate of formula (II) where Q is selected from the group consisting of dimethylamino, methylthio and methoxy.

35)- A method for treating or preventing diseases associated with $GABA_A$ receptor modulation in a mammal which comprises administering to said mammal an effective amount of a compound of claim 1.

36) - A method for treating or preventing diseases associated with α_1 - $GABA_A$ receptor modulation in a mammal which comprises administering to said mammal an effective amount of a compound of claim 1.

37)- A method for treating or preventing diseases associated with α_2 - $GABA_A$ receptor modulation in a mammal

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which comprises administering to said mammal an effective amount of a compound of claim 1.

5 38) - A method for treating or preventing anxiety in a mammal which comprises administering to said mammal an effective amount of a compound of claim 1.

10 39) - A method for treating or preventing epilepsy in a mammal which comprises administering to said mammal an effective amount of a compound of claim 1.

C 40) - A method for treating or preventing sleep disorders in a mammal which comprises administering to said mammal an effective amount of a compound of claim 1.

15 41) - A method for treating or preventing insomnia in a mammal which comprises administering to said mammal an effective amount of a compound of claim 1.

20 42) - A method for inducing sedation-hypnosis in a mammal which comprises administering to said mammal an effective amount of a compound of claim 1.

O 43) - A method for inducing anesthesia in a mammal 25 which comprises administering to said mammal an effective amount of a compound of claim 1.

30 44) - A method for modulating the necessary time to induce sleep and its duration in a mammal which comprises administering to said mammal an effective amount of a compound of claim 1.

45) - A method for inducing muscle relaxation in a mammal which comprises administering to said mammal an effective amount of a compound of claim 1.

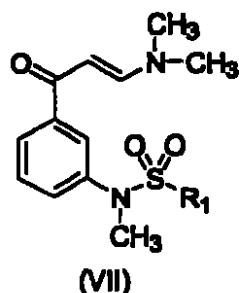
5 46) - A composition comprising a compound of claim 1 in association with a therapeutically inert carrier.

 47) - The use of a compound of claim 1 for preparing a medicament for treating or preventing diseases associated
10 with GABA_A receptor modulation.

 48) - The use of claim 47 wherein the diseases are associated with α_1 -GABA_A or α_2 -GABA_A receptor modulation.

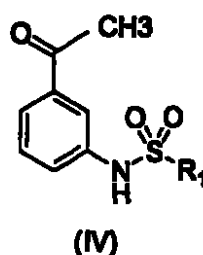
15 49) - The use of a compound of claim 1 for preparing a medicament for treating or preventing anxiety, epilepsy, sleep disorders, insomnia, for inducing sedation-hypnosis, anesthesia or muscle relaxation or for modulating the necessary time to include sleep and its duration.

20 50) - A process for preparing the intermediate of formula (VII):



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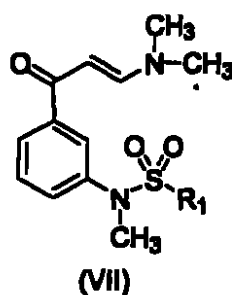
wherein R₁ is as described in (I), characterized by the reaction of the intermediate of formula (IV):



wherein R_1 is as described above, with N,N-dimethylformamide dimethyl acetal.

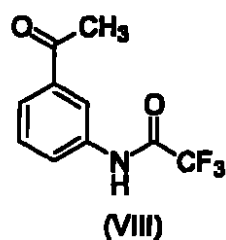
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51) - A process for preparing the intermediate of formula (VII):



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wherein R_1 is as described in (I), characterized by the reaction of N-(3-acetylphenyl)-2,2,2-trifluoroacetamide (VIII):



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and N,N-dimethylformamide dimethyl acetal, followed by the formation of sulfonamide by reaction with the corresponding sulfonic acid chloride.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/008208

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D487/04 A61K31/505 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GEORGE C F P: "Pyrazolopyrimidines" LANCET, XX, XX, vol. 358, no. 9293, 10 November 2001 (2001-11-10), pages 1623-1626, XP004322796 ISSN: 0140-6736 cited in the application p. 1624; figure 2 on the same page	1-51
A	US 4 654 347 A (ALBRIGHT JAY D ET AL) 31 March 1987 (1987-03-31) cited in the application claim 1; column 3, lines 38-47	1-51

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"S" document member of the same patent family

Date of the actual completion of the international search

22 November 2004

Date of mailing of the international search report

06/12/2004

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Wolf, C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2004/008208

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 35-45 in respect of industrial applicability
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 35-45 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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PCT

(10) Número de Publicación Internacional
WO 2005/014597 A1

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A61K 31/519, A61P 25/00
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(81) Estados Designados (a menos que se indique lo
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disponible): AE, AG, AL, AM, AT, AU, AZ, BA, BB,
BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ,
DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HY, ID, IL, IN, IS, JP, KE, KG, KP, KR,
KZ, LC, LK, LR, LS, LT, LU, LV, MAMD, MG, MK,
MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO,
RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT,
TZ, UAM, UG, UZ, VN, YU, ZA, ZM, ZW.

(84) Estados Designados (a menos que se indique lo
contrario, para todo tipo de protección regional
disponible): ARIPO (GH, GM, KE, LS, MW, MZ, SD,
SL, SZ, TZ, UG, ZM, ZW), Euroasiática (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), Europea (AT, BE,
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR,
IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI (BF, BJ,
CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG).

Publicado:

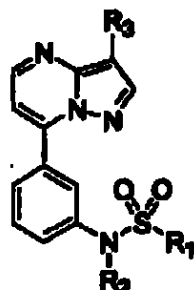
— con el informe de búsqueda internacional.

— antes del vencimiento del límite de tiempo para
corregir las reivindicaciones y a ser republicada en
el evento de recibir las correcciones.

Para códigos de dos letras y otras abreviaciones, referirse a
las "Notas de guía sobre Códigos y Abreviaturas" que
aparecen al comienzo de cada edición de la Gaceta del PCT

(54) Título: N-[3-(3-SUSTITUIDO-PIRAZOLO[1,5-a]PIRIMIDIN-7-IL)FENIL]-SULFONAMIDAS
COMPOSICIONES Y METODOS RELACIONADOS CON LAS MISMAS

Y



(57) Resumen: La presente invención se relaciona con compuestos de Fórmula (I):
en donde R₁, R₂ y R₃ son como se definen en las reivindicaciones. Los compuestos
tienen afinidad específica por el receptor GABA_A y por lo tanto son útiles en el
tratamiento y prevención de enfermedades moduladas por los receptores de α₁- y α₂-
GABA_A.

**N- [3- (3-SUSTITUIDAS-PIRAZOLO [1,5-a] PIRIMIDIN-7-IL) -FENIL] -
SULFONAMIDAS Y COMPOSICIONES Y MÉTODOS RELACIONADOS**

5 Sector de la técnica

Esta invención se encuadra en el sector técnico de agentes con afinidad sobre el receptor GABA-A, más concretamente en el relativo a las pirazolo[1,5-a]pirimidinas.

10

Estado de la técnica

15

El receptor GABA-A (ácido gama-aminobutírico_A) es una proteína de estructura pentamérica que forma un canal iónico de membrana. Está implicado en la regulación de la sedación, la ansiedad, la tensión muscular, la actividad epileptogénica y las funciones de la memoria. Estas acciones se deben a subunidades definidas de dicho receptor, principalmente la $\alpha 1$ y la $\alpha 2$.

20

La sedación es modulada por la subunidad $\alpha 1$. Así, la acción sedante e hipnótica del Zolpidem es mediada por los receptores $\alpha 1$ *in vivo*, por los que tiene gran afinidad. Análogamente, la acción hipnótica del Zaleplón está
25 mediada también por los receptores $\alpha 1$.

La acción ansiolítica del Diazepam está mediada por el aumento de la transmisión GABAérgica en una población de neuronas que expresan a los receptores $\alpha 2$. Esto indica que

los receptores $\alpha 2$ son dianas altamente específicas para el tratamiento de la ansiedad.

5 La relajación muscular en el Diazepam está mediada principalmente por los receptores $\alpha 2$, dado que estos receptores exhiben una expresión altamente específica en la médula espinal.

10 El efecto anticonvulsivo del Diazepam se debe parcialmente a los receptores $\alpha 1$. En el Diazepam, compuest que disminuye la memoria, la amnesia anterógrada está mediada por los receptores $\alpha 1$.

15 El receptor GABA-A y sus subunidades $\alpha 1$ y $\alpha 2$ han sido revisados ampliamente por H. Möhler et al., J. Pharmacol. Exp. Ther., 300, 2-8, 2002; H. Möhler et al., Curr. Opin. Pharmacol., 1, 22-25, 2001; U. Rudolph et al., Nature, 401, 796-800, 1999; y D. J. Nutt et al., Br. J. Psychiatry, 179, 390-396, 2001.

20 El Diazepam y otras benzodiazepinas clásicas se usan ampliamente como ansiolíticos, hipnóticos, anticonvulsivos y relajantes musculares, con efectos secundarios que incluyen la amnesia anterógrada, la disminución de la actividad motora y la potenciación de los efectos del etanol.

25

30 En este contexto, los compuestos de la presente invención son ligandos de las subunidades $\alpha 1$ y $\alpha 2$ del receptor GABA-A con aplicación clínica en las alteraciones del sueño,

preferentemente el insomnio, en la ansiedad ~~y~~ en la epilepsia. 62

El insomnio es una enfermedad altamente prevalente. En su forma crónica afecta a un 10% de la población, alcanzando un 30% cuando además se contabiliza el insomnio transitorio. Se considera insomnio la dificultad en quedarse dormido o en mantener el sueño, asociándose con importantes efectos al día siguiente como cansancio, falta de energía, baja concentración e irritabilidad. El impacto social y sanitario de esta dolencia es importante con evidentes repercusiones socioeconómicas.

Los tratamientos farmacológicos utilizados fueron en primer lugar los barbitúricos y el hidrato de cloral, presentando numerosos efectos adversos reconocidos (toxicidad por sobredosis, inducción metabólica, dependencia y tolerancia elevadas) además de afectar la arquitectura del sueño disminuyendo sobre todo la duración y el número de episodios de sueño REM. Posteriormente, las benzodiazepinas supusieron un importante avance terapéutico, con menor toxicidad pero siguieron presentando problemas graves de dependencia, relajación muscular, amnesia y fenómenos de rebote del insomnio al retirar la medicación.

La última aproximación terapéutica reconocida ha sido la introducción de los compuestos hipnóticos no-benzodiazepínicos como las pirrolo[3,4-b]pirazinas (Zopiclone), las imidazo[1,2-a]piridinas (Zolpidem) y por último las pirazolo[1,5-a]pirimidinas (Zaleplón).

Posteriormente, han entrado en desarrollo dos nuevas pirazolo[1,5-a]pirimidinas, el Indiplón y el Ocina-plón, este último con acción más bien ansiolítica. Todos estos compuestos presentan una rápida inducción del sueño, tienen menores efectos al día después, menor potencial de abuso y menor fenómeno de rebote que las benzodiazepinas. El mecanismo de acción de estos compuestos es la activación alostérica del receptor GABA-A mediante su unión al sitio de unión de las benzodiazepinas (C. F. P. George, The Lancet, 358, 1623-1626, 2001). En tanto que las benzodiazepinas son ligandos inespecíficos en el sitio de unión del receptor GABA-A, Zolpidem y Zaleplón muestran una mayor selectividad por la subunidad $\alpha 1$. A pesar de ello siguen afectando la arquitectura del sueño y en tratamientos prolongados pueden inducir dependencia.

En los documentos de patente US 4.626.538 (Zaleplón), US 4.654.347, US 6.399.621 (Indiplón) y EP 129.847 (Ocina-plón) se proponen pirazolo[1,5-a]pirimidinas hipnóticas.

La investigación de nuevos compuestos activos para el tratamiento del insomnio responde a una necesidad sanitaria primordial porque incluso los hipnóticos de reciente introducción en terapéutica siguen afectando la arquitectura del sueño y en tratamientos prolongados pueden inducir dependencia.

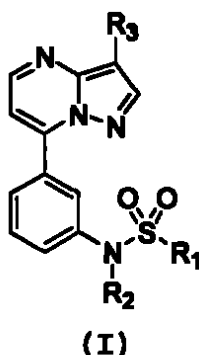
Es por tanto deseable la obtención de nuevos hipnóticos con menor riesgo de efectos secundarios.

[Handwritten signature] 63

Para ello, la presente invención se centra en nuevas N-[3-(3-sustituidas-pirazolo[1,5-a]pirimidin-7-il)-fenil]-sulfonamidas activas frente al receptor GABA-A y en concreto frente a las subunidades $\alpha 1$ y $\alpha 2$ de dicho receptor. Como consecuencia, los compuestos de la presente invención son útiles para el tratamiento y la prevención de todas aquellas enfermedades mediadas por las subunidades $\alpha 1$ y $\alpha 2$ del receptor GABA-A. Son ejemplos no limitativos de dichas enfermedades, las alteraciones del sueño, preferentemente el insomnio, la ansiedad y la epilepsia. Son ejemplos no limitativos de las indicaciones propias de los compuestos de la presente invención todas aquellas enfermedades o situaciones en que se necesite una inducción del sueño, tales como el insomnio la anestesia, de la sedación o de la relajación muscular.

Descripción detallada de la invención

La presente invención se refiere a las nuevas N-[3-(3-sustituidas-pirazolo[1,5-a]pirimidin-7-il)-fenil]-sulfonamidas de fórmula (I)

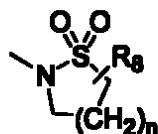


y sus sales farmacéuticamente aceptables;
donde

R_1 se selecciona entre alquil(C_1-C_6), alquenil(C_2-C_6),
 ω,ω,ω -trifluoroalquil(C_1-C_6), cicloalquil(C_3-C_6),
 cicloalquil(C_3-C_6)alquil(C_1-C_6), -O-alquil(C_1-C_6), -NH-
 alquil(C_1-C_6), -N(dialquil(C_1-C_6)), alquil(C_1-C_6)-O-
 5 alquil(C_1-C_6), alquil(C_1-C_6)-NH-alquil(C_1-C_6), alquil(C_1-C_6)-
 N(dialquil(C_1-C_6)), fenil, fenil monosustituido, fenil
 disustituido, fenilalquil(C_1-C_6), fenilalquenil(C_2-C_6),
 furanil, furanil sustituido, isoxazolil, isoxazolil
 10 sustituido, pirazolil, pirazolil sustituido, tienil, tienil
 sustituido, tiazolil, tiazolil sustituido, piridil y
 piridil sustituido;

R_2 se selecciona entre hidrógeno, alquil(C_1-C_6),
 alquenil(C_2-C_6), alquinil(C_2-C_6) y cicloalquil(C_3-C_6);
 o bien

15 R_1 y R_2 forman un ciclo de estructura:



donde n es un entero de 0 a 3 inclusive;

20 R_3 se selecciona entre hidrógeno, halógeno, alquil(C_1-C_6),
 cicloalquil(C_3-C_6), alquenil(C_2-C_6), alquinil(C_2-C_6), -O-
 alquil(C_1-C_6), halo-alquil(C_1-C_6), -CN, -SO₂-R₄, -NH-R₄, -
 NR₄R₅, -COR₆, -CO-NHR₆, COOR₆, -C(NR₇)R₆, fenil, fenil
 sustituido, heteroaril y heteroaril sustituido;

25 R_4 y R_5 se seleccionan independientemente entre alquil(C_1-C_6),
 cicloalquil(C_3-C_6), aril y heteroaril;

R_6 se selecciona entre hidrógeno, alquil(C_1-C_6),
 alquenil(C_2-C_6), alquinil(C_2-C_6), cicloalquil(C_3-C_6), fenil,
 fenil sustituido, furanil, furanil sustituido, tienil,
 30 tienil sustituido, tiazolil, tiazolil sustituido, piridil
 y piridil sustituido;

R₇ se selecciona entre alquil, cicloalquil(C₃-C₆), ~~OH~~, -O-alquil(C₁-C₆), alquil(C₁-C₆)-O-alquil(C₁-C₆), alquil(C₁-C₆)-NH-alquil(C₁-C₆), alquil(C₁-C₆)-N(dialquil(C₁-C₆)), fenil, fenil monosustituido, furanil, tienil, tiazolil y piridil;

R₈ se selecciona entre hidrógeno, alquil(C₁-C₆), cicloalquil(C₃-C₆), aril y heteroaril sustituido o no; a condición de que:

R₁ no puede ser p-tolil y R₂ metil y R₃ benzoil simultáneamente; y

R₁ no puede ser p-tolil y R₂ etil y R₃ furanil-2-carbonil simultáneamente.

La patente US 4.654.347 describe en su ejemplo 80 el compuesto N-[3-(3-benzoil-pirazolo[1,5-a]pirimidin-7-il)fenil]-N,4-dimetil-bencenosulfonamida y la patente EP 129.847 describe en su ejemplo 166 el compuesto N-etil-N-[3-[3-(2-furanilcarbonil)-pirazolo[1,5-a]pirimidin-7-il]fenil]-4-metil-bencenosulfonamida. En dichas patentes estos dos compuestos aparecen simplemente como intermedios de síntesis, sin que se consideren sustancias con actividad farmacológica de interés. Por tanto, este hecho no sugiere que compuestos análogos, como los de la presente invención, puedan tener un interesante valor terapéutico, hallazgo que ha sido descubierto por los solicitantes de forma inesperada. Dichos dos compuestos están comprendidos en la fórmula general (I), por lo que ambos se han excluido expresamente del ámbito de la presente invención.

Preferentemente la presente invención se refiere a las nuevas N-[3-(3-sustituidas-pirazolo[1,5-a]pirimidin-7-il)-fenil]-sulfonamidas de fórmula (I) donde R₁ se selecciona entre metil, etil, n-propil, i-propil, n-butil, 2-feniletetil, 2,2,2-trifluoroetil, fenil, 2-clorofenil, 3-clorofenil, 4-clorofenil, 2,4-diclorofenil, 3,4-diclorofenil, 2-cianofenil, 3-cianofenil, 4-cianofenil, 4-metoxifenil, 3-nitrofenil, 4-nitrofenil, 2-tienil, 5-metil-4-isoxazolil, 5-metil-2-trifluorometil-3-furil, 4-(4-morfolinil)-3-piridil, 2,4-dimetil-5-tiazolil, ciclopropil, bencil, vinil, 3,5-dimetil-4-isoxazolil, 1,3,5-trimetil-4-pirazolil and ciclopentilmetil; R₂ se selecciona entre hidrógeno metil, etil, n-propil, i-propil, n-butil, ciclopropil y 2-propinil, o bien R₁ y R₂ forman junto con el grupo -N-SO₂- un anillo de isotiazolidina-1,1-dioxido, de tal manera que R₁ y R₂ forman conjuntamente un grupo 1,3-propileno, y R₃ se selecciona entre un grupo ciano, un grupo benzoil, un grupo 4-fluorobenzoil, un grupo 4-metilbenzoil, un grupo 4-metoxibenzoil, un grupo 5-metil-1,2,4-oxadiazol-3-il, un grupo piridil-2-carbonil, un grupo piridil-4-carbonil y un grupo tiofen-2-carbonil.

El término sales farmacéuticamente aceptables, según se utiliza aquí, incluye cualquier sal tanto con ácidos inorgánicos como orgánicos, tales como el bromhídric, el clorhídrico, el fosfórico, el nítrico, el sulfúrico, el acético, el adípico, el aspártico, el bencenosulfónico, el benzoico, el cítrico, el etansulfónico, el fórmico, el fumárico, el glutámico, el láctico, el maleico, el málico, el malónico, el mandélico, el metansulfónico, el 1,5-naftalendisulfónico, el oxálico, el piválico, el

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propiónico, el p-toluensulfónico, el succínico, el tartárico y similares.

Son compuestos preferidos de la presente invención los siguientes:

N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-metil-metansulfonamida;

N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-etil-metansulfonamida;

N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-metil-bencenosulfonamida;

N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-etil-bencenosulfonamida;

N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

N-etil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-bencenosulfonamida;

N-etil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-bencenosulfonamida.

N-prop-2-inil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

N-propil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

N-etil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

N-prop-2-inil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2-propansulfonamida;

N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

- N-butil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;
 7-(3-(2-isotiazolidinil-1,1-dioxido)-fenil)-3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidina;
- 5 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2-propansulfonamida;
 N-etil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2-propansulfonamida;
- 10 N-propil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2-propansulfonamida;
 N-butil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2-propansulfonamida;
 N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-prop-2-inil-metansulfonamida;
- 15 N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-propil-etansulfonamida;
 N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-etil-etansulfonamida;
 N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-prop-2-inil-propan-2-sulfonamida;
- 20 N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-metil-etansulfonamida;
 N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-butil-etansulfonamida;
- 25 7-(3-(2-isotiazolidinil-1,1-dioxido)-fenil)-3-ciano-pirazolo[1,5-a]pirimidina;
 N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-metil-2-propansulfonamida;
 N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-etil-2-propansulfonamida;
- 30 N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-butil-2-propansulfonamida;

N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-propil-2-propansulfonamida;

N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-prop-2-inil-etansulfonamida;

5 N-metil-N-{3-[3-(piridin-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

N-etil-N-{3-[3-(piridin-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

10 N-prop-2-inil-N-{3-[3-(piridin-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

N-metil-N-{3-[3-(piridin-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

N-etil-N-{3-[3-(piridin-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

15 N-prop-2-inil-N-{3-[3-(piridin-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

N-metil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

20 N-etil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

N-metil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

N-etil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

25 N-prop-2-inil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

N-prop-2-inil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

30 N-metil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

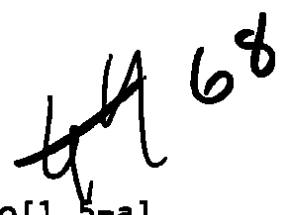
N-etil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

- N-metil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-etansulfonamida;
- N-etil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-etansulfonamida;
- 5 N-prop-2-inil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;
- N-prop-2-inil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;
- 10 N-metil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;
- N-etil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;
- N-metil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;
- 15 N-etil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;
- N-prop-2-inil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;
- N-prop-2-inil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;
- 20 N-metil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;
- N-etil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;
- 25 N-metil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;
- N-etil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;
- N-prop-2-inil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;
- 30 N-prop-2-inil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

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- N-metil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;
- N-etil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;
- 5 N-metil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;
- N-etil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;
- 10 N-prop-2-inil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;
- N-prop-2-inil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;
- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2-feniletenesulfonamida;
- 15 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2,2,2-trifluoroetansulfonamida;
- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2-clorobencenosulfonamida;
- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-3-clorobencenosulfonamida;
- 20 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-4-clorobencenosulfonamida;
- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2,4-diclorobencenosulfonamida;
- 25 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-3,4-diclorobencenosulfonamida;
- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2-cianobencenosulfonamida;
- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-3-cianobencenosulfonamida;
- 30 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-4-cianobencenosulfonamida;

- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-3-nitrobencenosulfonamida;
 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-4-nitrobencenosulfonamida;
 5 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-2-tiofensulfonamida;
 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-5-metil-4-isoxazolilsulfonamida;
 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-2-trifluorometil-5-metil-3-furilsulfonamida;
 10 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-6-(morfolin-4-il)-3-piridilsulfonamida;
 15 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-2,4-dimetil-5-tiazolilsulfonamida;
 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-ciclopropilsulfonamida;
 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-bencilsulfonamida;
 20 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-vinilsulfonamida;
 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-3,5-dimetil-4-isoxazolilsulfonamida;
 25 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-1,3,5-trimetil-4-pirazolil-sulfonamida;
 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-propansulfonamida;
 30 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-butansulfonamida;
 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-ciclopentilmetansulfonamida;



N-{3-[3-(5-metil-[1,2,4]oxadiazol-3-il)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida; y
N-etil-N-{3-[3-(5-metil-[1,2,4]oxadiazol-3-il)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida.

5

Otro aspecto de esta invención es proporcionar un procedimiento para la obtención de los compuestos de fórmula (I) y de sus sales farmacéuticamente aceptables.

10

Otro aspecto de esta invención se refiere al uso de un compuesto de fórmula (I) o de sus sales farmacéuticamente aceptables para tratar o prevenir las enfermedades relacionadas con la modulación del receptor GABA-A en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de dicho compuesto.

15

Otro aspecto de esta invención se refiere al uso de un compuesto de fórmula (I) o de sus sales farmacéuticamente aceptables para tratar o prevenir las enfermedades relacionadas con la modulación de la subunidad $\alpha 1$ del receptor GABA-A en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de dicho compuesto.

20

Otro aspecto de esta invención se refiere al uso de un compuesto de fórmula (I) o de sus sales farmacéuticamente aceptables para tratar o prevenir las enfermedades relacionadas con la modulación de la subunidad $\alpha 2$ del receptor GABA-A en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de dicho compuesto.

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30

Otro aspecto de esta invención se refiere al uso de un compuesto de fórmula (I) o de sus sales farmacéuticamente

aceptables para el tratamiento o la prevención de la ansiedad en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de dicho compuesto.

5 Otro aspecto de esta invención se refiere al uso de un compuesto de fórmula (I) o de sus sales farmacéuticamente aceptables para el tratamiento o la prevención de la epilepsia en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de dicho compuesto.

10

Otro aspecto de esta invención se refiere al uso de un compuesto de fórmula (I) o de sus sales farmacéuticamente aceptables para el tratamiento o la prevención de las alteraciones del sueño en un mamífero que comprende
15 administrar a dicho mamífero una cantidad eficaz de dicho compuesto.

20

Otro aspecto de esta invención se refiere al uso de un compuesto de fórmula (I) o de sus sales farmacéuticamente aceptables para el tratamiento o la prevención del insomnio en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de dicho compuesto.

25

Otro aspecto de esta invención se refiere al uso de un compuesto de fórmula (I) o de sus sales farmacéuticamente aceptables para la inducción de sedación-hipnosis en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de dicho compuesto.

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Otro aspecto de esta invención se refiere al uso de un compuest de fórmula (I) o de sus sales farmacéuticamente

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aceptables para la inducción de anestesia en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de dicho compuesto.

5 Otro aspecto de esta invención se refiere al uso de un compuesto de fórmula (I) o de sus sales farmacéuticamente aceptables para modular el tiempo necesario para inducir el sueño y su duración en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de dicho

10 compuesto.

Otro aspecto de esta invención se refiere al uso de un compuesto de fórmula (I) o de sus sales farmacéuticamente aceptables para la inducción de relajación muscular en un

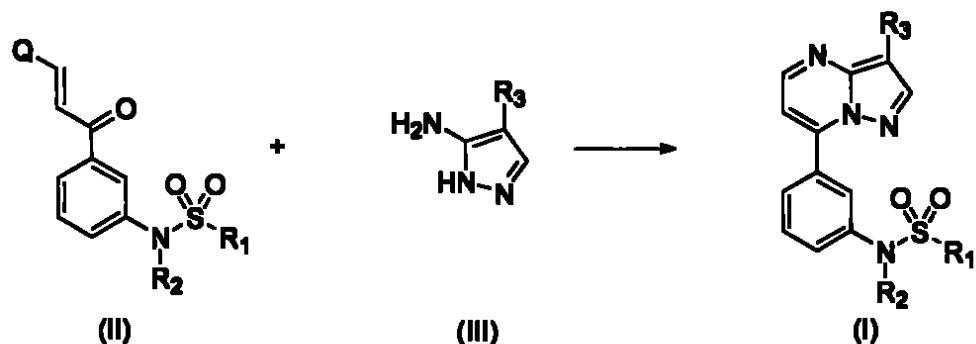
15 mamífero que comprende administrar a dicho mamífero una cantidad eficaz de dicho compuesto.

Otro aspecto de esta invención es proporcionar una composición farmacéutica que comprende un compuesto de

20 fórmula (I) o de sus sales farmacéuticamente aceptables en asociación con excipientes terapéuticamente inertes.

Los compuestos de fórmula general (I) pueden prepararse según la reacción del Esquema 1.

25



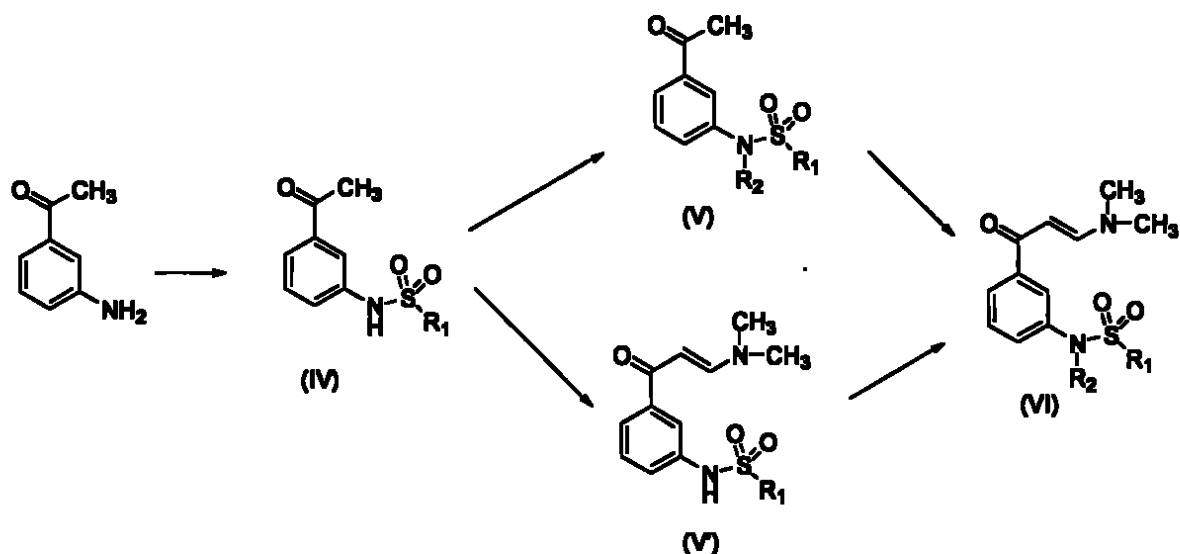
Esquema 1

5 R_1 , R_2 y R_3 tienen los valores indicados anteriormente y Q es un grupo saliente adecuado seleccionado entre N(dialquil(C_1-C_6))), alquiltio(C_1-C_6) y alcoxi(C_1-C_6). Preferentemente Q se elige entre dimetilamino, metiltio metoxi.

10 La reacción entre el amino pirazol de fórmula general (III) y la adecuadamente sustituida 1-aril-2-propen-1-ona (II) se lleva a cabo en un disolvente prótico o aprótico polar inerte tal como ácido acético glacial, etanol, metanol, dimetilformamida o dimetilsulfóxido a temperaturas comprendidas entre 50° y 130 °C. El tiempo de
15 reacción es de varias horas, transcurridas las cuales se elimina el disolvente y se reparte el residuo obtenido entre una disolución acuosa de bicarbonato sódico y diclorometano. El crudo resultante de evaporar a sequedad la fase orgánica puede purificarse por uno de los
20 siguientes métodos: (a) Cromatografía sobre sílica gel utilizando acetato de etilo o diclorometano/metanol como eluyente; o (b) Cristalización en un disolvente adecuado (acetato de etilo, etanol, metanol, etc).

25 El intermedio de fórmula (II) cuando Q es dimetilamino (intermedio (VI)) puede obtenerse siguiendo la secuencia de reacciones del Esquema 2.

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Esquema 2

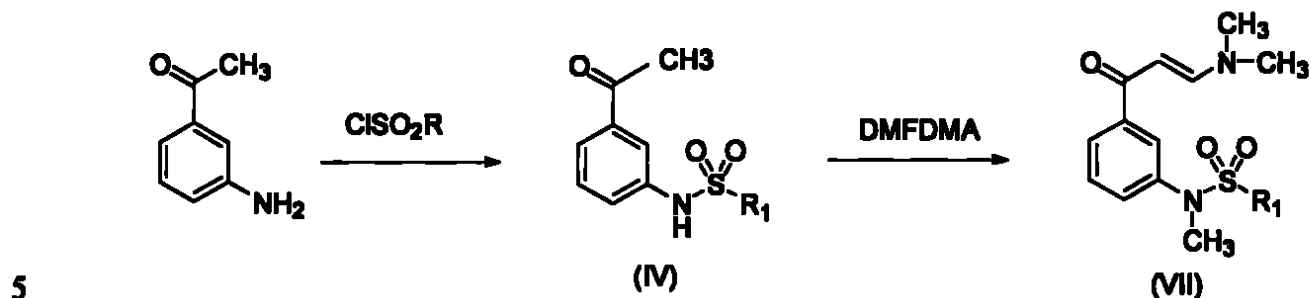
R_1 y R_2 tienen los significados indicados anteriormente.

5 Las sulfonamidas de fórmula (IV) se preparan según el método descrito por R. H. Uloth et al (J. Med. Chem. 9, 88-96, 1966).

10 La correspondiente alquilación de las sulfonamidas (IV) para alcanzar los intermedios de fórmula (V) se efectúa, según metodología bien conocida por los expertos en química orgánica, vía formación del correspondiente anión y posterior reacción con un haluro de alquilo.

15 Las enaminonas de fórmula (VI) se preparan de acuerdo con los métodos generales de síntesis de enaminas descritos por J. M. Domagala et al (J. Heterocyclic Chem., 26(4), 1147-58, 1989); y K. Sawada et al (Chem. Pharm. Bull., 49(7), 799-813, 2001), por reacción entre la
20 correspondiente acetofenona y el dimetil acetal de la *N,N*-dimetilformamida o el reactivo de Bredereck (tert-butoxibis(dimetilamino) metano).

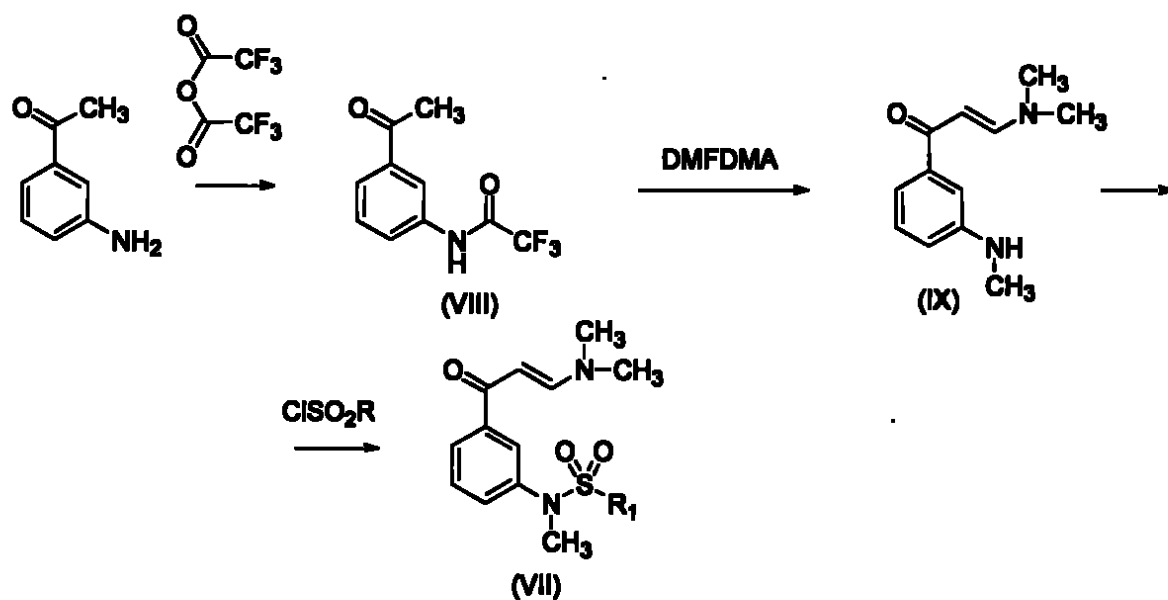
Alternativamente, los intermedios de fórmula (II) cuando Q es dimetilamino y R₂ es metilo (VII), pueden prepararse según el Esquema 3.

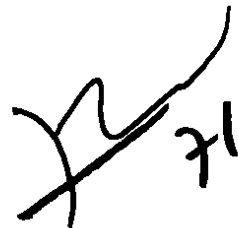


Esquema 3

10 En la transformación de (IV) a (VII), tiene lugar la formación de la enaminona y simultáneamente la formación de la N-metil-sulfonamida como resultado del aprovechamiento de las propiedades como agente metilante del dimetil acetal de la N,N-dimetilformamida.

15 El intermedio (VII) también puede prepararse según el Esquema 4.





Esquema 4

La ventaja que presenta este procedimiento radica en que la formación de la sulfonamida se efectúa en la última etapa. Como consecuencia, cuando se preparan amplias series de productos, se reduce el número total de pasos de síntesis. Por otra parte, según se pone de manifiesto en el esquema, en la transformación de (VIII) a (IX) tienen lugar de forma encadenada y en un solo paso las tres reacciones siguientes: (a) formación de la enaminona; (b) metilación de la trifluoroacetamida; y (c) desacilación para rendir la amina N-metilada. La posterior reacción de (IX) con el cloruro del ácido sulfónico correspondiente conduce a la obtención del intermedio (VII).

La obtención de los intermedios (VII) por reacción entre los intermedios (IV) y el dimetil acetal de la N,N-dimetilformamida no ha sido descrita hasta el presente en la literatura química y constituye otro aspecto de la presente invención.

Asimismo, la obtención de los intermedios (VII) por reacción entre la N-(3-acetilfenil)-2,2,2-trifluoroacetamida (VIII) y el dimetil acetal de la N,N-dimetilformamida, seguido de la formación de la sulfonamida por reacción con el correspondiente cloruro de ácido sulfónico, tampoco han sido descritos hasta el presente en la literatura química y constituyen otro aspecto de la presente invención.

A partir de los compuestos de fórmula general (I) es posible la obtención de sus sales farmacéuticamente

aceptables por tratamiento con los ácidos correspondientes.

5 Los solicitantes han descubierto que los compuestos de la presente invención presentan una relevante afinidad por las subunidades $\alpha 1$ y $\alpha 2$ del receptor GABA-A, según se demuestra en las Tablas 1 y 2. Estos resultados *in vitro* se han corroborado en las pruebas de sedación-hipnosis *in vivo*, cuyos resultados se recogen en la Tabla 3.

10

De acuerdo con los resultados obtenidos, ciertos compuestos de la presente invención manifiestan sorprendentemente unas actividades farmacológicas tanto *in vitro* como *in vivo* análogas o superiores a los compuestos del estado de la técnica. Todos estos resultados apoyan su uso en todas aquellas enfermedades o situaciones moduladas por las subunidades $\alpha 1$ y $\alpha 2$ del receptor GABA-A en las que se necesite una inducción del sueño, tales como el insomnio o la anestesia, una inducción de la sedación o una inducción de la relajación muscular.

15

20

La determinación de las actividades farmacológicas de los compuestos de la presente invención se ha efectuado de la manera siguiente.

25

(a) *Ensayos de unión a ligando. Determinación de la afinidad de los compuestos por las subunidades $\alpha 1$ y $\alpha 2$ del receptor GABA-A.*

30

Se utilizaron ratas macho Sprague-Dawley de peso comprendido entre 200-250 g en el momento del experimento.

Tras decapitación del animal, el cerebelo (tejido que contiene mayoritariamente la subunidad $\alpha 1$ del receptor del GABA-A) y la médula espinal (tejido que contiene mayoritariamente la subunidad $\alpha 2$ del receptor del GABA-A) fueron extraídos. La preparación de las membranas se realizó según el método descrito por J. Lamé et al (Prog. Neuro-Psychopharmacol.Biol.Psychiatry, 24, 979-991, 2000). Los tejidos, una vez pesados, se suspendieron en tampón tris·HCl 50 mM pH 7.7 en una relación 1:40 (P/V) y fueron homogeneizados. A continuación, se centrifugaron a 20000 g durante 10 min a 7°C. El pellet obtenido se resuspendió en las mismas condiciones, centrifugándose otra vez. El pellet final obtenido se resuspendió en el mínimo volumen y se guardó durante la noche congelado a -80°C. Al día siguiente, se repitió el proceso hasta resuspenderse el pellet final en una relación 1:10 (P/V).

Para estudiar la afinidad de los compuestos se realizaron ensayos de competición utilizando como ligando marcado flumazenilo. Los ensayos se realizaron según los métodos descritos por S. Arbilla et al (Eur. J. Pharmacol., 130, 257-263, 1986); e Y. Wu et al (Eur. J. Pharmacol., 278, 125-132, 1995). Se incubaron las membranas que contienen los receptores objetos de estudio, el flumazenilo marcado radiactivamente a una concentración final de 1 nM, y concentraciones crecientes de la entidad química a estudiar, en un volumen total de 500 μ l en tampón de ensayo Tris·HCl 50 mM pH 7.4. En paralelo, se incubaron las membranas únicamente con el flumazenilo marcado (totales, 100% unión) y en presencia de una concentración elevada de flumazenilo sin marcar (inespecífico, estimación del % de unión inespecífica del ligando

marcado). Las reacciones se iniciaron al añadir el ligand
 marcado y se incubaron durante 60 minutos a una
 temperatura de 0°C. Al finalizar el periodo de incubación,
 los tubos se filtraron utilizando un "harvester" Brandel
 modelo M-48R, y se lavaron tres veces con tampón de ensayo
 frío. El "harvester" contiene un filtro GF/B en el cual
 quedan retenidas las membranas con los receptores y el
 ligando marcado que se ha unido a éstos. Los filtros son
 retirados y se dejan secar. Una vez secos, se cortan, se
 introducen en viales y se les añade líquido de centelleo
 dejándose durante toda la noche en agitación hasta el día
 siguiente que se pondrán a contar. Para el contaje se
 utilizó una contador de centelleo Packard modelo Tricarb.
 Para el análisis de los resultados se calculó el % de
 unión específica para cada concentración del compuesto a
 estudiar según:

$$\% \text{ unión específica} = (X-I/T-I) * 100$$

donde,

X: cantidad de ligando unido para cada concentración del
 compuesto.

T: totales, cantidad máxima unida del ligando marcado.

I: inespecífico, cantidad de ligando marcado unido de
 forma inespecífica, independiente del receptor de estudio.

Cada concentración de compuesto se ensayó por duplicado y
 con el valor medio se obtuvieron los valores
 experimentales de % de unión específica representándose
 frente a la concentración de compuesto. Los valores así
 obtenidos se ajustaron a una ecuación para ensayos de
 competición (SigmaPlot, SPSS Inc.) calculándose el valor
 de la CI_{50} (concentración del compuesto que inhibe el 50%
 de la unión específica). A partir de los valores de CI_{50} se

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calcularon las K_i (constantes de inhibición) según la fórmula de Cheng-Prusoff (Y. Cheng y W. H. Prusoff, Biochem. Pharmacol., 22(23), 3099-3108, 1973). Alternativamente, los datos de afinidad para la subunidad α_2 se expresan como % de inhibición a las concentraciones de 10^{-5} M y 10^{-7} M. Los resultados de estas pruebas se detallan en las Tablas 1 y 2.

Tabla 1. Afinidad para la subunidad α_1 del receptor GABA_A

Compuesto	Ki (nM)
Ejemplo 2	74.5
Ejemplo 3	7.4
Ejemplo 5	13.4
Ejemplo 6	3.0
Ejemplo 16	0.7
Ejemplo 17	28.0
Ejemplo 18	5.9
Ejemplo 19	0.5
Ejemplo 20	12.5
Ejemplo 22	20.9
Ejemplo 23	26.7
Ejemplo 24	30.7
Ejemplo 25	26.6
Ejemplo 27	28.2
Ejemplo 29	53.2
Ejemplo 30	52.1
Ejemplo 33	608.7
Ejemplo 34	33.2
Ejemplo 35	88.9
Ejemplo 37	577.8
Ejemplo 38	119.4
Ejemplo 39	37.2
Ejemplo 40	7.3
Ejemplo 46	41.0
Ejemplo 51	38.7
Ejemplo 52	48.1
Ejemplo 53	33.2
Ejemplo 58	47.9
Ejemplo 63	62.1
Ejemplo 64	32.9
Ejemplo 68	8.9
Ejemplo 69	16.6
Ejemplo 70	6.2

Ejemplo 72	14.6
Ejemplo 76	201.2
Ejemplo 77	35.6
Ejemplo 78	2031.0
Ejemplo 79	499.0
Ejemplo 82	63.6
Ejemplo 83	42.0
Ejemplo 84	28.9
Ejemplo 87	1.9
Ejemplo 91	2.8
Ejemplo 92	0.4
Ejemplo 94	0.5
Zaleplon	198.9

Table 2. Afinidad para la subunidad α_2 del receptor GABA_A

Compuesto	K _i (nM)	
Ejemplo 2	831.3	
Ejemplo 3	36.7	
Ejemplo 5	290.2	
Ejemplo 6	34.9	
Zaleplon	1302.5	
Compuesto	% Inhibición (10 ⁻⁵ M)	% Inhibición (10 ⁻⁷ M)
Ejemplo 16	100.2	87.2
Ejemplo 17	74.5	0
Ejemplo 18	93.7	20.7
Ejemplo 19	94.4	45.2
Ejemplo 20	97.7	40.3
Ejemplo 22	98.2	24.2
Ejemplo 23	93.8	45.5
Ejemplo 24	83.0	10.4
Ejemplo 25	78.9	9.1
Ejemplo 27	85.2	2.9
Ejemplo 29	92.7	13.4
Ejemplo 30	73.3	0
Ejemplo 33	45.2	0
Ejemplo 34	87.6	6.9

29

Ejemplo 35	86.5	24.5
Ejemplo 37	40.2	0
Ejemplo 38	77.6	17.4
Ejemplo 39	96.6	23.3
Ejemplo 40	99.5	47.3
Ejemplo 46	97.6	11.9
Ejemplo 51	94.7	16.8
Ejemplo 52	61.2	0
Ejemplo 53	89.8	1.0
Ejemplo 58	93.8	24.0
Ejemplo 63	91.3	0
Ejemplo 64	61.5	20.9
Ejemplo 68	92.7	31.6
Ejemplo 69	99.0	36.7
Ejemplo 70	99.9	63.4
Ejemplo 72	98.6	44.9
Ejemplo 76	41.7	0
Ejemplo 77	88.5	13.8
Ejemplo 78	36.2	0
Ejemplo 79	52.9	0
Ejemplo 82	31.8	0
Ejemplo 83	94.4	39.1
Ejemplo 84	89.5	0
Ejemplo 87	97.6	65.1
Ejemplo 91	84.1	4.8
Ejemplo 92	95.7	36.5
Ejemplo 94	99.5	41.2
Zaleplon	78.4	--

(b) *Determinación de la actividad predictiva de sedación-hipnosis in vivo.*

Los efectos *in vivo* de estos compuestos fueron evaluados mediante una prueba predictiva de sedación-hipnosis en ratón (D. J. Sanger et al., Eur. J. Pharmacol., 313, 35-42, 1996; y G. Griebel et al., Psychopharmacology, 146, 205-213, 1999).

Se utilizaron grupos de 5 a 8 ratones macho CD1 de 22 a 26 g de peso en el momento de la prueba. Los compuestos se administraron, en suspensión en agar al 0.25% con una gota de Tween 80, por vía intraperitoneal en dosis únicas equimoleculares y a un volumen de administración de 10 ml/Kg. Los animales control recibieron sólo vehículo. Se cuantificó, mediante un Actisystem DAS16 (Panlab SL), el desplazamiento (número de contajes) realizado por los animales durante 30 min, en intervalos de 5 min, tras la administración de los compuestos. Se calculó el porcentaje de inhibición del desplazamiento de los animales tratados respecto a los animales control despreciando los primeros 5 min. Los resultados de esta prueba se detallan en la Tabla 3.

Tabla 3. Determinación de la sedación-hipnosis en ratón.

Compuesto	% Inhibición Actividad Motora
Ejemplo 2	71.39
Ejemplo 3	93.58
Ejemplo 5	80.91
Ejemplo 6	66.55
Ejemplo 16	95.36
Ejemplo 17	94.21
Ejemplo 18	93.39
Ejemplo 19	89.88

7.10
75

Ejemplo 20	95.23
Ejemplo 22	91.39
Ejemplo 23	94.57
Ejemplo 24	94.01
Ejemplo 25	92.79
Ejemplo 27	93.12
Ejemplo 29	93.73
Ejemplo 30	94.86
Ejemplo 33	77.58
Ejemplo 34	92.58
Ejemplo 35	92.55
Ejemplo 37	92.13
Ejemplo 38	94.85
Ejemplo 39	95.28
Ejemplo 40	94.32
Ejemplo 46	93.98
Ejemplo 51	90.04
Ejemplo 52	92.83
Ejemplo 53	94.89
Ejemplo 58	93.31
Ejemplo 63	95.32
Ejemplo 64	90.32
Ejemplo 68	87.78
Ejemplo 69	96.90
Ejemplo 70	94.54
Ejemplo 72	93.78
Ejemplo 76	78.36
Ejemplo 77	70.12
Ejemplo 78	36.12
Ejemplo 79	51.50
Ejemplo 82	39.87
Ejemplo 83	53.38

Ejemplo 84	68.98
Ejemplo 87	74.88
Ejemplo 91	72.85
Ejemplo 92	74.36
Ejemplo 94	88.69
Zaleplon	47.17

Los siguientes ejemplos ilustran, pero no limitan, el ámbito de la presente invención.

5 **Ejemplo 1: N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-metansulfonamida**

1.58 g (6.96 mmoles) de N-(3-acetil-fenil)-N-metil-metansulfonamida se disuelven en 15 ml de dimetil acetal
 10 de la N,N-dimetilformamida y la disolución resultante se mantiene a reflujo por espacio de 18 horas. Se elimina el exceso de reactivo volátil por destilación a presión reducida obteniéndose un crudo que se cromatografía sobre
 15 silica gel utilizando un gradiente de acetato de etilo/metanol como eluyente. Se obtienen 1.12 g (R= 88.6%) en forma de un sólido blanco amarillento que corresponde a la N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil metansulfonamida.

20 ¹H NMR(400 MHz, DMSO-d₆): δ 2.91 (3H, s), 2.94 (3H, s), 3.14 (3H, s), 3.26 (3H, s), 5.79 (1H, d, J= 12.4 Hz), 7.44 (1H, t, J= 7.6 Hz), 7.49-7.52 1H, m), 7.71 (1H, d, J= 12.4 Hz), 7.78-7.81 (2H, m).

MS (ES) m/z = 283 (MH⁺)

25 HPLC = 99.2%

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Ejemplo 2: N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-metil-metansulfonamida

5 0.1 g (0.93 mmoles) de 4-ciano-2H-pirazol-3-ilamina y 0.26
g (0.93 mmoles) de N-[3-[3-(dimetilamino)-1-oxo-2-
propenil]fenil]-N-metil-metansulfonamida disueltos en 10
ml de ácido acético glacial se mantienen a reflujo durante
8 horas. Transcurrido este tiempo, el disolvente se
10 elimina por destilación a presión reducida y sobre el
residuo resultante se añaden 10 ml de diclorometano y 10
ml de disolución saturada de bicarbonato sódico. Separadas
las dos fases, se lava la fase acuosa con 10 ml de
diclorometano. Las fases orgánicas reunidas se lavan con
15 10 ml de agua y se secan en presencia de sulfato de
magnesio. La fase de diclorometano, evaporada a sequedad
conduce a un aceite que en presencia de acetato de etilo
da un sólido de coloración amarillenta que pesa 217 mg (R=
71%) correspondiente a la N-[3-(3-ciano-pirazolo[1,5-a]
20 pirimidin-7-il)-fenil]-N-metil-metansulfonamida, m.p.=
193-195 °C.

¹H NMR(400 MHz, DMSO-d₆): δ 3.01 (3H, s), 3.30 (3H, s),
7.60 (1H, d, J= 4.8 Hz), 7.65-7.67 (2H, m), 8.00-8.02 (1H,
25 m), 8.09 (1H, s), 8.85 (1H, s), 8.91 (1H, d, J= 4.8 Hz).
MS (ES) m/z = 328 (MH+)
HPLC = 95.9%

**Ejemplo 3: N-Metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
30 [1,5-a]pirimidin-7-il]-fenil}-metansulfonamida**

0.1 g (0.52 mmoles) de (5-amino-1H-pirazol-4-il)-tiofen-2-il-metanona y 0.146 g (0.93 mmoles) de N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-metansulfonamida (obtenido según se describe en el ejemplo anterior) disueltos en 10 ml de ácido acético glacial se mantienen a reflujo durante 8 horas. Transcurrido este tiempo, el disolvente se elimina por destilación a presión reducida y sobre el residuo resultante se añaden 10 ml de diclorometano y 10 ml de disolución saturada de bicarbonato sódico. Separadas las dos fases, se lava la fase acuosa con 10 ml de diclorometano. Las fases orgánicas reunidas se lavan con 10 ml de agua y se secan en presencia de sulfato de magnesio. La fase de diclorometano, evaporada a sequedad conduce a un aceite que en presencia de acetato de etilo da un sólido de coloración amarillenta que pesa 178 mg (R= 83%) correspondiente a la N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida m.p. = 169-170 °C .

20

¹H NMR(400 MHz, DMSO-d₆): δ 3.02 (3H, s), 3.32 (3H, s), 7.29 (1H, t, J= 6 Hz), 7.54 (1H, d, J= 4.4 Hz), 7.62-7.67 (2H, m), 8.02-8.04 (2H, m), 8.11 (1H, s), 8.20 (1H, d, J= 6 Hz), 8.80 (1H, s), 8.89 (1H, d, J= 4.4 Hz).

25

MS (ES) m/z = 413 (MH⁺)

HPLC = 99.2%

Ejemplo 4: N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-etil-metansulfonamida

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1.1 g (4.56 mmoles) de N-(3-acetil-fenil)-N-etil-metansulfonamida se disuelven en 10 ml de dimetil acetal de la N,N-dimetilformamida y la disolución resultante se mantiene a reflujo por espacio de 18 horas. Se elimina el exceso de reactivo volátil por destilación a presión reducida obteniéndose un crudo que se cromatografía sobre silica gel utilizando un gradiente de acetat de etilo/metanol como eluyente. Se obtienen 1.2 g (R= 88.6%) en forma de un sólido blanco amarillento que corresponde a la N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-etil metansulfonamida.

^1H NMR(400 MHz, CDCl_3): δ 1.23 (3H, t, $J = 7.2$ Hz), 2.88 (3H, s), 2.94 (3H, s), 3.16 (3H, s), 3.76 (2H, q, $J = 7.2$ Hz), 5.66 (1H, d, $J = 12$ Hz), 7.41-7.44 (2H, m), 7.79 (1H, d, $J = 12$ Hz), 7.80-7.84 (2H, m).

HPLC = 95.6%

Ejemplo 5: N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-etil-metansulfonamida

0.196 g (1.82 mmoles) de 4-ciano-2H-pirazol-3-ilamina y 0.54 g (1.82 mmoles) de N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-etil-metansulfonamida disueltos en 10 ml de ácido acético glacial se mantienen a reflujo durante 8 horas. Transcurrido este tiempo, el disolvente se elimina por destilación a presión reducida y sobre el residuo resultante se añaden 10 ml de diclorometano y 10 ml de disolución saturada de bicarbonato sódico. Separadas las dos fases, se lava la fase acuosa con 10 ml de diclorometano. Las fases orgánicas reunidas se lavan con

10 ml de agua y se secan en presencia de sulfat de magnesio. La fase de diclorometano, evaporada a sequedad conduce a un aceite que en presencia de acetato de etilo da un sólido de coloración amarillenta que pesa 324 mg (R= 52.4%) correspondiente a la N-[3-(3-ciano-pirazolo[1,5-a] pirimidin-7-il)-fenil]-N-etil-metansulfonamida.

¹H NMR(400 MHz, CDCl₃): δ 1.21 (3H, t, J= 7.2 Hz), 2.95 (3H, s), 3.81 (2H, q, J= 6.8 Hz), 7.21 (1H, d, J= 4.4 Hz), 7.58-7.60 (1H, m), 7.64 (1H, t, J= 7.6 Hz), 7.98 (1H, d, J= 7.2 Hz), 8.06 (1H, s), 8.41 (1H, s), 8.78 (1H, d, J= 4 Hz).

MS (ES) m/z = 342 (MH⁺)

HPLC = 98.9%

15

Ejemplo 6: N-etil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

0.36 g (1.86 mmoles) de 5-amino-1H-pirazol-4-il)-tiofen-2-il-metanona y 0.55 g (1.86 mmoles) de N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-etil-metansulfonamida disueltos en 10 ml de ácido acético glacial se mantienen a reflujo durante 8 horas. Transcurrido este tiempo, y al enfriarse la mezcla de reacción, se forma un precipitado que se filtra, se lava primero con ácido acético, después con solución saturada de bicarbonato sódico y finalmente con agua. Se obtiene un sólido de coloración amarillenta que pesa 472 mg (R= 59.6%) correspondiente a la N-etil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida.

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¹H NMR(400 MHz, CDCl₃): δ 1.23 (3H, t, J= 7.6 Hz), 2.97 (3H, s), 3.82 (2H, q, J= 6.8 Hz), 7.17 (1H, d, J= 4.4 Hz), 7.18-7.20 (1H, m), 7.57-7.60 (2H, m), 7.62 (1H, t, J= 7.2 Hz), 7.69 1H, dd, J= 4.8 y 1.2 Hz), 7.99-8.02 (1H, m), 8.07-8.1 (3H, m), 8.69 (1H, s), 8.80 (1H, d, J= 4.4 Hz).

MS (ES) m/z = 427 (MH⁺).

HPLC = 98.3%

10 **Ejemplo 7: N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-bencenosulfonamida**

1.25 g (4.32 mmoles) de N-(3-acetil-fenil)-N-metil-bencenosulfonamida se disuelven en 10 ml de dimetil acetal de la N,N-dimetilformamida y la disolución resultante se mantiene a reflujo por espacio de 18 horas. Se elimina el exceso de reactivo volátil por destilación a presión reducida obteniéndose un crudo que se cromatografía sobre silica gel utilizando un gradiente de acetato de etilo/metanol como eluyente. Se obtienen 1.25 g (R= 84%) en forma de un sólido blanco amarillento que corresponde a la N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-bencenosulfonamida.

25 ¹H NMR(400 MHz, CDCl₃): δ 2.92 (3H, s), 3.15 (3H, s), 3.19 (3H, s), 5.58 (1H, d, J= 12 Hz), 7.21-7.23 (1H, m), 7.33 (1H, t, J= 8 Hz), 7.41-7.46 (2H, m), 7.52-7.58 (4H, m), 7.76 (1H, d, J=12 Hz), 7.77-7.80 (1H, m).

HPLC = 100%

Ejemplo 8: N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-metil-bencenosulfonamida

0.134 g (1.24 mmoles) de 4-ciano-2H-pirazol-3-ilamina y
 5 0.43 g (1.24 mmoles) de N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-bencenosulfonamida disueltos en
 10 ml de ácido acético glacial se mantienen a reflujo durante 8 horas. Transcurrido este tiempo, el disolvente se elimina por destilación a presión reducida y sobre el
 10 residuo resultante se añaden 10 ml de diclorometano y 10 ml de disolución saturada de bicarbonato sódico. Separadas las dos fases, se lava la fase acuosa con 10 ml de diclorometano. Las fases orgánicas reunidas se lavan con
 15 10 ml de agua y se secan en presencia de sulfato de magnesio. La fase de diclorometano, evaporada a sequedad conduce a un aceite que en presencia de acetato de etilo da un sólido de coloración amarillenta que pesa 205 mg (R= 42%) correspondiente a la N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-metil-bencenosulfonamida.

20

¹H NMR(400 MHz, CDCl₃): δ 3.23 (3H, s), 7.13 (1H, d, J= 4.8 Hz), 7.25-7.30 (1H, m), 7.45-7.63 (6H, m), 7.83 (1H, s), 7.93-7.97 (1H, m), 8.37 (1H, s), 8.75 (1H, d, J= 4.4 Hz).

25

MS (ES) m/z = 390 (MH⁺)

HPLC = 99.0%

Ejemplo 9: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo [1,5-a]pirimidin-7-il]-fenil}-bencenosulfonamida

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0.43 g (2.23 mmoles) de (5-amino-1H-pirazol-4-il)-tiofen-2-il-metanona y 0.8 g (2.23 mmoles) de N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-metan-sulfonamida disueltos en 10 ml de ácido acético glacial se
5 mantienen a reflujo durante 8 horas. Transcurrido este tiempo, el disolvente se elimina por destilación a presión reducida y sobre el residuo resultante se añaden 10 ml de diclorometano y 10 ml de disolución saturada de bicarbonato sódico. Separadas las dos fases, se lava la
10 fase acuosa con 10 ml de diclorometano. Las fases orgánicas reunidas se lavan con 10 ml de agua y se secan en presencia de sulfato de magnesio. La fase de diclorometano, evaporada a sequedad conduce a un aceite que en presencia de acetato de etilo da un sólido de
15 coloración amarillenta que pesa 872 mg (R= 82.3%) correspondiente a la N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-benceno-sulfonamida.

¹H NMR(400 MHz, CDCl₃): δ 3.24 (3H, s), 7.07 (1H, d, J= 4.4 Hz), 7.19 (1H, t, J= 4 Hz), 7.28-7.31 (1H, m), 7.46-7.62 (6H, m), 7.7 (1H, d, J= 5.2 Hz), 7.82 (1H, t, J= 2 Hz), 7.97 (1H, d, J= 6.8 Hz), 8.09 (1H, d, J= 3.6 Hz), 8.66 (1H, s), 8.79 (1H, d, J= 4.4 Hz).

MS (ES) m/z = 475 (MH⁺)

25 HPLC = 97.9%

Ejemplo 10: N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-etil-bencenosulfonamida

30 1.05 g (3.46 mmoles) de N-(3-acetil-fenil)-N-etil-bencenosulfonamida se disuelven en 10 ml de dimetil acetal

de la N,N-dimetilformamida y la disolución resultante se mantiene a reflujo por espacio de 18 horas. Se elimina el exceso de reactivo volátil por destilación a presión reducida obteniéndose un crudo que se cromatografía sobre sílica gel utilizando un gradiente de acetato de etilo/metanol como eluyente. Se obtienen 1.2 g (R= 96%) en forma de un sólido blanco amarillento que corresponde a la N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-etil-bencenosulfonamida.

^1H NMR(400 MHz, CDCl_3): δ 1.06 (3H, t, $J= 7.2$ Hz), 2.92 (3H, s), 3.15 (3H, s), 3.62 (2H, q, $J= 7.6$ Hz), 5.56 (1H, d, $J= 12.4$ Hz), 7.14-7.17 (1H, m), 7.35 (1H, t, $J= 7.6$ Hz), 7.42-7.49 (3H, m), 7.52-7.60 (3H, m), 7.76 (1H, d, $J=12.4$ Hz), 7.81 (1H, d, $J= 8$ Hz).

HPLC = 100%

Ejemplo 11: N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-etil-bencenosulfonamida

0.15 g (1.38 mmoles) de 4-ciano-2H-pirazol-3-ilamina y 0.50 g (1.38 mmoles) de N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-etil-bencenosulfonamida disueltos en 10 ml de ácido acético glacial se mantienen a reflujo durante 8 horas. Transcurrido este tiempo, el disolvente se elimina por destilación a presión reducida y sobre el residuo resultante se añaden 10 ml de diclorometano y 10 ml de disolución saturada de bicarbonato sódico. Separadas las dos fases, se lava la fase acuosa con 10 ml de diclorometano. Las fases orgánicas reunidas se lavan con 10 ml de agua y se secan en presencia de sulfato de

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magnesio. La fase de diclorometano, evaporada a sequedad conduce a un aceite que en presencia de acetato de etilo da un sólido de coloración amarillenta que pesa 260 mg (R= 47%) correspondiente a la N-[3-(3-ciano-pirazolo[1,5-a] pirimidin-7-il)-fenil]-N-etil-bencenosulfonamida.

^1H NMR(400 MHz, CDCl_3): δ 1.14 (3H, t, J = 6.8 Hz), 3.66 (2H, q, J = 7.2 Hz), 7.12 (1H, d, J = 4.8 Hz), 7.26 (1H, d, J = 7.6 Hz), 7.46-7.65 (6H, m), 7.76 (1H, s), 8.02 (1H, d, J = 7.6 Hz), 8.38 (1H, s), 8.76 (1H, d, J = 4.4 Hz).

MS (ES) m/z = 404 (MH $^+$)

HPLC = 98.9%

Ejemplo 12: N-etil-N-{3-[3-(tiofen-2-carbonil)-pirazolo [1,5-a]pirimidin-7-il]-fenil}-bencenosulfonamida

0.33 g (1.70 mmoles) de (5-amino-1H-pirazol-4-il)-tiofen-2-il-metanona y 0.61 g (1.70 mmoles) de N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-etil-bencenosulfonamida disueltos en 10 ml de ácido acético glacial se mantienen a reflujo durante 8 horas. Transcurrido este tiempo, el disolvente se elimina por destilación a presión reducida y sobre el residuo resultante se añaden 10 ml de diclorometano y 10 ml de disolución saturada de bicarbonato sódico. Separadas las dos fases, se lava la fase acuosa con 10 ml de diclorometano. Las fases orgánicas reunidas se lavan con 10 ml de agua y se secan en presencia de sulfato de magnesio. La fase de diclorometano, evaporada a sequedad conduce a un aceite que en presencia de acetato de etilo da un sólido de coloración amarillenta que pesa 535 mg (R= 64.4%)

correspondiente a la N-etil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-benceno-sulfonamida.

¹H NMR(400 MHz, CDCl₃): δ 1.15 (3H, t, J= 7.6 Hz), 3.67 (2H, q, J= 7.6 Hz), 7.07 (1H, d, J= 4.4 Hz), 7.18-7.21 (1H, m), 7.27-7.30 (1H, m), 7.51 (2H, t, J= 7.6 Hz), 7.56 (1H, t, J= 7.6 Hz), 7.60-7.67 (4H, m), 7.69 (1H, dd, J= 5.2 Hz y J= 1.2 Hz), 7.75 (1H, t, J= 2 Hz), 8.06 (1H, d, J= 7.6 Hz), 8.09 (1H, d, J= 3.6 Hz), 8.67 (1H, s), 8.79 (1H, d, J= 4.4 Hz).

MS (ES) m/z = 489 (MH⁺)

HPLC = 97.9%

Ejemplo 13: Procedimiento general para la obtención de las N-metil-enamino-sulfonamidas de formula general (VI) siguiendo el Esquema 2

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-etil-etansulfonamida

2 g (8.8 mmoles) de N-(3-acetil-fenil)-etansulfonamida se disuelven en 15 ml de dimetil acetal de la N,N-dimetilformamida y se calienta a 150°C durante 12 h. Se elimina el disolvente por destilación a presión reducida obteniéndose un crudo que se cromatografía sobre silica gel utilizando un gradiente de acetato de etilo/metanol como eluyente. Se obtienen 1.4 g (R= 56%) correspondientes a la N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-etan-sulfonamida.



0.25 g (0.89 mmoles) de N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-etansulfonamida se disuelven en 6 ml de N,N-dimetilformamida seca. Sobre la disolución formada, a 0°C y bajo atmósfera inerte, se adicionan 0.043 g (1.08 mmoles) de hidruro sódico. Después de agitar durante 30 minutos, se adicionan 0.15 g (0.98 mmoles) de yoduro de etilo y se mantiene la agitación a temperatura ambiente durante 5 h. Sobre la mezcla de reacción se adicionan 1 ml de agua y después 20 ml de NaOH 0.5 M. Se extrae con 3x25 ml de diclorometano y las fases orgánicas reunidas se lavan con 25 ml de agua, se secan sobre sulfato sódico anhidro, se filtra y se evapora a sequedad por destilación a presión reducida. Se obtienen 0.25 g (R= 90%) en forma de un aceite que corresponde a la N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-etil-etansulfonamida.

^1H NMR (400 MHz, CDCl_3): δ 1.12 (3H, t, $J = 6.8$ Hz), 1.37 (3H, t, $J = 7.6$ Hz), 2.94 (3H, s), 3.01 (2H, q, $J = 7.6$ Hz), 3.15 (3H, s), 4.79 (2H, q, $J = 8.2$ Hz), 5.66 (1H, d, $J = 12.4$ Hz), 7.39-7.46 (2H, m), 7.77-7.84 (3H, m)
HPLC = 99%

Siguiendo el procedimiento general descrito se preparan:

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-etil-isopropansulfonamida

^1H NMR (400 MHz, CDCl_3): δ 1.12 (3H, t, $J = 7.2$ Hz), 1.37 (6H, d, $J = 6.8$ Hz), 2.95 (3H, s), 3.18 (3H, s), 3.18-3.25 (1H, m), 3.82 (2H, q, $J = 7.6$ Hz), 5.67 (1H, d, $J = 12.4$ Hz), 7.39-7.49 (2H, m), 7.78-7.81 (2H, m), 7.85-7.87 (1H, m)
HPLC = 99.4%

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-propil-
metansulfonamida

5 ^1H NMR (400 MHz, DMSO- d_6): δ 0.83 (3H, t, J = 7.6 Hz), 1.31-
1.36 (2H, m), 2.49 (3H, s), 2.91 (3H, s), 3.14 (3H, s),
3.61 (2H, t, J = 7.2 Hz), 7.78 (1H, d, J = 12 Hz), 7.42-7.51
(2H, m), 7.71 (1H, d, J = 12.4 Hz), 7.77-7.78 (1H, m), 7.82-
7.85 (1H, m)
HPLC = 88.8%

10

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-propil-
etansulfonamida

15 ^1H NMR (400 MHz, CDCl_3): δ 0.89 (3H, t, J = 7.6 Hz), 1.37
(3H, t, J = 7.6 Hz), 1.42-1.51 (2H, m), 2.71 (1H, s), 2.94
(3H, s), 3.02 (2H, q, J = 7.6 Hz), 3.16 (3H, s, J = 12.4 Hz),
3.69 (2H, t, J = 7.2 Hz), 7.39-7.47 (2H, m), 7.78-7.85 (3H,
m)
HPLC = 98%

20

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-propil-
isopropansulfonamida

25 ^1H NMR (400 MHz, CDCl_3): δ 0.88 (3H, t, J = 7.2 Hz), 1.37
(6H, d, J = 6.8 Hz), 1.45-1.51 (2H, m), 2.94 (3H, s), 3.17
(3H, s), 3.17-3.24 (1H, m), 3.73 (2H, t, J = 7.6 Hz), 5.67
(1H, d, J = 12.8 Hz), 7.41 (1H, t, J = 8 Hz), 7.48-7.51 (1H,
m), 7.77-7.87 (3H, m)
HPLC = 99.6%

30

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-butil-
metansulfonamida

8782

^1H NMR (400 MHz, CDCl_3): δ 0.81 (3H, t, J = 7.6 Hz), 1.25-1.31 (4H, m), 2.92 (3H, s), 3.14 (3H, s), 3.64 (2H, t, J = 6.8 Hz), 5.78 (1H, d, J = 12 Hz), 7.44-7.50 (2H, m), 7.71 (1H, d, J = 12 Hz), 7.76-7.77 (1H, m), 7.82-7.85 (1H, m)

5 HPLC = 98%

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-butil-etansulfonamida

10 ^1H NMR (400 MHz, CDCl_3): δ 0.86 (3H, t, J = 7.6 Hz), 1.3-1.46 (7H, m), 2.94 (3H, s), 3.01 (2H, q, J = 7.2 Hz), 3.17 (3H, s), 3.73 (2H, t, J = 7.6 Hz), 5.63 (1H, d), 7.39-7.47 (2H, m), 7.78-7.85 (3H, m)

HPLC = 98.1%

15

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-butil-isopropansulfonamida

20 ^1H NMR (400 MHz, CDCl_3): δ 0.86 (3H, t, J = 7.6 Hz), 1.28-1.34 (2H, m), 1.36 (6H, d, J = 7.2 Hz), 1.41-1.45 (2H, m), 2.94 (3H, s), 3.16-3.24 (4H, m), 3.76 (2H, t, J = 7.2 Hz), 5.67 (1H, d, J = 12.4 Hz), 7.41 (1H, t, J = 8 Hz), 7.47-7.51 (1H, m), 7.78-7.82 (2H, m), 7.86-7.88 (1H, m)

HPLC = 99.4%

25

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-propargil-metansulfonamida

30 ^1H NMR (400 MHz, CDCl_3): δ 2.5 (1H, t, J = 2.8 Hz), 2.94 (3H, s), 3.05 (3H, s), 3.17 (3H, s), 4.46 (2H, s), 5.67 (1H, d, J = 12.4 Hz), 7.44 (1H, t, J = 8 Hz), 7.63-7.66 (1H, m), 7.81 (1H, m, J = 12 Hz), 7.84-7.87 (1H, m), 8.09 (1H, t, J = 2 Hz)

HPLC = 98.8%

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-propargil-etansulfonamida

5

^1H NMR (400 MHz, CDCl_3): δ 1.39 (3H, t, $J = 7.2$ Hz), 2.4 (1H, t, $J = 2.8$ Hz), 2.94 (3H, s), 3.14-3.22 (5H, m), 4.47 (2H, d, $J = 2.4$ Hz), 5.66 (1H, d, $J = 12.4$ Hz), 7.42-7.44 (2H, m), 7.61-7.64 (1H, m), 7.78-7.85 (3H, m), 8.05 (1H, t, $J = 2$ Hz)

10

MS (ES) $m/z = 321$ (MH $^+$)

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-propargil-isopropansulfonamida

15

^1H NMR (400 MHz, CDCl_3): δ 1.4 (6H, d, $J = 6.4$ Hz), 2.37 (1H, t, $J = 2.4$ Hz), 2.94 (3H, s), 3.17 (3H, s), 3.34-3.41 (1H, m), 4.49 (2H, d, $J = 2.8$ Hz), 5.66 (1H, d, $J = 12.4$ Hz), 7.40-7.44 (1H, m), 7.59-7.62 (1H, m), 7.78-7.87 (2H, m), 7.99-8.00 (1H, m)

20

HPLC = 81%

Ejemplo 14: Procedimiento general para la obtención de las N-metil-enamino-sulfonamidas de formula general (VII) siguiendo el Esquema 3

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N-(3-acetilfenil)-1-propano-sulfonamida

1 g (7.4 mmoles) de 3-aminoacetofenona se disuelven en 35 ml de diclorometano seco. Sobre la disolución resultante enfriada a 0°C se adicionan 0.89 ml (11.09 mmoles) de piridina anhidra y 1.26 g (8.87 mmoles) de cloruro del ácido 1-propanosulfónico. La mezcla de reacción se mantiene

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20 h en agitación a temperatura ambiente y en atmósfera inerte. Transcurrido este tiempo, se vierte sobre 15 ml de agua. Separadas las dos fases, se lava la fase acuosa con 2x15 ml de diclorometano. Las fases orgánicas reunidas se lavan con 30 ml de agua y se secan en presencia de sulfato sódico anhidro. La fase de diclorometano, evaporada a sequedad, conduce a un sólido amarillo que pesa 1.8 g (R=100%) correspondiente a la N-(3-acetilfenil)-1-propano-sulfonamida y que se utiliza directamente para la siguiente reacción.

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-1-propano-sulfonamida

1 g (4.14 mmoles) de N-(3-acetilfenil)-1-propano-sulfonamida se disuelven en 10 ml de N,N-dimetilformamida. Sobre la disolución resultante se adicionan 2.77 ml (20.74 mmoles) de dimetil acetal de la N,N-dimetilformamida y se calienta a 150°C durante 2 h. Se elimina el disolvente por destilación a presión reducida obteniéndose una aceite. Este se trata con una mezcla de acetato de etilo-éter etílico. Precipita una pequeña cantidad de sólido que se deshecha. El filtrado se evapora a sequedad, se disuelve en diclorometano, se lava la fase orgánica con 4x50 ml de agua y se evapora a sequedad. Se obtienen 1.23 g (R = 96%) correspondientes a la N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-1-propano-sulfonamida.

¹H NMR (400 MHz, CDCl₃): δ 0.99 (3H, t, J= 7.6 Hz), 1.75-1.90 (2H, m), 2.91-2.97 (5H, m), 3.15 (3H, a), 3.35 (3H, s), 5.66 (1H, d, J= 12.5 Hz), 7.36-7.52 (2H, m), 7.73-7.88 (3H, m)

Siguiendo el procedimiento general descrito se preparan:

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-butansulfonamida

5

^1H NMR (400 MHz, CDCl_3): δ 0.92 (3H, t, $J = 7.4$ Hz), 1.35-1.5 (2H, m), 1.75-1.87 (2H, m), 2.97-3.03 (5H, m), 3.18 (3H, a), 3.39 (3H, s), 5.7 (1H, d, $J = 12.2$ Hz), 7.39-7.46 (1H, m), 7.52-7.56 (1H, m), 7.77-7.87 (1H, m), 7.83 (1H, d, $J = 12.2$ Hz), 7.9-7.91 (1H, m)

10

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-ciclopentilmetansulfonamida

^1H NMR (400 MHz, CDCl_3): δ 1.22-1.3 (2H, m), 1.55-1.63 (4H, m), 1.91-1.98 (2H, m), 2.27-2.4 (1H, m), 2.86-2.93 (5H, m), 3.15 (3H, a), 3.34 (3H, s), 5.67 (1H, d, $J = 12.5$ Hz), 7.37-7.52 (2H, m), 7.44-7.98 (3H, m)

15

Ejemplo 15: Procedimiento general para la obtención de las N-metil-enamino-sulfonamidas de formula general (VII) siguiendo el Esquema 4

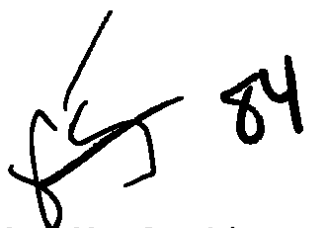
20

N-(3-acetilfenil)-2,2,2-trifluoroacetamida

25

5 g (37 mmoles) de 3-aminoacetofenona se disuelven en 30 ml de diclorometano anhidro. Sobre la disolución resultante se adicionan 3.15 ml (38.84 mmoles) de piridina anhidra y 5.5 ml (38.84 mmoles) de anhídrido trifluoroacético manteniendo la temperatura a 0°C . Se agita la mezcla de reacción durante 30 minutos a la misma temperatura y se vierte sobre

30



100 ml de agua-hielo. Se adicionan 100 ml de disolución saturada de cloruro sódico y se extrae con 2x70 ml de diclorometano y 3x50 ml de acetato de etilo. Las fases orgánicas reunidas se lavan con agua, se secan sobre sulfato sódico anhidro y se evaporan a sequedad por destilación a presión reducida. Se obtienen 8.7 g (R= 100%) en forma de un sólido que corresponde a la N-(3-acetilfenil)-2,2,2-trifluoroacetamida.

¹H NMR (400 MHz, CDCl₃): δ 2.64 (3H, s), 7.53 (1H, t, J= 7.6 Hz), 7.82 (1H, d, J= 7.6 Hz), 8.15 (1H, d, J= 8.2 Hz), 8.25 (1H, s), 9.12 (1H, a)

3-(dimetilamino)-1-[3-(metilamino)fenil]prop-2-en-1-ona

8.37 g (36.21 mmoles) de N-(3-acetilfenil)-2,2,2-trifluoroacetamida se disuelven en 80 ml de N,N-dimetilformamida. Sobre la disolución resultante se adicionan 24.23 ml (181.02 mmoles) de dimetil acetal de la N,N-dimetilformamida y se calienta a 150°C durante 2 h. Se elimina el disolvente por destilación a presión reducida obteniéndose una aceite. Éste se trata con 50 ml de agua y se extrae con 3x100 ml de diclorometano. Los extractos orgánicos reunidos se lavan con 2x200 ml de disolución saturada de cloruro sódico, se secan sobre sulfato sódico anhidro y se evaporan a sequedad por destilación a presión reducida. Se obtiene un sólido que precipita de una mezcla de etanol-éter etílico (9:1) que pesa 4.1 g (R= 55%) correspondiente a la 3-(dimetilamino)-1-[3-(metilamino)fenil]prop-2-en-1-ona.

^1H NMR (400 MHz, CDCl_3): δ 2.85 (3H, s), 2.87 (3H, s), 3.11 (3H, s), 3.85 (1H, a), 5.68 (1H, d, $J = 12.2$ Hz), 6.67-6.72 (1H, m), 7.16-7.24 (3H, m), 7.77 (1H, d, $J = 12.2$ Hz)

5 N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-2-fenil-etilensulfonamida

0.4 g (1.96 mmoles) de 3-(dimetilamino)-1-[3-(metilamino) fenil]prop-2-en-1-ona se disuelven en 10 ml de
 10 diclorometano seco. Sobre la disolución resultante se adicionan 0.24 ml (2.91 mmoles) de piridina anhidra y 0.48 g (2.37 mmoles) del cloruro del ácido 2-fenil-eteno sulfónico. La mezcla de reacción se mantiene 17 h en
 15 agitación a temperatura ambiente y en atmósfera inerte. Transcurrido este tiempo, se vierte sobre 15 ml de agua. Separadas las dos fases, se lava la fase acuosa con 2x15 ml de diclorometano. Las fases orgánicas reunidas se lavan con
 20 30 ml de agua y se secan en presencia de sulfato sódico anhidro. La fase de diclorometano, evaporada a sequedad, conduce a un crudo que se cromatografía sobre silica gel utilizando un gradiente de diclorometano/metanol como eluyente. Se obtienen 0.53 g ($R = 73\%$) en forma de un sólido que corresponde a N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-2-fenil-etilensulfonamida.

25

^1H NMR (400 MHz, CDCl_3): δ 2.9 (3H, a), 3.16 (3H, a), 3.31 (3H, s), 5.65 (1H, d, $J = 12.5$ Hz), 6.7 (1H, d, $J = 15.5$ Hz), 7.38-7.5 (8H, m), 7.77-7.85 (3H, m)

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Siguiendo el procedimiento general descrito se preparan:

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-3-clorobencenosulfonamida



^1H NMR (400 MHz, CDCl_3): δ 2.93 (3H, a), 3.16 (3H, a), 3.22 (3H, s), 5.6 (1H, d), 7.23-7.27 (1H, m), 7.35-7.41 (3H, m), 7.52-7.58 (3H, m), 7.76 (1H, s), 7.79-7.83 (1H, m)

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N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-4-clorobencenosulfonamida

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^1H NMR (400 MHz, CDCl_3): δ 2.94 (3H, a), 3.18 (3H, a), 3.2 (3H, a), 5.59 (1H, d, $J=12.2$ Hz), 7.23-7.29 (1H, m), 7.34-7.55 (6H, m), 7.77-7.83 (2H, m)

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-2-clorobencenosulfonamida

15

^1H NMR (400 MHz, CDCl_3): δ 2.73 (3H, a), 2.96 (3H, a), 3.24 (3H, s), 5.6 (1H, d, $J=12.5$ Hz), 7.06-7.14 (3H, m), 7.21-7.32 (2H, m), 7.5-7.6 (3H, m), 7.68 (1H, dd), $J=7.9$ Hz, $J=1.5$ Hz)

20

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-2,2,2-trifluoroetansulfonamida

25

^1H NMR (400 MHz, CDCl_3): δ 2.95 (3H, a), 3.18 (3H, s), 3.42 (3H, s), 3.73 (2H, c, $J=9.1$ Hz), 5.66 (1H, d, $J=12.2$ Hz), 7.42-7.53 (2H, m), 7.8 (1H, s), 7.83-7.89 (2H, m)

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-2,4-diclorobencenosulfonamida

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^1H NMR (400 MHz, CDCl_3): δ 2.96 (3H, a), 3.19 (3H, s), 3.46 (3H, s), 5.6 (1H, d, $J=12.2$ Hz), 7.27 (1H, d, $J=2.1$ Hz),

7.31 (1H, d, J= 1.8 Hz), 7.34-7.38 (1H, m), 7.53 (1H, d, J= 2.1 Hz), 7.71-7.84 (4H, m)

5 N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-3,4-diclorobencenosulfonamida

10 ¹H NMR (400 MHz, CDCl₃): δ 2.86 (3H, s), 3.09 (3H, s), 3.15 (3H, s), 5.52 (1H, d, J= 12.2 Hz), 7.16-7.23 (1H, m), 7.26 (1H, d, J= 2.1 Hz), 7.32 (1H, t, J= 7.9 Hz), 7.45 (1H, d, J= 8.5 Hz), 7.49 (1H, m), 7.61 (1H, d, J= 2.1 Hz)

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-2-cianobencenosulfonamida

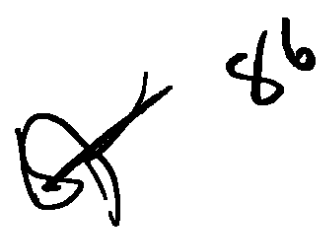
15 ¹H NMR (400 MHz, CDCl₃): δ 2.97 (3H, a), 3.19 (3H, a), 3.43 (3H, s), 5.64 (1H, d, J= 12.2 Hz), 7.35 (1H, m), 7.41 (1H, t, J= 7.9 Hz), 7.6-7.89 (7H, m)

20 N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-3-cianobencenosulfonamida

25 ¹H NMR (400 MHz, CDCl₃): δ 2.94 (3H, a), 3.16 (3H, a), 3.23 (3H, s), 5.62 (1H, d, J= 12.2 Hz), 7.24-7.29 (1H, m), 7.39 (1H, t, J= 7.6 Hz), 7.5 (1H, m), 7.55-7.62 (1H, m), 7.69-7.86 (5H, m)

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-4-cianobencenosulfonamida

30 ¹H NMR (400 MHz, CDCl₃): δ 2.94 (3H, a), 3.17 (3H, a), 3.22 (3H, s), 5.6 (1H, d, J= 12.2 Hz), 7.24-7.3 (1H, m), 7.39 (1H, t, J= 7.9 Hz), 7.51 (1H, m), 7.64-7.7 (2H, m), 7.73-7.82 (4H, m)



N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-3-nitrobencenosulfonamida

5 ^1H NMR (400 MHz, CDCl_3): δ 2.93 (3H, a), 3.16 (3H, a), 3.26 (3H, s), 5.6 (1H, d, $J = 12.2$ Hz), 7.27-7.32 (2H, m), 7.39 (1H, t, $J = 7.9$ Hz), 7.48 (1H, m), 7.62-7.82 (4H, m), 8.4-8.44 (1H, m)

10 N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-4-nitrobencenosulfonamida

15 ^1H NMR (400 MHz, CDCl_3): δ 2.92 (3H, a), 3.17 (3H, a), 3.25 (3H, s), 5.6 (1H, d, $J = 12.5$ Hz), 7.25-7.29 (1H, m), 7.39 (1H, t, $J = 7.9$ Hz), 7.53 (1H, m), 7.73 (2H, d, $J = 9$ Hz), 8.4-8.44 (1H, m), 7.77-7.84 (2H, m), 8.3 (2H, d, $J = 9$ Hz)

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-2-tiofenosulfonamida

20 ^1H NMR (400 MHz, CDCl_3): δ 2.85 (3H, a), 3.07 (3H, a), 3.19 (3H, s), 5.54 (1H, d, $J = 12.5$ Hz), 6.99 (1H, dd, $J = 4.8$ Hz), 7.19-7.32 (3H, m), 7.48-7.53 (2H, m), 7.67-7.74 (2H, m)

25 N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-5-metil-4-isoxazolsulfonamida

30 ^1H NMR (400 MHz, CDCl_3): δ 2.13 (3H, s), 2.88 (3H, a), 3.11 (3H, s), 3.19 (3H, m), 5.53 (1H, d, $J = 12.5$ Hz), 7.21-7.28 (1H, m), 7.35 (1H, t, $J = 7.9$ Hz), 7.56-7.81 (3H, m), 8.15 (1H, m)

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-2-trifluorometil-5-metil-3-furansulfonamida

5 ^1H NMR (400 MHz, CDCl_3): δ 2.13 (3H, s), 2.94 (3H, a), 3.27 (3H, s), 5.61 (1H, d, $J=12.2$ Hz), 6.8 (1H, m), 7.3-7.44 (2H, m), 7.66 (1H, t), 7.79-7.86 (2H, m)

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-6-(morfolin-4-il)-3-piridinsulfonamida

10

^1H NMR (400 MHz, CDCl_3): δ 2.88 (3H, a), 3.13 (3H, s), 3.54-3.58 (4H, m), 3.71-3.75 (4H, m), 5.59 (1H, d, $J=12.5$ Hz), 6.43 (1H, dd, $J=9.1$ Hz), 7.21-7.3 (2H, m), 7.35 (1H, dd, $J=9.1$ Hz), 7.58-7.6 (1H, m), 7.69-7.74 (2H, m), 8.3 (1H, dd, $J=2.6$ y 0.8 Hz)

15

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-2,4-dimetil-5-tiazolsulfonamida

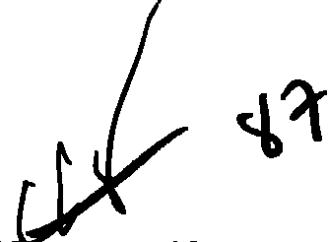
20 ^1H NMR (400 MHz, CDCl_3): δ 2.06 (3H, s), 2.6 (3H, s), 2.88 (3H, a), 3.1 (3H, a), 3.23 (3H, s), 5.56 (1H, dd, $J=12.2$ Hz), 7.23-7.38 (2H, m), 7.7-7.8 (3H, m)

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-ciclopropansulfonamida

25

^1H NMR (400 MHz, CDCl_3): δ 1.03-1.12 (1H, m), 1.23-1.32 (1H, m), 1.5-1.54 (1H, m), 2.26-2.37 (1H, m), 2.88 (3H, a), 3.09 (3H, a), 3.16-3.28 (1H, m), 3.31 (3H, s), 5.62 (1H, d, $J=12.2$ Hz), 7.3-7.37 (1H, m), 7.44-7.48 (1H, m), 7.7-7.77 (2H, m), 7.87-7.88 (1H, m)

30



N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-bencilsulfonamida

5 ^1H NMR (400 MHz, CDCl_3): δ 3.05 (3H, a), 3.25 (6H, s), 4.37 (2H, s), 5.76 (1H, d, $J = 12.2$ Hz), 7.44-7.51 (7H, m), 7.83-7.93 (3H, m)

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil-vinilsulfonamida

10 ^1H NMR (400 MHz, CDCl_3): δ 2.92 (3H, a), 3.14 (3H, a), 5.66 (1H, d, $J = 12.2$ Hz), 5.97 (1H, dd), 6.13 (1H, dd), 6.39 (1H, dd), 7.31-7.47 (2H, m), 7.7-7.75 (2H, m), 7.87 (1H, d, $J = 12.2$ Hz)

15 N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil 3,5-dimetil-4-isoxazolsulfonamida

20 ^1H NMR (400 MHz, CDCl_3): δ 2.03 (3H, s), 2.27 (3H, s), 2.94 (3H, a), 3.16 (3H, a), 3.27 (3H, s), 5.58 (1H, d, $J = 12.2$ Hz), 7.31-7.43 (2H, m), 7.66 (1H, m), 7.77-7.85 (2H, m)

N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-metil 1,3,5-trimetil-4-pirazolsulfonamida

25 ^1H NMR (400 MHz, CDCl_3): δ 1.96 (3H, s), 2.84 (3H, a), 3.16 (3H, a), 3.2 (3H, a), 3.68 (3H, s), 5.63 (1H, d, $J = 12.5$ Hz), 7.34-7.37 (2H, m), 7.63 (1H, m), 7.76-7.82 (2H, m)

30 **Ejemplo 16:** Procedimiento general para la obtención pirazolo[1,5-a]pirimidinas de fórmula general (I) según reacción descrita en el Esquema 1

N-prop-2-inil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

0.1 g (0.33 mmoles) de 4-tiofen-2-carbonil-2H-pirazol-3-ilamina y 0.063 g (0.33 mmoles) de N-[3-[3-(dimetilamino)-1-oxo-2-propenil]fenil]-N-prop-2-inil-metansulfonamida disueltos en 10 ml de ácido acético glacial se mantienen a reflujo durante 8 horas. Transcurrido este tiempo, el disolvente se elimina por destilación a presión reducida y sobre el residuo resultante se añaden 10 ml de diclorometano y 10 ml de disolución saturada de bicarbonato sódico. Separadas las dos fases, se lava la fase acuosa con 10 ml de diclorometano. Las fases orgánicas reunidas se lavan con 10 ml de agua y se secan en presencia de sulfato de magnesio. La fase de diclorometano, evaporada a sequedad conduce a un aceite que en presencia de acetato de etilo da un sólido de coloración amarillenta que pesa 111 mg (R= 78%) correspondiente a la N-prop-2-inil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metan-sulfonamida.

^1H NMR (400 MHz, CDCl_3): δ 2.54 (1H, s), 3.12 (3H, s), 4.54 (2H, s), 7.15 (1H, d, $J = 4$ Hz), 7.19-7.21 (1H, m), 7.65 (1H, t, $J = 7.6$ Hz), 7.69-7.71 (1H, m), 7.84-7.87 (1H, m), 8.03-8.06 (1H, m), 8.08-8.10 (1H, m), 8.31 (1H, t, $J = 2$ Hz), 8.71 (1H, s), 8.82 (1H, d, $J = 4.4$ Hz)
MS (ES) $m/z = 437$ (MH+)
HPLC = 100%

Siguiendo el procedimiento general descrito en el Ejemplo 16 se preparan los productos relacionados en los ejemplos siguientes:

~~28~~ 48

Ejemplo 17: N-propil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 0.94 (3H, t, J= 7.6 Hz), 1.42
5 (3H, t, J= 7.6 Hz), 1.54-1.63 (2H, m), 3.08-3.31 (2H, m),
3.75 (2H, t, J= 7.2 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.19-7.21
(1H, m), 7.59-7.65 (2H, m), 7.69-7.71 (1H, m), 7.99-8.02
(1H, m), 8.09-8.11 (2H, m, J= 2 Hz), 8.71 (1H, s), 8.82 (1H,
d, J= 4.4 Hz)
10 MS (ES) m/z = 455 (MH+)
HPLC = 97.86%

Ejemplo 18: N-etil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

15 ¹H NMR (400 MHz, CDCl₃): δ 1.22 (3H, t, J= 6.8 Hz), 1.43
(3H, t, J= 7.6 Hz), 3.11 (2H, c, J= 7.6 Hz), 3.85 (2H, c,
J= 6.8 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.19-7.21 (1H, m, J=
4.4 Hz), 7.58-7.66 (2H, m), 7.69-7.71 (1H, m), 7.99-8.02
20 (1H, m), 8.09-8.11 (2H, m), 8.71 (1H, s), 8.82 (1H, d, J= 4.4
Hz)
MS (ES) m/z = 441 (MH+)
HPLC = 97.73%

25 **Ejemplo 19:** N-prop-2-inil-N-{3-[3-(tiofen-2-carbonil)-
pirazolo[1,5-a]pirimidin-7-il]-fenil}-2-propansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.44 (6H, d, J= 6.4 Hz), 2.42
(1H, m), 3.44-3.51 (1H, m), 4.56 (1H, s), 7.15 (1H, d, J= 4
30 Hz), 7.19-7.20 (1H, m), 7.65 (1H, t, J= 8 Hz), 7.69-7.71
(1H, m), 7.76-7.79 (1H, m), 8.02-8.05 (1H, m), 8.09-8.11

(1H, m).8.24-8.25 (1H, m).8.7 (1H, s).8.82 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 465 (MH+)

HPLC = 100%

5

Ejemplo 20: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo [1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.41 (3H, t, J= 7.2 Hz), 3.12 (2H, c, J= 7.6 Hz), 3.45 (3H, s), 7.15 (1H, d, J= 4.4 Hz), 7.19-7.23 (1H, m, J= 4.4 Hz), 7.61-7.63 (2H, m), 7.69-7.71 (1H, m), 7.92-7.95 (1H, m), 8.09-8.11 (1H, m), 8.13-8.14 (1H, m).8.71 (1H, s).8.82 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 427 (MH+)

HPLC = 84.2%

Ejemplo 21: N-butil-N-{3-[3-(tiofen-2-carbonil)-pirazolo [1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 0.91 (3H, t, J= 7.2 Hz), 1.36-1.44 (5H, m), 1.52-1.57 (2H, m), 3.1 (2H, c, J= 7.6 Hz), 3.78 (2H, t, J= 7.2 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.20-7.25 (1H, m), 7.61-7.63 (2H, m), 7.69-7.71 (1H, m), 7.99-8.02 (1H, m).8.09-8.11 (2H, m).8.71 (1H, s).8.82 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 469 (MH+)

HPLC = 99.06%

Ejemplo 22: 7-(3-(2-isotiazolidinil-1,1-dioxido)-fenil)-3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidina

~~88~~ 89

¹H NMR (400 MHz, CDCl₃): δ 2.57-2.61 (2H, m), 3.43 (2H, t, J= 7.6 Hz), 3.87 (2H, t, J= 6.4 Hz), 7.14 (1H, d, J= 4 Hz), 7.19 (1H, t), 7.46-7.50 (1H, m), 7.58 (1H, t), 7.68-7.69 (1H, d, J= 4 Hz), 7.78-7.79 (1H, d), 7.9 (1H, s). 8.09 (1H, d, J= 3.2 Hz). 8.69 (1H, s). 8.79 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 425 (MH+)
HPLC = 97.1%

Ejemplo 23: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo [1,5-a]pirimidin-7-il]-fenil}-2-propansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.4 (6H, d, J= 6.8 Hz), 3.36-3.41 (1H, m), 3.47 (3H, s), 7.15 (1H, d, J= 4.4 Hz), 7.18-7.21 (1H, m), 7.58-7.64 (2H, m), 7.69-7.71 (1H, m), 7.89-7.93 (1H, m), 8.09-8.10 (1H, m), 8.14-8.16 (1H, m). 8.7 (1H, s). 8.81 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 441 (MH+)
HPLC = 96.35%

Ejemplo 24: N-etil-N-{3-[3-(tiofen-2-carbonil)-pirazolo [1,5-a]pirimidin-7-il]-fenil}-2-propansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.21 (3H, t, J= 6.8 Hz), 1.41 (6H, d, J= 6.4 Hz), 3.28-3.32 (1H, m), 3.87 (2H, c, J= 7.2 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.18-7.21 (1H, m), 7.61-7.62 (2H, m), 7.69-7.71 (1H, m), 7.9-8.1 (1H, m), 8.09-8.12 (1H, m). 8.7 (1H, s). 8.81 (1H, d, J= 4.4 Hz).
MS (ES) m/z = 455 (MH+)
HPLC = 88.35%

Ejemplo 25: N-propil-N-{3-[3-(tiofen-2-carbonil)-pirazolo [1,5-a]pirimidin-7-il]-fenil}-2-propansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 0.93 (3H, t, J= 7.2 Hz), 1.41 (6H, d, J= 6.8 Hz), 1.57 (2H, q, J= 7.2 Hz), 3.3 (1H, m, J= 6.8 Hz), 3.77 (2H, t, J= 7.2 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.19-7.21 (1H, m), 7.61-7.63 (2H, m), 7.69-7.71 (1H, m), 7.99-8.11 (1H, m), 8.09-8.13 (2H, m), 8.7 (1H, s), 8.81 (1H, d, J= 4.4 Hz)
 MS (ES) m/z = 469 (MH+)
 HPLC = 97%

Ejemplo 26: N-butil -N-{3-[3-(tiofen-2-carbonil)-pirazolo [1,5-a]pirimidin-7-il]-fenil}-2-propansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 0.9 (3H, t, J= 7.2 Hz), 1.36 (2H, q, J= 8 Hz), 1.41 (6H, d, J= 6.8 Hz), 1.51-1.55 (2H, m), 3.29 (1H, m, J= 6.4 Hz), 8.81 (2H, t, J= 6.8 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.19-7.21 (1H, m), 7.62-7.63 (2H, m), 7.70-7.71 (1H, m), 7.99-8.01 (1H, m), 8.10-8.14 (2H, m), 8.7 (1H, s), 8.82 (1H, d, J= 4.4 Hz)
 MS (ES) m/z = 483 (MH+)
 HPLC = 100%

Ejemplo 27: N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-prop-2-inil-metansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 2.53 (1, s), 3.1 (3H, s), 4.53 (2H, s), 7.19 (1H, d, J= 4.4 Hz), 7.65 (1H, t, J= 7.6 Hz), 7.85-7.88 (1H, m, J= 4.4 Hz), 8.0-8.29 (1H, m), 8.27-8.28 (1H, m), 8.42 (1H, s), 8.79 (1H, d, J= 4.4 Hz)
 MS (ES) m/z = 352 (MH+)
 HPLC = 95.78%

Ejemplo 28: N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-propil-etansulfonamida

4 90

¹H NMR (400 MHz, CDCl₃): δ 0.93 (3H, t, J= 7.6 Hz), 1.41 (3H, t, J= 7.2 Hz), 1.54-1.59 (2H, m), 3.01 (2H, q, J= 7.2 Hz), 3.74 (2H, t, J= 7.2 Hz), 7.2 (1H, d, J= 4.4 Hz), 7.59-7.65 (2H, m), 7.96-7.99 (1H, m), 8.07-8.08 (1H, m), 8.41 (1H, s), 8.78 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 370 (MH⁺)

HPLC = 98%

Ejemplo 29: N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-etil-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.21 (3H, t, J= 7.2 Hz), 1.42 (3H, t, J= 7.6 Hz), 3.09 (2H, q, J= 7.6 Hz), 3.84 (2H, q, J= 7.2 Hz), 7.2 (1H, d, J= 4 Hz), 7.58-7.65 (2H, m), 7.97-7.99 (1H, m), 8.07 (1H, t, J= 1.6 Hz), 8.42 (1H, s), 8.78 (1H, d, J= 4.8 Hz)

MS (ES) m/z = 356 (MH⁺)

HPLC = 99%

Ejemplo 30: N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-prop-2-inil-propan-2-sulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.43 (6H, d, J= 7.2 Hz), 2.41-2.42 (1H, m), 3.43-3.50 (1H, m), 3.54 (2H, s), 7.2 (1H, d, J= 4 Hz), 7.63 (1H, t, J= 7.6 Hz), 7.77-7.80 (1H, m), 7.99-8.02 (1H, m), 8.21-8.22 (1H, m), 8.42 (1H, s), 8.78 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 380 (MH⁺)

HPLC = 97.46%

Ejemplo 31: N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-metil-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.4 (3H, t, J= 7.2 Hz), 3.11 (2H, q, J= 7.2 Hz), 3.43 (3H, s), 7.19 (1H, d, J= 4.4 Hz), 7.60-7.63 (2H, m), 7.89-7.92 (1H, m), 8.11 (1H, a), 8.42 (1H, s), 8.78 (1H, d, J= 4.4 Hz)
 5 MS (ES) m/z = 342 (MH+)
 HPLC = 91%

Ejemplo 32: N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-butil-etansulfonamida
 10

¹H NMR (400 MHz, CDCl₃): δ 1.43 (3H, t, J= 7.2 Hz), 2.49 (1H, t, J= 2.4 Hz), 3.26 (2H, q, J= 7.2 Hz), 4.54 (2H, d, J= 2.4 Hz), 7.2 (1H, d, J= 4 Hz), 7.64 (1H, t, J= 8 Hz), 7.82-7.85 (1H, m), 8.00-8.03 (1H, m), 8.25 (1H, t, J= 2 Hz), 8.42 (1H, s), 8.79 (1H, d, J= 4.4 Hz)
 15 MS (ES) m/z = 366 (MH+)
 HPLC = 98%

Ejemplo 33: 7-(3-(2-isotiazolidinil-1,1-dioxido)-fenil)-3-ciano-pirazolo[1,5-a]pirimidina
 20

¹H NMR (400 MHz, DMSO-d₆): δ 2.47-2.51 (2H, m), 3.61 (2H, t, J= 7.6 Hz), 3.87 (2H, t, J= 6.8 Hz), 7.52-7.56 (1H, m), 7.6 (1H, d, J= 4.8 Hz), 7.66 (1H, t), 7.8-7.85 (2H, m), 8.88 (1H, s), 8.95 (1H, d, J= 4.4 Hz)
 25 MS (ES) m/z = 340 (MH+)
 HPLC = 91.47%

Ejemplo 34: N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-metil-2-propansulfonamida
 30

91

^1H NMR (400 MHz, CDCl_3): δ 1.39 (6H, d, $J = 6.8$ Hz), 3.38 (1H, m), 3.45 (3H, s), 7.19 (1H, d, $J = 4$ Hz), 7.56-7.66 (2H, m), 7.87-7.90 (1H, m), 8.125 (1H, t, $J = 2$ Hz), 8.41 (1H, s), 8.78 (1H, d, $J = 4$ Hz)

5 MS (ES) $m/z = 356$ (MH+)

HPLC = 91%

Ejemplo 35: N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-etil-2-propansulfonamida

10

^1H NMR (400 MHz, CDCl_3): δ 1.95 (3H, t, $J = 7.2$ Hz), 1.41 (6H, d, $J = 6.8$ Hz), 3.28 (1H, m), 3.86 (2H, q, $J = 7.2$ Hz), 7.2 (1H, d, $J = 4.4$ Hz), 7.61-7.62 (2H, m), 7.96-7.99 (1H, m), 8.08-8.09 (1H, m), 8.41 (1H, s), 8.78 (1H, d, $J = 4$ Hz)

15 MS (ES) $m/z = 370$ (MH+)

HPLC = 98%

Ejemplo 36: N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-butil-2-propansulfonamida

20

^1H NMR (400 MHz, CDCl_3): δ 0.89 (3H, t, $J = 7.2$ Hz), 1.32-1.36 (2H, m), 1.53-1.56 (6H, d, $J = 6.8$ Hz), 1.49-1.51 (2H, m), 3.27 (1H, m), 3.79 (2H, t, $J = 7.6$ Hz), 7.2 (1H, d, $J = 4.4$ Hz), 7.61-7.63 (2H, m), 7.95-7.98 (1H, m), 8.1 (1H, a), 8.41 (1H, s), 8.78 (1H, d, $J = 4$ Hz)

25

MS (ES) $m/z = 398$ (MH+)

HPLC = 95%

Ejemplo 37: N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-propil-2-propansulfonamida

30

^1H NMR (400 MHz, CDCl_3): δ 0.92 (3H, t, $J = 7.2$ Hz), 1.4 (6H, d, $J = 6.8$ Hz), 1.53-1.56 (2H, m), 3.27 (1H, m), 3.76

(2H, t, J= 7.6 Hz), 7.2 (1H, d, J= 4.4 Hz), 7.61-7.63 (2H, m), 7.96-7.98 (1H, m), 8.1 (1H, a), 8.41 (1H, s), 8.78 (1H, d, J= 4 Hz)

MS (ES) m/z = 384 (MH+)

5

HPLC = 98.05%

Ejemplo 38: N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-prop-2-inil-etansulfonamida

10

¹H NMR (400 MHz, CDCl₃): δ 7.2 (3H, t, J= 7.6 Hz), 2.48 (1H, s), 3.25 (2H, c, J= 7.2 Hz), 4.54 (2H, s), 7.2 (1H, d, J= 4 Hz), 7.64 (1H, t, J= 8.4 Hz), 7.82-7.85 (1H, m), 7.99-8.03 (1H, m), 8.26-8.26 (1H, m), 8.42 (1H, s), 8.79 (1H, d, J= 4.1 Hz)

15

MS (ES) m/z = 366 (MH+)

HPLC = 97.7%

Ejemplo 39: N-metil-N-{3-[3-(piridin-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

20

¹H NMR (400 MHz, CDCl₃): δ 2.92 (3H, s), 3.41 (3H, s), 7.17 (1H, d, J= 4.4 Hz), 7.48-7.51 (1H, m), 7.62-7.63 (2H, m), 7.90-7.94 (2H, m), 8.16-8.16 (1H, m), 8.24 (1H, d, J= 6.8 Hz), 8.73-8.75 (1H, m), 8.90 (1H, d, J= 4.4 Hz), 9.36 (1H, s)

25

MS (ES) m/z = 408 (MH+)

HPLC = 99%

Ejemplo 40: N-etil-N-{3-[3-(piridin-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

30

¹H NMR (400 MHz, CDCl₃): δ 1.22 (3H, t, J= 7.2 Hz), 2.97 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.18 (1H, d, J= 4 Hz),

7.48-7.51 (1H, m), 7.59-7.67 (2H, m), 7.90-7.94 (1H, m),
7.98-8.00 (1H, m), 8.15 (1H, s), 8.24 (1H, d, J= 7.6 Hz),
8.75 (1H, d, J= 4.8 Hz), 8.9 (1H, d, J= 4.4 Hz), 9.36 (1H,
s)

5 MS (ES) m/z = 422 (MH+)
HPLC = 100%

Ejemplo 41: N-prop-2-inil-N-{3-[3-(piridin-2-carbonil)-
pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

10

¹H NMR (400 MHz, CDCl₃): δ 2.52-2.53 (1H, m), 3.12 (3H, s),
4.53-4.54 (2H, m), 7.17 (1H, d, J= 4.4 Hz), 7.48-7.52 (1H,
m), 7.65 (2H, t, J= 8 Hz), 7.82-7.85 (1H, m), 7.92 (1H, t,
J= 0.8 Hz), 8.03-8.06 (1H, m), 8.24 (1H, d, J= 8.4 Hz),
15 8.35 (1H, s), 8.75 (1H, d, J= 5.6 Hz), 8.9 (1H, d, J= 5.6
Hz), 9.37 (1H, s)

MS (ES) m/z = 432 (MH+)
HPLC = 96%

20 **Ejemplo 42:** N-metil-N-{3-[3-(piridin-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.4 (3H, t, J= 7.6 Hz), 3.12
(2H, q, J= 7.6 Hz), 3.44 (3H, s), 7.17 (1H, d, J= 4.4 Hz),
25 7.48-7.51 (1H, m), 7.61-7.64 (2H, m), 7.88-7.93 (2H, m),
8.16 (1H, t, J= 2 Hz), 8.24 (1H, d, J= 8.4 Hz), 8.74-8.75
(1H, m), 8.89 (1H, d, J= 5.2 Hz), 9.36 (1H, s)

MS (ES) m/z = 422 (MH+)
HPLC = 100%

30

Ejemplo 43: N-etil-N-{3-[3-(piridin-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.35 (3H, t, J= 7.2 Hz), 1.33 (3H, t, J= 7.2 Hz), 3.05 (2H, q, J= 7.2 Hz), 3.77 (2H, q, J= 7.2 Hz), 7.14 (1H, d, J= 4.8 Hz), 7.40-7.43 (1H, m), 7.54-7.56 (2H, m), 7.82-7.85 (1H, m), 7.92-7.93 (1H, m), 8.1 (1H, s), 8.13 (1H, d, J= 8 Hz), 8.66 (1H, d, J= 4.4 Hz), 8.81 (1H, d, J= 4.4 Hz), 9.28 (1H, s)
 MS (ES) m/z = 436 (MH+)
 HPLC = 95%

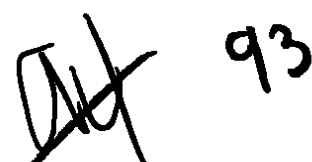
Ejemplo 44: N-prop-2-inil-N-{3-[3-(piridin-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.42 (3H, t, J= 7.2 Hz), 2.47 (1H,), 3.26 (2H, q, J= 7.2 Hz), 4.54 (2H, d, J= 2.4 Hz), 7.17 (1H, d, J= 4.8 Hz), 7.48-7.51 (1H, m), 7.63 (1H, t, J= 7.6 Hz), 7.8-7.82 (1H, m), 7.89-7.93 (1H, m), 8.02-8.05 (1H, m), 8.23 (1H, d, J= 8 Hz), 8.3 (1H, t, J= 2 Hz), 8.73-8.75 (1H, m), 8.89 (1H, d, J= 5.2 Hz), 9.36 (1H, s)
 MS (ES) m/z = 446 (MH+)
 HPLC = 98%

Ejemplo 45: N-metil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 2.92 (3H, s), 3.41 (3H, s), 7.2 (1H, d, J= 4.4 Hz), 7.26-7.64 (2H, m), 7.71-7.73 (2H, m), 7.93-7.96 (1H, m), 8.127-8.129 (1H, m), 8.57 (1H, s), 8.81-8.83 (3H, m)
 MS (ES) m/z = 408 (MH+)
 HPLC = 95%

Ejemplo 46: N-etil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida



¹H NMR (400 MHz, CDCl₃): δ 1.22 (3H, t, J= 7.2 Hz), 2.96 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.22 (1H, d, J= 4.4 Hz), (1H, m), 5.73 (2H, d, J= 5.6 Hz), 8.01 (1H, d, J= 7.6 Hz), 8.1 (1H, t, J= 2 Hz), 8.57 (1H, s), 8.82-8.84 (3H, m)
MS (ES) m/z = 422 (MH+)
HPLC = 89%

Ejemplo 47: N-metil-N-{3-[3-(piridin-4-carbonil)-pirazolo [1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.39 (3H, t, J= 7.2 Hz), 3.11 (2H, q, J= 7.2 Hz), 3.44 (3H, s), 7.2 (1H, d, J= 4.8 Hz), 7.62-7.63 (2H, m), 7.71-7.72 (2H, m), 7.92-7.94 (1H, m), 8.13-8.14 (1H, m), 8.57 (1H, s), 8.81-8.83 (3H, m)
MS (ES) m/z = 422 (MH+)
HPLC = 94%

Ejemplo 48: N-etil-N-{3-[3-(piridin-4-carbonil)-pirazolo [1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.13 (3H, t, J= 7.2 Hz), 1.318 (3H, t, J= 7.2 Hz), 3.04 (2H, q, J= 7.2 Hz), 3.77 (2H, q, J= 7.2 Hz), 7.18 (1H, d, J= 4.8 Hz), 7.52-7.58 (2H, m), 7.61-7.94 (2H, m), 8.05 (1H, s), 8.47 (1H, s), 8.71-8.73 (3H, m)
MS (ES) m/z = 436 (MH+)
HPLC = 89%

Ejemplo 49: N-prop-2-inil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.22 (3H, t, J= 7.2 Hz), 2.96 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.22 (1H, d, J= 4.4 Hz), 7.58-7.60 (1H, m), 7.66 (1H, t, J= 8 Hz), 7.71-7.73 (2H, m), 8.01 (1H, d, J= 7.6 Hz), 8.1 (1H, t, J= 2 Hz), 8.57 (1H, s), 8.82-8.84 (3H, m)

MS (ES) m/z = 422 (MH⁺)

HPLC = 89%

Ejemplo 50: N-prop-2-inil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 2.53 (1H, t, J= 2 Hz), 3.11 (3H, s), 4.54 (2H, d, J= 2.4 Hz), 7.2 (1H, d, J= 4.4 Hz), 7.66 (1H, t, J= 7.6 Hz), 7.72-7.73 (2H, m), 7.86-7.89 (1H, m), 8.03-8.05 (1H, m), 8.31 (1H, t, J= 2 Hz), 8.56 (1H, s), 8.82-8.84 (3H, m)

MS (ES) m/z = 432 (MH⁺)

HPLC = 93%

Ejemplo 51: N-metil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 2.93 (3H, s), 3.42 (3H, s), 7.15-7.20 (3H, m), 7.61-7.63 (2H, m), 7.94-7.99 (3H, m), 8.12-8.13 (1H, m), 8.55 (1H, s), 8.78 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 425 (MH⁺)

HPLC = 98%

Ejemplo 52: N-etil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.23 (3H, t, J= 7.2 Hz), 2.97 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.16-7.20 (3H, m), 7.56-

94

7.60 (1H, m), 7.65 (1H, t, J= 8 Hz), 7.96-8.02 (3H, m), 8.1 (1H, t, J= 2 Hz), 8.55 (1H, s), 8.79 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 439 (MH+)
HPLC = 98%

5

Ejemplo 53: N-metil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.38 (3H, t, J= 7.2 Hz), 3.11 (2H, q, J= 7.2 Hz), 3.42 (3H, s), 7.13-7.17 (3H, m), 7.59-7.61 (2H, m), 7.90-7.97 (3H, m, J= 8 Hz), 8.13 (1H, a), 8.53 (1H, s), 8.76 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 439 (MH+)
HPLC = 94%

15

Ejemplo 54: N-etil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.21 (3H, t, J= 7.2 Hz), 1.41 (3H, t, J= 7.2 Hz), 3.1 (2H, q, J= 7.2 Hz), 3.84 (2H, q, J= 7.2 Hz), 7.14-7.18 (3H, m), 7.58 (2H, m), 7.94-8.01 (3H, m), 8.1 (1H, a), 8.54 (1H, s), 8.77 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 453 (MH+)
HPLC = 99%

25

Ejemplo 55: N-prop-2-inil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.43 (3H, t, J= 7.2 Hz), 2.48 (1H, t, J= 2.4 Hz), 3.27 (2H, q, J= 7.2 Hz), 4.54 (2H, d, J= 2.4 Hz), 7.15-7.2 (3H, m), 7.64 (1H, t, J= 8 Hz), 7.81-

30

7.84 (1H, m), 7.96-8.04 (3H, m), 8.28 (1H, a), 8.56 (1H, s), 8.79 (1H, d, J= 4.4 Hz)

MS (ES) m/z = 463 (MH+)

HPLC = 96%

5

Ejemplo 56: N-prop-2-inil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

10 ¹H NMR (400 MHz, CDCl₃): δ 2.54 (1H, t, J= 2 Hz), 3.1 (3H, s), 4.52 (2H, d, J= 2 Hz), 7.14-7.18 (3H, m), 7.64 (1H, t, J= 7.6 Hz), 7.83-7.86 (1H, m), 7.94-7.96 (2H, m), 8.02-8.04 (1H, m), 8.3 (1H, t, J= 2 Hz), 8.54 (1H, s), 8.77 (1H, d, J= 4 Hz)

15 MS (ES) m/z = 449 (MH+)

HPLC = 96%

Ejemplo 57: N-metil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

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¹H NMR (400 MHz, CDCl₃): δ 2.93 (3H, s), 3.42 (3H, s), 3.9 (3H, s), 6.97-7.01 (2H, m), 7.12 (1H, d, J= 4.4 Hz), 7.61-7.65 (2H, m), 7.94-7.99 (3H, m), 8.13 (1H, a), 8.55 (1H, s), 8.78 (1H, d, J= 3.6 Hz)

25 MS (ES) m/z = 437 (MH+)

HPLC = 99%

Ejemplo 58: N-etil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

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¹H NMR (400 MHz, CDCl₃): δ 1.23 (3H, t, J= 7.2 Hz), 2.97 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 3.9 (3H, s), 6.98-7.00 (2H, m), 7.14 (1H, d, J= 4 Hz), 7.59-7.60 (1H, m), 7.65

OK 95

(1H, t, J= 8 Hz), 7.96-8.03 (3H, m), 8.1 (1H, t, J= 2 Hz). 8.55 (1H, s), 8.78 (1H, d, J= 4 Hz)
MS (ES) m/z = 451 (MH+)
HPLC = 98%

5

Ejemplo 59: N-metil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

10 ^1H NMR (400 MHz, CDCl_3): δ 1.41 (3H, t, J= 7.2 Hz), 3.13 (2H, q, J= 7.2 Hz), 3.45 (3H, s), 3.9 (3H, s), 6.98-7.00 (2H, m), 7.12 (1H, d, J= 4.4 Hz), 7.61-7.63 (2H, m), 7.93-7.98 (3H, m), 8.14 (1H, t, J= 1.2 Hz), 8.55 (1H, s), 8.78 (1H, d, J= 4 Hz)
MS (ES) m/z = 451 (MH+)
15 HPLC = 97%

Ejemplo 60: N-etil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

20 ^1H NMR (400 MHz, CDCl_3): δ 1.23 (3H, t, J= 7.2 Hz), 1.43 (3H, t, J= 7.2 Hz), 3.12 (2H, q, J= 7.2 Hz), 3.86 (2H, q, J= 7.2 Hz), 3.91 (3H, s), 6.98-7.00 (2H, m), 7.14 (1H, d, J= 4 Hz), 7.6-7.65 (2H, m), 7.96-8.02 (3H, m), 8.11 (1H, t, J= 1.6 Hz), 8.55 (1H, s), 8.78 (1H, d, J= 4 Hz)
25 MS (ES) m/z = 465 (MH+)
HPLC = 98%

Ejemplo 61: N-prop-2-inil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

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^1H NMR (400 MHz, CDCl_3): δ 1.43 (3H, t, J= 7.2 Hz), 2.48 (1H, t, J= 2.4 Hz), 3.27 (2H, q, J= 7.2 Hz), 3.9 (3H, s), 4.55 (2H, d, J= 2.4 Hz), 6.98-7.00 (2H, m), 7.13 (1H, d, J=

4.4 Hz), 7.64 (1H, t, J= 8 Hz), 7.80-7.83 (1H, m), 7.96-7.98 (2H, m), 8.03-8.05 (1H, m), 8.28 (1H, a), 8.55 (1H, s), 8.78 (1H, d, J= 3.6 Hz)

MS (ES) m/z = 475 (MH⁺)

5

HPLC = 97%

Ejemplo 62: N-prop-2-inil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

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¹H NMR (400 MHz, CDCl₃): δ 2.53 (1H, t, J= 2 Hz), 3.11 (3H, s), 3.87 (3H, s), 4.53 (2H, d, J= 2 Hz), 6.98 (2H, d, J= 8.8 Hz), 7.12 (1H, d, J= 4.4 Hz), 7.63 (1H, t, J= 7.6 Hz), 7.82-7.84 (1H, m), 7.95 (2H, d, J= 8.8 Hz), 8.03 (1H, d, J= 7.6 Hz), 8.31 (1H, t, J= 2 Hz), 8.54 (1H, s), 8.76 (1H, d, J= 4.4 Hz)

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MS (ES) m/z = 461 (MH⁺)

HPLC = 100%

Ejemplo 63: N-metil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

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¹H NMR (400 MHz, CDCl₃): δ 2.5 (3H, s), 2.97 (3H, s), 3.46 (3H, s), 7.18 (1H, d, J= 4.4 Hz), 7.34 (2H, d, J= 8.4 Hz), 7.65-7.67 (2H, m), 7.89 (2H, d, J= 8 Hz), 7.98-8.00 (1H, m), 8.17 (1H, s), 8.58 (1H, s), 8.83 (1H, d, J= 4.4 Hz)

25

MS (ES) m/z = 421 (MH⁺)

HPLC = 99%

Ejemplo 64: N-etil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

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¹H NMR (400 MHz, CDCl₃): δ 1.23 (3H, t, J= 7.2 Hz), 2.45 (3H, s), 2.96 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.15 (1H,

d, J= 4.4 Hz), 7.29-7.3 (2H, m), 7.58-7.64 (2H, m), 7.83-7.85 (2H, m), 7.99-8.02 (1H, m), 8.1 (1H, t, J= 2 Hz), 8.53 (1H, s), 8.79 (1H, d, J= 4.8 Hz)

MS (ES) m/z = 435 (MH+)

5 HPLC = 96%

Ejemplo 65: N-metil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

10 ^1H NMR (400 MHz, CDCl_3): δ 1.41 (3H, t, J= 7.2 Hz), 2.46 (3H, s), 3.12 (2H, q, J= 7.2 Hz), 3.44 (3H, s), 7.13 (1H, d, J= 4 Hz), 7.31 (2H, d, J= 8.4 Hz), 7.61-7.63 (2H, m), 7.85-7.87 (2H, m), 7.92-7.93 (1H, m), 8.13-8.14 (1H, m), 8.54 (1H, s), 8.79 (1H, d, J= 4.4 Hz)

15 MS (ES) m/z = 435 (MH+)
HPLC = 98%

Ejemplo 66: N-etil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

20

^1H NMR (400 MHz, CDCl_3): δ 1.22 (3H, t, J= 7.2 Hz), 1.42 (3H, t, J= 7.2 Hz), 2.46 (3H, s), 3.11 (2H, q, J= 7.2 Hz), 3.85 (2H, q, J= 7.2 Hz), 7.15 (1H, d, J= 4.4 Hz), 7.31 (2H, d, J= 8.2 Hz), 7.60-7.66 (2H, m), 7.84-7.86 (2H, m), 8 (1H, d, J= 7.6 Hz), 8.11 (1H, t, J= 1.6 Hz), 8.54 (1H, s), 8.8 (1H, d, J= 4.4 Hz)

25

MS (ES) m/z = 449 (MH+)
HPLC = 100%

30 **Ejemplo 67:** N-prop-2-inil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.43 (3H, t, J= 7.2 Hz), 2.46 (3H, s), 2.48 (1H, t, J= 2.4 Hz), 3.27 (2H, q, J= 7.2 Hz), 4.54 (2H, d, J= 2.4 Hz), 7.14 (1H, d, J= 4 Hz), 7.31 (2H, d, J= 8 Hz), 7.63 (1H, t, J= 8 Hz), 7.81-7.86 (3H, m), 8.03 (1H, d, J= 8 Hz), 8.28 (1H, t, J= 2 Hz), 8.54 (1H, s), 8.8 (1H, d, J= 4.4 Hz)
 MS (ES) m/z = 459 (MH+)
 HPLC = 98%

Ejemplo 68: N-prop-2-inil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 2.46 (3H, s), 2.53 (1H, t, J= 2.4 Hz), 3.11 (3H, s), 4.54 (2H, d, J= 2.4 Hz), 7.14 (1H, d, J= 4 Hz), 7.3 (2H, d, J= 8 Hz), 7.64 (1H, t, J= 8 Hz), 7.83-7.86 (3H, m), 8.03-8.05 (1H, m), 8.31 (1H, t, J= 2 Hz), 8.54 (1H, s), 8.8 (1H, d, J= 4.4 Hz)
 MS (ES) m/z = 445 (MH+)
 HPLC = 98%

20

Ejemplo 69: N-metil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 2.93 (3H, s), 3.42 (3H, s), 7.15 (1H, d, J= 4.4 Hz), 7.49-7.52 (2H, m), 7.58-7.63 (3H, m), 7.92-7.94 (3H, m), 8.13 (1H, a), 8.54 (1H, s), 8.81 (1H, d, J= 4.4 Hz)
 MS (ES) m/z = 407 (MH+)
 HPLC = 96%

30

Ejemplo 70: N-etil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

97

¹H NMR (400 MHz, CDCl₃): δ 1.22 (3H, t, J= 7.2 Hz), 2.97 (3H, s), 3.82 (2H, q, J= 7.2 Hz), 7.17 (1H, d, J= 4.4 Hz), 7.49-7.52 (2H, m), 7.56-7.67 (3H, m), 7.91-7.94 (2H, m), 7.80-8.02 (1H, m), 8.11 (1H, t, J= 2 Hz), 8.53 (1H, s), 8.82 (1H, d, J= 4.4 Hz)
MS (ES) m/z = 421 (MH+)
HPLC = 98%

10 **Ejemplo 71:** N-metil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.39 (3H, t, J= 7.2 Hz), 3.11 (2H, q, J= 7.2 Hz), 3.43 (3H, s), 7.15 (1H, a), 7.47-7.61 (5H, m), 7.91 (3H, d, J= 7.6 Hz), 8.14 (1H, s), 8.52 (1H, s), 8.79 (1H, a)
MS (ES) m/z = 421 (MH+)
HPLC = 98%

20 **Ejemplo 72:** N-etil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.23 (3H, t, J= 7.2 Hz), 1.42 (3H, t, J= 7.2 Hz), 1.56 (3H, s), 3.11 (2H, q, J= 7.2 Hz), 3.85 (2H, q, J= 7.2 Hz), 7.17 (1H, d, J= 4.4 Hz), 7.49-7.53 (2H, m), 7.58-7.66 (3H, m), 7.92-7.94 (2H, m), 8.01 (1H, d, J= 7.6 Hz), 8.11 (1H, t, J= 1.6 Hz), 8.54 (1H, s), 8.82 (1H, d, J= 4.8 Hz)
MS (ES) m/z = 435 (MH+)
HPLC = 100%

30 **Ejemplo 73:** N-prop-2-inil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.43 (3H, t, J= 7.2 Hz), 2.48 (1H, t, J= 2.8 Hz), 3.27 (2H, q, J= 7.2 Hz), 4.54 (2H, d, J= 2.8 Hz), 7.16 (1H, d, J= 4.4 Hz), 7.49-7.52 (2H, m), 7.58-7.66 (2H, m), 7.82 (1H, d, J= 8 Hz), 7.93 (2H, d, J= 6.8 Hz), 8.04 (1H, d, J= 8 Hz), 8.29 (1H, a), 8.54 (1H, s), 8.81 (1H, d, J= 4.4 Hz)
 MS (ES) m/z = 445 (MH+)
 HPLC = 97%

10

Ejemplo 74: N-prop-2-inil-N-(3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil)-metansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 2.53 (1H, t, J= 2.4 Hz), 3.12 (3H, s), 4.54 (2H, d, J= 2.4 Hz), 7.16 (1H, d, J= 4.8 Hz), 7.49-7.53 (2H, m), 7.58-7.60 (1H, m), 7.65 (1H, t, J= 8 Hz), 7.84-7.86 (1H, m), 7.92-7.94 (2H, m), 8.04 (1H, d, J= 8 Hz), 8.32 (1H, t, J= 2 Hz), 8.54 (1H, s), 8.82 (1H, d, J= 4.4 Hz)
 MS (ES) m/z = 431 (MH+)
 HPLC = 97%

20

Ejemplo 75: N-metil-N-(3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil)-2-feniletenesulfonamida

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¹H NMR (400 MHz, CDCl₃): δ 3.35 (3H, s), 6.78 (1H, d, J= 15.5 Hz), 7.13 (1H, d, J= 4.6 Hz), 7.21 (1H, dd), 7.48-7.52 (6H, m), 7.6-7.63 (2H, m), 7.71 (1H, dd), 7.92-7.96 (1H, m), 8.06 (1H, dd), 8.13 (1H, m), 8.53 (1H, m), 8.8 (1H, d, J= 4.6 Hz)
 MS (ES) m/z = 501 (MH+)
 HPLC = 96.98%

30

98

Ejemplo 76: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-2,2,2-trifluoroetan-
sulfonamida

5 ^1H NMR (400 MHz, CDCl_3): δ 3.48 (3H, s), 3.87 (2H, c, J= 9.1 Hz), 7.16 (1H, d, J= 4.6 Hz), 7.21 (1H, dd), 7.65-7.67 (1H, m), 7.68 (1H, s), 7.72 (1H, dd), 7.98-8.02 (1H, m), 8.09 (1H, dd), 8.2 (1H, m), 8.7 (1H, s), 8.84 (1H, d, J= 4.6 Hz)

10 MS (ES) m/z = 481 (MH+)

HPLC = 99.05%

Ejemplo 77: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-2-clorobencenosulfonamida

15

^1H NMR (400 MHz, CDCl_3): δ 3.47 (3H, s), 7.06 (1H, d, J= 4.6 Hz), 7.19-7.23 (1H, m), 7.32-7.39 (1H, m), 7.46-7.57 (4H, m), 7.7-7.72 (1H, m), 7.92-8 (3H, m), 8.09-8.11 (1H, m), 8.67 (1H, s), 8.8 (1H, d, J= 4.6 Hz)

20 MS (ES) m/z = 510 (MH+)

HPLC = 99.81%

Ejemplo 78: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-3-clorobencenosulfonamida

25

^1H NMR (400 MHz, CDCl_3): δ 3.27 (3H, s), 7.11 (1H, d, J= 4.6 Hz), 7.19-7.61 (7H, m), 7.7-7.72 (1H, m), 7.85 (1H, m), 7.97-8.01 (1H, m), 8.09-8.11 (1H, m), 8.68 (1H, s), 8.81 (1H, d, J= 4.6 Hz)

30 MS (ES) m/z = 510 (MH+)

HPLC = 97.44%

Ejemplo 79: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-4-clorobencenosulfonamida

¹H NMR (400 MHz, CDCl₃): δ 3.25 (3H, s), 7.1 (1H, d, J= 4.6
Hz), 7.2-7.24 (1H, m), 7.33-7.37 (1H, m), 7.46-7.6 (5H, m),
7.72 (1H, dd), 7.85-7.87 (1H, m), 7.95-8 (1H, m), 8.09-8.11
(1H, m), 8.69 (1H, s). 8.82 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 510 (MH⁺)

HPLC = 99.69%

Ejemplo 80: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-2,4-diclorobencenosulfonamida

¹H NMR (400 MHz, CDCl₃): δ 3.46 (3H, s), 7.08 (1H, d, J=
4.6 Hz), 7.21 (1H, dd), 7.33 (1H, dd), 7.46-7.59 (3H, m),
7.71 (1H, dd), 7.87-7.98 (3H, m), 8.09 (1H, dd), 8.67 (1H,
s), 8.81 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 543 (MH⁺)

HPLC = 98.04%

Ejemplo 81: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-3,4-diclorobencenosulfonamida

¹H NMR (400 MHz, CDCl₃): δ 3.27 (3H, s), 7.11 (1H, d, J=
4.6 Hz), 7.21 (1H, dd), 7.37-7.47 (2H, m), 7.56-7.62 (2H,
m), 7.7-7.72 (2H, m), 7.86-7.88 (1H, m), 7.94-7.99 (1H, m),
8.09 (1H, dd), 8.67 (1H, s). 8.81 (1H, d, J= 4.6 Hz)

MS (ES) m/z = 543 (MH⁺)

HPLC = 98.03%

Ejemplo 82: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-2-cianobencenosulfonamida

100 99

¹H NMR (400 MHz, CDCl₃): δ 3.41 (3H, s), 7.15 (1H, d, J= 4.6 Hz), 7.2 (1H, dd), 7.34-7.39 (1H, m), 7.53-7.59 (1H, m), 7.69-7.77 (3H, m), 7.83-7.87 (1H, m), 7.91-8.01 (3H, m), 8.1 (1H, dd), 8.63 (1H, s), 8.79 (1H, d, J= 4.6 Hz)

5 MS (ES) m/z = 500 (MH⁺)

HPLC = 99.32%

Ejemplo 83: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo [1,5-a]pirimidin-7-il]-fenil}-3-cianobencenosulfonamida

10

¹H NMR (400 MHz, CDCl₃): δ 3.28 (3H, s), 7.13 (1H, d, J= 4.6 Hz), 7.19-7.22 (1H, m), 7.33-7.36 (1H, m), 7.56-7.72 (3H, m), 7.83-7.97 (5H, m), 8.09 (1H, d, J= 3.6 Hz), 8.66 (1H, s), 8.81 (1H, d, J= 4.6 Hz)

15 MS (ES) m/z = 500 (MH⁺)

HPLC = 96.69%

Ejemplo 84: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo [1,5-a]pirimidin-7-il]-fenil}-4-cianobencenosulfonamida

20

¹H NMR (400 MHz, CDCl₃): δ 3.28 (3H, s), 7.12 (1H, d, J= 4.2 Hz), 7.2-7.32 (3H, m), 7.58 (1H, t, J= 8 Hz), 7.71-7.83 (4H, m), 7.91 (1H, a), 7.99 (1H, d, J= 7.6 Hz), 8.09 (1H, d, J= 3.3 Hz), 8.68 (1H, s), 8.83 (1H, d, J= 3.9 Hz)

25 MS (ES) m/z = 500 (MH⁺)

HPLC = 97.9%

Ejemplo 85: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo [1,5-a]pirimidin-7-il]-fenil}-3-nitrobencenosulfonamida

30

¹H NMR (400 MHz, CDCl₃): δ 3.3 (3H, s), 7.12 (1H, d, J= 4.6 Hz), 7.22 (1H, dd), 7.38-7.43 (1H, m), 7.6 (1H, t, J= 7.9

Hz), 7.7-7.77 (2H, m), 7.86-7.97 (3H, m), 8.09 (1H, dd),
 8.4-8.5 (2H, m), 8.6 (1H, s).8.8 (1H, d, J= 4.6 Hz)
 MS (ES) m/z = 520 (MH+)
 HPLC = 99.14%

5

Ejemplo 86: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
 [1,5-a]pirimidin-7-il]-fenil}-4-nitrobencenosulfonamida

¹H NMR (400 MHz, CDCl₃): δ 3.3 (3H, s), 7.13 (1H, d, J= 4.6
 10 Hz), 7.23 (1H, dd, J= 4.8 - 0.9 Hz), 7.32-7.37 (1H, m), 7.6
 (1H, t, J= 7.9 Hz), 7.73 (1H, dd, J= 4.8 - 3.6 Hz), 7.82
 (2H, d, J= 9.1 Hz), 7.9 (1H, m), 7.95-7.99 (1H, m), 8.07
 (1H, dd).8.36 (2H, d, J= 9.1 Hz).8.66 (1H, s).8.83 (1H, d,
 J= 4.6 Hz)
 15 MS (ES) m/z = 520 (MH+)
 HPLC = 96.18%

Ejemplo 87: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
 [1,5-a]pirimidin-7-il]-fenil}-2-tiofensulfonamida

20

¹H NMR (400 MHz, CDCl₃): δ 3.35 (3H, s), 7.13-7.18 (2H, d),
 7.23-7.31 (1H, m), 7.39-7.46 (2H, m), 7.58-7.68 (2H, m),
 7.74-7.77 (1H, m), 7.93 (1H, d, J= 1.5 Hz), 8.06 (1H, dd,
 J= 7.9 - 1.2 Hz), 8.14 (1H, m), 8.72 (1H, s).8.85 (1H, d,
 25 J= 4.3 Hz)
 MS (ES) m/z = 481 (MH+)
 HPLC = 98.82%

Ejemplo 88: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
 30 [1,5-a]pirimidin-7-il]-fenil}-5-metil-4-isoxazolil-
 sulfonamida

~~100~~ 100

¹H NMR (400 MHz, CDCl₃): δ 2.3 (3H, s), 3.29 (3H, s), 7.11 (1H, d, J= 4.2 Hz), 7.21 (1H, dd, J= 5.2 - 3.9 Hz), 7.51-7.55 (1H, m), 7.63 (1H, t, J= 7.9 Hz), 7.71 (1H, dd, J= 5.2 - 1.2 Hz), 7.91-7.94 (2H, m), 8.07 (1H, dd), 8.32 (1H, d, J= 0.6 Hz), 8.7 (1H, s), 8.82 (1H, d, J= 4.2 Hz)
 MS (ES) m/z = 480 (MH+)
 HPLC = 96.78%

Ejemplo 89: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo [1,5-a]pirimidin-7-il]-fenil}-2-trifluorometil-5-metil-3-furilsulfonamida

¹H NMR (400 MHz, CDCl₃): δ 2.23 (3H, s), 3.3 (3H, s), 7.11 (1H, d, J= 4.6 Hz), 7.2-7.24 (1H, m), 7.52-7.66 (2H, m), 7.72 (1H, dd, J= 4.9 - 1.2 Hz), 7.91-7.95 (2H, m), 8.07 (1H, dd), 8.67 (1H, s), 8.82 (1H, d, J= 4.2 Hz)
 MS (ES) m/z = 547 (MH+)
 HPLC = 98.88%

Ejemplo 90: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo [1,5-a]pirimidin-7-il]-fenil}-6-(morfolin-4-il)-3-piridilsulfonamida

¹H NMR (400 MHz, CDCl₃): δ 3.24 (3H, s), 3.62-3.67 (4H, m), 3.78-3.82 (4H, m), 6.55 (1H, d, J= 9.1 Hz), 7.14 (1H, d, J= 4.2 Hz), 7.21 (1H, dd, J= 4.9 - 3.6 Hz), 7.36-7.4 (1H, m), 7.53-7.6 (2H, m), 7.72 (1H, dd, J= 4.9 - 1.2 Hz), 7.93-8.01 (2H, m), 8.1-8.12 (1H, m), 8.39 (1H, d, J= 2.4 Hz), 8.69 (1H, s), 8.81 (1H, d, J= 4.6 Hz)
 MS (ES) m/z = 561 (MH+)
 HPLC = 98.7%

Ejemplo 91: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-2,4-dimetil-5-tiazolil-
sulfonamida

5 ^1H NMR (400 MHz, CDCl_3): δ 2.22 (3H, s), 2.69 (3H, s), 3.35
(3H, s), 7.11 (1H, d, $J = 4.6$ Hz), 7.2 (1H, dd), 7.43-7.47
(1H, m), 7.59 (1H, m), 7.71 (1H, dd), 7.93-7.94 (1H, m),
7.97-8.02 (1H, m), 8.09 (1H, dd, $J = 3.7 - 1.1$ Hz), 8.68 (1H,
s), 8.81 (1H, d, $J = 4.6$ Hz)

10 MS (ES) $m/z = 510$ (MH $^+$)

HPLC = 99.18%

Ejemplo 92: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-ciclopropilsulfonamida

15

^1H NMR (400 MHz, CDCl_3): δ 0.95-1.06 (2H, m), 1.09-1.18
(2H, m), 2.4-2.51 (1H, m), 3.44 (3H, s), 7.16 (1H, d, $J =$
4.6 Hz), 7.19-7.23 (1H, m), 7.58-7.73 (3H, m), 7.96 (1H,
m), 8.11 (1H, m), 8.16 (1H, m), 8.71 (1H, s), 8.82 (1H, d, $J =$
20 4.2 Hz)

MS (ES) $m/z = 439$ (MH $^+$)

HPLC = 96.7%

Ejemplo 93: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-bencilsulfonamida

25

^1H NMR (400 MHz, CDCl_3): δ 3.21 (3H, s), 4.39 (2H, s), 7.1
(1H, d, $J = 4.6$ Hz), 7.2-7.24 (1H, m), 7.33-7.47 (6H, m),
7.54-7.6 (1H, m), 7.71 (1H, d, $J = 4.9$ Hz), 7.87-7.92 (2H,
30 m), 8.12 (1H, d, $J = 3.3$ Hz), 8.74 (1H, s), 8.83 (1H, d, $J =$
4.6 Hz)

MS (ES) $m/z = 489$ (MH $^+$)

HPLC = 97.95%

101

Ejemplo 94: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-vinilsulfonamida

5 ^1H NMR (400 MHz, CDCl_3): δ 3.32 (3H, s), 6.08 (1H, d, $J=$
9.7 Hz), 6.26 (1H, d, $J= 16.4$ Hz), 6.51 (1H, dd, $J= 16.4 -$
9.7 Hz), 7.15 (1H, d, $J= 4.2$ Hz), 7.2 (1H, dd, $J= 4.8 - 3.9$
Hz), 7.53-7.64 (2H, m), 7.7 (1H, dd, $J= 4.8 - 1.2$ Hz),
7.94-7.98 (1H, m), 8.06-8.11 (2H, m)

10 MS (ES) $m/z = 425$ (MH $^+$)

HPLC = 97.53%

Ejemplo 95: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-3,5-dimetil-4-isoxazolil-
15 sulfonamida

^1H NMR (400 MHz, CDCl_3): δ 2.12 (3H, s), 2.33 (3H, s), 3.31
(3H, s), 7.1 (1H, d, $J= 4.5$ Hz), 7.19-7.23 (1H, m), 7.52-
7.66 (2H, m), 7.71 (1H, d, $J= 5.5$ Hz), 7.93-7.96 (2H, m),
20 8.07 (1H, d, $J= 3.6$ Hz), 8.69 (1H, s), 8.82 (1H, d, $J= 4.2$
Hz)

MS (ES) $m/z = 494$ (MH $^+$)

HPLC = 99.17%

25 **Ejemplo 96:** N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-1,3,5-trimetil-4-pirazolil-
sulfonamida

30 ^1H NMR (400 MHz, CDCl_3): δ 2.09 (3H, s), 2.1 (3H, s), 3.24
(3H, s), 3.7 (3H, s), 7.1 (1H, d, $J= 4.2$ Hz), 7.2 (1H, dd,
 $J= 4.8 - 3.6$ Hz), 7.45-7.59 (2H, m), 7.71 (1H, dd), 7.9-
7.98 (2H, m), 8.09-8.11 (1H, m), 8.67 (1H, s), 8.8 (1H, d,
 $J= 4.2$ Hz)

MS (ES) m/z = 507 (MH⁺)

HPLC = 94.68%

Ejemplo 97: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
5 [1,5-a]pirimidin-7-il]-fenil}-propansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.06 (3H, t, J= 7.5 Hz), 1.92-
1.97 (2H, m), 3.02-3.08 (2H, m), 3.43 (3H, s), 7.16 (1H, d, .
J= 4.2 Hz), 7.19-7.23 (1H, m), 7.62-7.64 (2H, m), 7.72 (1H,
10 m), 7.93-7.97 (1H, m), 8.11-8.14 (2H, m).8.71 (1H, s).8.83
(1H, d, J= 4.6 Hz)

MS (ES) m/z = 441 (MH⁺)

HPLC = 97.75%

Ejemplo 98: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
15 [1,5-a]pirimidin-7-il]-fenil}-butansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 0.93 (3H, t, J= 7.5 Hz), 1.44
(2H, m), 1.77-1.89 (2H, m), 3.04-3.11 (2H, m), 3.43 (3H,
20 s), 7.16 (1H, d, J= 4.6 Hz), 7.2 (1H, dd, J= 5.2 - 3.9 Hz),
7.61-7.64 (2H, m), 7.71 (1H, dd, J= 5.2 - 1.2 Hz), 7.91-
7.96 (1H, m).8.1 (1H, dd, J= 3.9 - 1.2 Hz).8.14 (1H, m).8.7
(1H, s).8.82 (1H, d, J= 4.3 Hz)

MS (ES) m/z = 455 (MH⁺)

25 HPLC = 98.54%

Ejemplo 99: N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo
[1,5-a]pirimidin-7-il]-fenil}-ciclopentilmetansulfonamida

30 ¹H NMR (400 MHz, CDCl₃): δ 1.23-1.34 (2H, m), 1.56-1.66
(4H, m), 1.95-2.03 (2H, m), 2.32-2.44 (1H, m), 3.08 (2H, d,
J= 7 Hz), 3.42 (3H, s), 7.16 (1H, d, J= 4.2 Hz), 7.2 (1H,
dd, J= 4.9 - 3.9 Hz), 7.61-7.63 (2H, m), 7.71 (1H, dd, J=

~~107~~ 102

4.9 - 1.2 Hz). 7.91-7.96 (1H, m). 8.09-8.14 (2H, m). 8.7 (1H, s). 8.82 (1H, d, J = 4.2 Hz)

MS (ES) m/z = 481 (MH⁺)

HPLC = 96.43%

5

Ejemplo 100: N-{3-[3-(5-metil-[1,2,4]oxadiazol-3-il)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 2.71 (3H, s), 3.12 (3H, s), 7.08 (1H, d, J = 4.4 Hz), 7.1 (1H, a), 7.43-7.46 (1H, m), 7.57 (1H, t, J = 7.6 Hz), 7.80-7.83 (1H, m), 7.95 (1H, t, J = 2 Hz), 8.69 (1H, s), 8.8 (1H, d, J = 4.4 Hz)

MS (ES) m/z = 371 (MH⁺)

HPLC = 94%

10

15

Ejemplo 101: N-etil-N-{3-[3-(5-metil-[1,2,4]oxadiazol-3-il)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida

¹H NMR (400 MHz, CDCl₃): δ 1.21 (3H, t, J = 7.2 Hz), 2.69 (3H, s), 2.95 (3H, s), 3.81 (2H, q, J = 7.2 Hz), 7.1 (1H, d, J = 4.8 Hz), 7.56-7.58 (1H, m), 7.64 (1H, t, J = 8 Hz), 8.04 (1H, d, J = 8 Hz), 8.09 (1H, t, J = 2 Hz), 8.69 (1H, s), 8.817 (1H, d, J = 4.8 Hz)

MS (ES) m/z = 399 (MH⁺)

HPLC = 94%

20

25

Ejemplo 102: Comprimidos de 5 mg

Compuesto del Ejemplo 2	5.0 mg
Dióxido de silicio coloidal	0.6 mg
Croscaramelosa sódica	12.0 mg
Talco	4.0 mg

Estearato de magnesio	1.5	mg
Polisorbato 80	1.0	mg
Lactosa	75.0	mg
Hidroxipropil metilcelulosa	3.0	mg
Polietilenglicol 4000	0.5	mg
Dióxido de titanio E171	1.5	mg
Celulosa microcristalina c.s.h.	125.0	mg

Ejemplo 103: Cápsulas de 10 mg

Compuesto del Ejemplo 2	10.0	mg
Dióxido de silicio coloidal	0.6	mg
Crospovidona	12.0	mg
Talco	4.0	mg
Estearato de magnesio	1.5	mg
Laurilsulfato sódico	1.5	mg
Lactosa	77.0	mg
Gelatina	28.5	mg
Dióxido de titanio E171	1.5	mg
Indigotina E132	0.02	mg
Celulosa microcristalina c.s.h.	155.0	mg

5 Ejemplo 104: Gotas orales

Compuesto del Ejemplo 2	0.5	g
Propilenglicol	10.0	g
Glicerina	5.0	g
Sacarina sódica	0.1	g
Polisorbato 80	1.0	g
Esencia de limón	0.2	g

~~103~~ 103

Etanol	25.0	mL
Agua purificada c.s.h.	100.0	mL

5

Ejemplo 105: Comprimidos de 2.5 mg

Compuesto del Ejemplo 16	2.5	mg
Dióxido de silicio coloidal	0.6	mg
Croscaramelosa sódica	12.0	mg
Talco	4.0	mg
Estearato de magnesio	1.5	mg
Polisorbato 80	1.0	mg
Lactosa	75.0	mg
Hidroxipropil metilcelulosa	3.0	mg
Polietilenglicol 4000	0.5	mg
Dióxido de titanio E171	1.5	mg
Celulosa microcristalina c.s.h.	125.0	mg

10

Ejemplo 106: Cápsulas de 5 mg

Compuesto del Ejemplo 16	5.0	mg
Dióxido de silicio coloidal	0.6	mg
Crospovidona	12.0	mg
Talco	4.0	mg
Estearato de magnesio	1.5	mg
Laurilsulfato sódico	1.5	mg
Lactosa	77.0	mg
Gelatina	28.5	mg
Dióxido de titanio E171	1.5	mg

Indigotina E132	0.02 mg
Celulosa microcristalina c.s.h.	155.0 mg

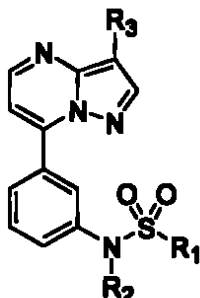
Ejemplo 107: Gotas orales

Compuesto del Ejemplo 2	0.25 g
Propilenglicol	10.0 g
Glicerina	5.0 g
Sacarina sódica	0.1 g
Polisorbato 80	1.0 g
Esencia de limón	0.2 g
Etanol	25.0 mL
Agua purificada c.s.h.	100.0 mL

107 104

REIVINDICACIONES

1) - Un compuesto de fórmula (I):



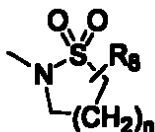
(I)

y sus sales farmacéuticamente aceptables;

donde

R_1 se selecciona entre alquil(C_1-C_6), alquenil(C_2-C_6),
 ω,ω,ω -trifluoroalquil(C_1-C_6), cicloalquil(C_3-C_6),
 cicloalquil(C_3-C_6)alquil(C_1-C_6), -O-alquil(C_1-C_6), -NH-
 alquil(C_1-C_6), -N(dialquil(C_1-C_6)), alquil(C_1-C_6)-O-
 alquil(C_1-C_6), alquil(C_1-C_6)-NH-alquil(C_1-C_6), alquil(C_1-C_6)-
 N(dialquil(C_1-C_6)), fenil, fenil monosustituido, fenil
 disustituido, fenilalquil(C_1-C_6), fenilalquenil(C_2-C_6),
 furanil, furanil sustituido, isoxazolil, isoxazolil
 sustituido, pirazolil, pirazolil sustituido, tienil, tienil
 sustituido, tiazolyl, tiazolil sustituido, piridil y
 piridil sustituido;

R_2 se selecciona entre hidrógeno, alquil(C_1-C_6),
 alquenil(C_2-C_6), alquinil(C_2-C_6) y cicloalquil(C_3-C_6); o bien
 R_1 y R_2 forman un ciclo de estructura:



donde n es un entero de 0 a 3 inclusive;

- R_3 se selecciona entre hidrógeno, halógeno, alquil(C_1-C_6), cicloalquil(C_3-C_6), alquenil(C_2-C_6), alquinil(C_2-C_6), -O-alquil(C_1-C_6), halo-alquil(C_1-C_6), -CN, -SO₂-R₄, -NH-R₄, -NR₄R₅, -COR₆, -CO-NHR₆, COOR₆, -C(NR₇)R₆, fenil, fenil sustituido, heteroaril y heteroaril sustituido;
- R_4 y R_5 se seleccionan independientemente entre alquil(C_1-C_6), cicloalquil(C_3-C_6), aril y heteroaril;
- R_6 se selecciona entre hidrógeno, alquil(C_1-C_6), alquenil(C_2-C_6), alquinil(C_2-C_6), cicloalquil(C_3-C_6), fenil, fenil sustituido, furanil, furanil sustituido, tienil, tienil sustituido, tiazolil, tiazolil sustituido, piridil y piridil sustituido;
- R_7 se selecciona entre alquil, cicloalquil(C_3-C_6), -OH, -O-alquil(C_1-C_6), alquil(C_1-C_6)-O-alquil(C_1-C_6), alquil(C_1-C_6)-NH-alquil(C_1-C_6), alquil(C_1-C_6)-N(dialquil(C_1-C_6))), fenil, fenil monosustituido, furanil, tienil, tiazolil y piridil;
- y
- R_8 se selecciona entre hidrógeno, alquil(C_1-C_6), cicloalquil(C_3-C_6), aril y heteroaril sustituido o no;
- a condición de que:
- R_1 no puede ser p-tolil y R_2 metil y R_3 benzoil simultáneamente; y
- R_1 no puede ser p-tolil y R_2 etil y R_3 furanil-2-carbonil simultáneamente.
- 2) - Un compuesto de acuerdo con la reivindicación 1 donde R_1 y R_2 son grupos independientes y tienen los significados definidos en la fórmula (I) y R_3 es un grupo ciano.
- 3) - Un compuesto de acuerdo con la reivindicación 2 donde R_1 se selecciona entre metil, etil, n-propil, i-propil n-butil, fenil y 4-metoxi-fenil; y R_2 se selecciona

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entre metil, etil, n-propil, i-propil, n-butil, ciclopropil y 2-propinil.

4) - Un compuesto de acuerdo con la reivindicación 2 donde R_1 y R_2 forman conjuntamente un grupo 1,3-propileno.

5) - Un compuesto de acuerdo con la reivindicación 1 donde R_1 y R_2 son grupos independientes y tienen los significados definidos en la fórmula (I) y R_3 es un grupo tiofen-2-carbonil.

6) - Un compuesto de acuerdo con la reivindicación 5, donde R_1 se selecciona entre metil, etil, n-propil, i-propil, n-butil, 2-feniletetil, 2,2,2-trifluoroetil, fenil, 2-clorofenil, 3-clorofenil, 4-clorofenil, 2,4-diclorofenil, 3,4-diclorofenil, 2-cianofenil, 3-cianofenil, 4-cianofenil, 4-methoxyphenyl, 3-nitrofenil, 4-nitrofenil, 2-tienil, 5-metil-4-isoxazolil, 5-metil-2-trifluorometil-3-furil, 4-(4-morfolinil)-3-piridil, 2,4-dimetil-5-tiazolil, ciclopropil, bencil, vinil, 3,5-dimetil-4-isoxazolil, 1,3,5-trimetil-4-pirazolil and ciclopentilmetil; y R_2 se selecciona entre hidrógeno, metil, etil, n-propil, i-propil, n-butil, ciclopropil y 2-propinil.

7) - Un compuesto de acuerdo con la reivindicación 5 donde R_1 y R_2 forman conjuntamente un grupo 1,3-propileno.

8) - Un compuesto de acuerdo con la reivindicación 1 donde R_1 y R_2 son grupos independientes y tiene los significados definidos en la fórmula (I) y R_3 es un grupo benzoil.

9) - Un compuesto de acuerdo con la reivindicación 8 donde R_1 se selecciona entre metil y etil; y R_2 se selecciona entre metil, etil y 2-propinil.

10) - Un compuesto de acuerdo con la reivindicación 1 donde R_1 y R_2 son grupos independientes y tiene los

significados definidos en la fórmula (I) y R_3 es un grupo fluorobenzoil.

5 11) - Un compuesto de acuerdo con la reivindicación 10 donde R_1 se selecciona entre metil y etil; y R_2 se selecciona entre metil, etil y 2-propinil.

12) - Un compuesto de acuerdo con la reivindicación 1 donde R_1 y R_2 son grupos independientes y tiene los significados definidos en la fórmula (I) y R_3 es un grupo 4-metilbenzoil.

10 13) - Un compuesto de acuerdo con la reivindicación 12 donde R_1 se selecciona entre metil y etil; y R_2 se selecciona entre metil, etil y 2-propinil.

15 14) - Un compuesto de acuerdo con la reivindicación 1 donde R_1 y R_2 son grupos independientes y tiene los significados definidos en la fórmula (I) y R_3 es un grupo 4-metoxibenzoil.

15) - Un compuesto de acuerdo con la reivindicación 14 donde R_1 se selecciona entre metil y etil; y R_2 se selecciona entre metil, etil y 2-propinil.

20 16) - Un compuesto de acuerdo con la reivindicación 1 donde R_1 y R_2 son grupos independientes y tiene los significados definidos en la fórmula (I) y R_3 es un grupo 5-metil-1,2,4,-oxadiazol-3-il.

25 17) - Un compuesto de acuerdo con la reivindicación 16 donde R_1 es metil y R_2 se selecciona de hidrógeno y etil.

18) Un compuesto de acuerdo con la reivindicación 1 donde R_1 y R_2 son grupos independientes y tiene los significados definidos en la fórmula (I) y R_3 es un grupo piridil-2-carbonil.

30 19) - Un compuesto de acuerdo con la reivindicación 18 donde R_1 se selecciona entre metil y etil; y R_2 se selecciona entre metil, etil y 2-propinil.

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20) - Un compuesto de acuerdo con la reivindicación 1 donde R_1 y R_2 son grupos independientes y tiene los significados definidos en la fórmula (I) y R_3 es un grupo piridil-4-carbonil. 21) - Un compuesto de acuerdo con la

5 reivindicación 20 donde R_1 se selecciona entre metil y etil; y R_2 se selecciona entre metil, etil y 2-propinil.

22) - Un compuesto de acuerdo con las reivindicaciones 4 y 5, donde dicho compuesto se selecciona entre el grupo consistente en:

- 10 N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-metil-metansulfonamida;
N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-phenil]-N-etil-metansulfonamida;
N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-metil-
- 15 bencenosulfonamida;
N-[3-(3-ciano-pirolo[1,5-a]pirimidin-7-il)-fenil]-N-etil-bencenosulfonamida;
N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-prop-2-inil-metansulfonamida;
- 20 N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-propil-etansulfonamida;
N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-etil-etansulfonamida;
N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-prop-2-
- 25 inil-propan-2-sulfonamida;
N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-metil-etansulfonamida;
N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-butil-etansulfonamida;
- 30 N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-metil-2-propansulfonamida;
N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-etil-2-propansulfonamida;

N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-butil-2-propansulfonamida;

N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-propil-2-propansulfonamida; and

5 N-[3-(3-ciano-pirazolo[1,5-a]pirimidin-7-il)-fenil]-N-prop-2-inil-etansulfonamida.

23) - Un compuesto de acuerdo con la reivindicación 4 donde dicho compuesto es 7-(3-(2-isotiazolidinil-1,1-dioxido)-fenil)-3-ciano-pirazolo[1,5-a]pirimidina.

10 24) - Un compuesto de acuerdo con la reivindicación 5 y 6 donde dicho compuesto se selecciona entre el grupo consistente en:

N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

15 N-etil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-bencenosulfonamida;

20 N-etil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-bencenosulfonamida;

N-prop-2-inil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

N-propil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

25 N-etil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

N-prop-2-inil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-2-propansulfonamida;

30 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

N-butil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

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- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
pirimidin-7-il]-fenil}-2-propansulfonamida;
N-etil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
pirimidin-7-il]-fenil}-2-propansulfonamida;
5 N-propil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
pirimidin-7-il]-fenil}-2-propansulfonamida;
N-butil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
pirimidin-7-il]-fenil}-2-propansulfonamida;
N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
10 pirimidin-7-il]-fenil}-2-feniletene-sulfonamida;
N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
pirimidin-7-il]-fenil}-2,2,2-trifluoroetansulfonamida;
N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
pirimidin-7-il]-fenil}-2-clorobencenosulfonamida;
15 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
pirimidin-7-il]-fenil}-3-clorobencenosulfonamida;
N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
pirimidin-7-il]-fenil}-4-clorobencenosulfonamida;
N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
20 pirimidin-7-il]-fenil}-2,4-diclorobencenosulfonamida;
N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
pirimidin-7-il]-fenil}-3,4-diclorobencenosulfonamida;
N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
pirimidin-7-il]-fenil}-2-ciano-bencenosulfonamida;
25 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
pirimidin-7-il]-fenil}-3-ciano-bencenosulfonamida;
N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
pirimidin-7-il]-fenil}-4-ciano-bencenosulfonamida;
N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
30 pirimidin-7-il]-fenil}-3-nitro-bencenosulfonamida;
N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a]
pirimidin-7-il]-fenil}-4-nitro-bencenosulfonamida;

- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-2-tiofensulfonamida;
- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-5-metil-4-isoxazolil-sulfonamida;
- 5 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-2-trifluorometil-5-metil-3-furil-sulfonamida;
- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-6-(morfolin-4-il)-3-piridil-sulfonamida;
- 10 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-2,4-dimetil-5-tiazolil-sulfonamida;
- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-ciclopropilsulfonamida;
- 15 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-bencilsulfonamida;
- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-vinilsulfonamida;
- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-3,5-dimetil-4-isoxazolil-sulfonamida;
- 20 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-1,3,5-trimetil-4-pirazolil-sulfonamida;
- 25 N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-propansulfonamida;
- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-butansulfonamida; y
- N-metil-N-{3-[3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-ciclopentilmetansulfonamida.
- 30

25) - Un compuesto de acuerdo con la reivindicación 7 donde dicho compuesto es 7-(3-(2-isotiazolidinil-1,1-

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dioxido)-fenil)-3-(tiofen-2-carbonil)-pirazolo[1,5-a] pirimidina.

26) - Un compuesto de acuerdo con las reivindicaciones 8 y 9 donde dicho compuesto se selecciona entre:

N-metil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

N-etil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

10 N-metil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

N-etil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

15 N-prop-2-inil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida; y

N-prop-2-inil-N-{3-[3-(benzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida.

27) - Un compuesto de acuerdo con las reivindicaciones 10 y 11 donde dicho compuesto se selecciona entre:

20 N-metil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

N-etil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

25 N-metil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

N-etil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

N-prop-2-inil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida; y

30 N-prop-2-inil-N-{3-[3-(fluorobenceno-4-carbonil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida.

28) - Un compuesto de acuerdo con las reivindicaciones 12 y 13 donde dicho compuesto se selecciona entre:

N-metil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

N-etil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

5 N-metil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

N-etil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

10 N-prop-2-inil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida; y

N-prop-2-inil-N-{3-[3-(4-metilbenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida.

29) Un compuesto de acuerdo con las reivindicaciones 14 y 15 donde dicho compuesto se selecciona entre:

15 N-metil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

N-etil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida;

20 N-metil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

N-etil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida;

N-prop-2-inil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-etansulfonamida; y

25 N-prop-2-inil-N-{3-[3-(4-metoxibenzoil)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida.

30) - Un compuesto de acuerdo con las reivindicaciones 16 y 17 donde dicho compuesto se selecciona entre:

30 N-{3-[3-(5-metil-[1,2,4]oxadiazol-3-il)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida; y

N-etil-N-{3-[3-(5-metil-[1,2,4]oxadiazol-3-il)-pirazolo[1,5-a]pirimidin-7-il]-fenil}-metansulfonamida.

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31) - Un compuesto de acuerdo con las reivindicaciones 18 y 19 donde dicho compuesto se selecciona entre:

N-metil-N-{3-[3-(piridin-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-metansulfonamida;

5 N-etil-N-{3-[3-(piridin-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-metansulfonamida;

N-prop-2-inil-N-{3-[3-(piridin-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-metansulfonamida;

10 N-metil-N-{3-[3-(piridin-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-etansulfonamida;

N-etil-N-{3-[3-(piridin-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-etansulfonamida; y

N-prop-2-inil-N-{3-[3-(piridin-2-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-etansulfonamida.

15 32) - Un compuesto de acuerdo con las reivindicaciones 20 y 21 donde dicho compuesto se selecciona entre:

N-metil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-metansulfonamida;

20 N-etil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-metansulfonamida;

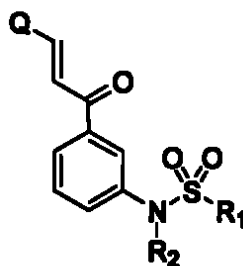
N-metil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-etansulfonamida;

N-etil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-etansulfonamida;

25 N-prop-2-inil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-etansulfonamida; y

N-prop-2-inil-N-{3-[3-(piridin-4-carbonil)-pirazolo[1,5-a] pirimidin-7-il]-fenil}-metansulfonamida.

30 33) - Un procedimiento para la obtención del compuesto de fórmula (I) y de sus sales farmacéuticamente aceptables según la reivindicación 1, caracterizado por la reacción del intermedio (II):



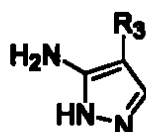
(II)

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donde R_1 y R_2 tienen igual significado que en (I) y Q es un grupo saliente adecuado seleccionado entre N(dialquil(C_1-C_6)), alquiltio(C_1-C_6) y alcoxi(C_1-C_6), con el intermedi

(III):

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(III)

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donde R_3 tiene igual significado que en (I) y opcionalmente, tratamiento de los compuestos de la reivindicación 1 en forma de base libre con un ácido para formar la sal correspondiente.

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34) - Un procedimiento según la reivindicación 33 caracterizado porque se utiliza el intermedio de fórmula (II) donde Q se selecciona entre dimetilamino, metiltio y metoxi.

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35)- El uso de un compuesto según la reivindicación 1 para la fabricación de un medicamento para el tratamient o prevención de las enfermedades relacionadas con la modulación del receptor GABA-A en un mamífero que

comprende administrar a dicho mamífero una cantidad eficaz de un compuesto de la reivindicación 1.

5 36)- El uso de un compuesto según la reivindicación 1 para la fabricación de un medicamento para el tratamiento o prevención de las enfermedades relacionadas con la modulación de la subunidad $\alpha 1$ del receptor GABA-A en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de un compuesto de la reivindicación 1.

10 37)- El uso de un compuesto según la reivindicación 1 para la fabricación de un medicamento para el tratamiento o prevención de las enfermedades relacionadas con la modulación de la subunidad $\alpha 2$ del receptor GABA-A en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de un compuesto de la reivindicación 1.

15 38) - El uso de un compuesto según la reivindicación 1 para la fabricación de un medicamento para el tratamiento o prevención de la ansiedad en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de un compuesto de la reivindicación 1.

20 39) - El uso de un compuesto según la reivindicación 1 para la fabricación de un medicamento para el tratamiento o prevención de la epilepsia en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de un compuesto de la reivindicación 1.

25 40) - El uso de un compuesto según la reivindicación 1 para la fabricación de un medicamento para el tratamiento o prevención de las alteraciones del sueño en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz un compuesto de la reivindicación 1.

30 41) - El uso de un compuesto según la reivindicación 1 para la fabricación de un medicamento para el

tratamiento o prevención del insomnio en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de un compuesto de la reivindicación 1.

5 42) - El uso de un compuesto según la reivindicación 1 para la fabricación de un medicamento para la inducción de sedación-hipnosis en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de un compuesto de la reivindicación 1.

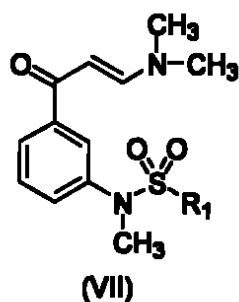
10 43) - El uso de un compuesto según la reivindicación 1 para la fabricación de un medicamento para la inducción de anestesia en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de dicho compuesto.

15 44) - El uso de un compuesto según la reivindicación 1 para la fabricación de un medicamento para modular el tiempo necesario para inducir el sueño y su duración en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de dicho compuesto.

20 45) - El uso de un compuesto según la reivindicación 1 para la fabricación de un medicamento para la inducción de relajación muscular en un mamífero que comprende administrar a dicho mamífero una cantidad eficaz de un compuesto de la reivindicación 1.

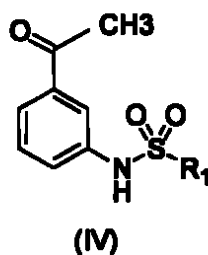
25 46) - Una composición farmacéutica que comprende un compuesto de la reivindicación 1 en asociación con excipientes terapéuticamente inertes.

 47) - Un procedimiento para la obtención del intermedio de fórmula (VII):



donde R_1 tiene igual significado que en (I), caracterizado por la reacción del intermedio de fórmula (IV):

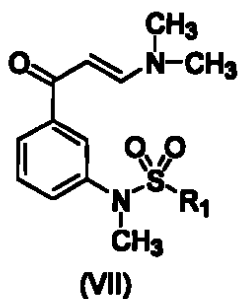
5



donde R_1 tiene igual significado que en las precedentes estructuras, con el dimetil acetal de la N,N-dimetilformamida.

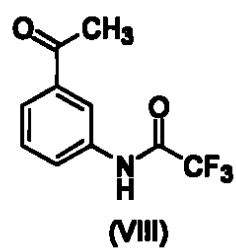
10

48) - Un procedimiento para la obtención del intermedio de fórmula (VII):



15

donde R_1 tiene igual significado que en (I), caracterizado por la reacción de la N-(3-acetilfenil)-2,2,2-trifluoroacetamida (VIII):



5 y el dimetil acetal de la N,N-dimetilformamida, seguido de la formación de la sulfonamida por reacción con el correspondiente cloruro de ácido sulfónico.

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

~~112~~
PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/008208

International filing date (day/month/year)
22.07.2004

Priority date (day/month/year)
24.07.2003

International Patent Classification (IPC) or both national classification and IPC
C07D487/04, A61K31/505, A61P25/00

Applicant
FERRER INTERNATIONAL S.A.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epru d
Fax: +49 89 2399 - 4485

Authorized Officer

Wolf, C

Telephone No. +49 89 2399-8285



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

113
International application No.
PCT/EP2004/008208

Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

114
International application No.
PCT/EP2004/008208

Box No. II Priority

1. ☒ The following document has not been furnished:

- ☒ copy of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(a)).
- ☐ translation of the earlier application whose priority has been claimed (Rule 43bis.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43bis.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

115
International application No.
PCT/EP2004/008208

Box No. III Non-establishment of opinion with regard to novelty, Inventive step and Industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 35-45 in respect of industrial applicability

because:

- ☒ the said international application, or the said claims Nos. 35-45 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- the written form ☐ has not been furnished
☐ does not comply with the standard
- the computer readable form ☐ has not been furnished
☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43bis.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-51
	No: Claims	
Inventive step (IS)	Yes: Claims	1-51
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-34,46-51
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

For the assessment of the present claims 35-45 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 35-45 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

The following documents are cited in the International Search Report:

- D1: GEORGE C F P: "Pyrazolopyrimidines" LANCET, XX, XX, vol. 358, no. 9293, 10 November 2001 (2001-11-10), pages 1623-1626, XP004322796
ISSN: 0140-6736
D2: US-A-4 654 347 (ALBRIGHT JAY D ET AL) 31 March 1987 (1987-03-31).

In the light of D1 and D2 the subject matter claimed appears to be novel and to involve an inventive step according to Articles 33(2) and 33(3) PCT.

D1 and D2 disclose pyrazolopyrimidines which exhibit an amide group instead of the sulfonamide group which is always present on the phenyl portion in the compounds as claimed in the present application.

The proviso in the claims appears to be present to exclude intermediates disclosed in the prior art (e.g. D1 example 80) which appear to be only synthetic intermediates without report on pharmacological effects.

The technical problem underlying the present application was the provision of

further compounds useful as ligands of α_1 - and α_2 -GABA_A-receptors.

The result of comparative tests provided in the description on pages 25-32 demonstrate a superior effect of the claimed compounds when compared to the compound Zaleplon disclosed in D1 (especially example 2 according to the present application which appears to be the closest structurally possible compound and differs from Zaleplon only in the sulfonamide group portion). On the basis of this unexpected effect the solution to the technical problem- the provision of the compounds as claimed - appears to be non-obvious in the light of the prior art teaching.

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

From the INTERNATIONAL BUREAU
Patentanwälte
Reitstötter, Kinzebach & Partner

To:

Eing. 05. Okt. 2004
afREITSTÖTTER, KINZEBACH & PARTNER
(GbR)
Sternwartstrasse 4
81679 München
Germany

Date of mailing (day/month/year) 15 September 2004 (15.09.2004)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference M/45174-PCT	International application No. PCT/EP2004/008208

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

FERRER INTERNACIONAL, S.A. (for all designated States except US)
ANGLADA, Luis et al (for US)

International filing date : 22 July 2004 (22.07.2004) ✓
Priority date(s) claimed : 24 July 2003 (24.07.2003) ✓
12 July 2004 (12.07.2004) ✓

Date of receipt of the record copy
by the International Bureau : 12 August 2004 (12.08.2004)

List of designated Offices :

AP : BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW
EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
EP : AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR
OA : BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
National : AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.88.75

Authorized officer:

Rosana REYES (Fax : 338 89 75)

Telephone No. (41-22) 338 8471

Continuation of Form PCT/IB/301

NOTIFICATION F RECEIPT OF RECORD COPY

Date of mailing (day/month/year) 15 September 2004 (15.09.2004)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference M/45174-PCT	International application No. PCT/EP2004/008208

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

☒ time limits for entry into the national phase - see updated Important information (as of April 2002)

☒ requirements regarding priority documents (if applicable)

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated on the cover sheet of this Notification by paying national fees and furnishing translations, as prescribed by Articles 22 and 39 and the applicable national laws. In addition, the applicant may also have to comply with other special requirements applicable in certain Offices. It is the applicant's responsibility to ensure the necessary steps to enter the national phase are taken in a timely fashion. Most Offices do not issue reminders to applicants in connection with the entry into the national phase.

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 18 months from the priority date (see Article 39(1)), but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of that designated Office. For further details, see PCT Gazette No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette ("Section IV" part published on a weekly basis), to the PCT Newsletter (on a monthly basis) and to the relevant National Chapters in Volume II of the PCT Applicant's Guide (the paper version of which is updated usually twice a year and the Internet version of which is updated usually on a weekly basis). Finally, a cumulative table of all applicable time limits for entering the national phase is available from WIPO's Internet site, via links from various pages the site including those of the Gazette, Newsletter and Guide, at <http://www.wipo.int/pct/en/index.html>.

Information about the requirements for filing a demand for international preliminary examination is set out in the PCT Applicant's Guide, Volume I/A, Chapter IX. Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 18 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 18-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 18-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within the time limit which is reasonable under the circumstances (Rule 17.1(c)).

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 18-month time limit (and all other PCT time limits) is the filing date of the earliest application whose priority is claimed (Article 2(x)(b)).

PATENT COOPERATION TREATY

Reitstötter, Kinzebach & Part.

PCT

Eing. 29. Nov. 2004

From the INTERNATIONAL BUREAU

Sternwartstr. 4 D-81679 München

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

REITSTÖTTER, KINZEBACH & PARTNER
(Gbr)
Sternwartstrasse 4
81679 München
Germany

Date of mailing (day/month/year) 18 November 2004 (18.11.2004)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference M/45174-PCT	
International application No. PCT/EP2004/008208	
International publication date (day/month/year) Not yet published	
International filing date (day/month/year) 22 July 2004 (22.07.2004)	Priority date (day/month/year) 24 July 2003 (24.07.2003)
Applicant FERRER INTERNACIONAL, S.A. et al	

- By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- (If applicable) An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
24 July 2003 (24.07.2003)	200301748	ES	09 Nove 2004 (09.11.2004)
12 July 2004 (12.07.2004)	200401697	ES	09 Nove 2004 (09.11.2004)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 338.89.75	Authorized officer Daniel VILLARS (Fax : 338 89 75) Telephone No. (41-22) 338 8919
--	--

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

FIRST NOTICE INFORMING THE APPLICANT OF
THE COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES WHICH
DO NOT APPLY THE 30 MONTH TIME LIMIT
UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

REITSTÖTTER, KINZEBACH & PARTNER (GmbH)
Stenwartstrasse 4
81679 München
ALLEMAGNE

Eing. - 7. März 2005

Stenwartstr. 4 81679 München

IMPORTANT NOTICE

Date of mailing (day/month/year)

24 February 2005 (24.02.2005)

Applicant's or agent's file reference
M/45174-PCTInternational application No.
PCT/EP2004/008208International filing date (day/month/year)
22 July 2004 (22.07.2004)Priority date (day/month/year)
24 July 2003 (24.07.2003)

Applicant

FERRER INTERNACIONAL, S.A. et al

1. **ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does apply, please see Form PCT/IB/308 (Second and Supplementary Notice) (to be issued promptly after the expiration of 28 months from the priority date).

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does not apply, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
17 February 2005 (17.02.2005)

CH

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does not apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

LU, SE, TZ, UG, ZM

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated Office(s) listed above, and unless a demand for international preliminary examination has been filed before the expiration of 19 months from the priority date (see Article 39(1)), the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 20 MONTHS from the priority date.

In practice, time limits other than the 20-month time limit will continue to apply, for various periods of time, in respect of certain of the designated Offices listed above. For regular updates on the applicable time limits (20 or 21 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 740 14 35

Authorized officer

Ellen Moyse

Facsimile No. +41 22 338 89 75

PATENT COOPERATION TREATY

WO 2005/014597
PCT/EP2004/0082

From the INTERNATIONAL BUREAU

PCT

SECOND AND SUPPLEMENTARY NOTICE
INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION (TO DESIGNATED OFFICES
WHICH APPLY THE 30 MONTH TIME
LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

REITSTÖTTER, KINZEBACH & PARTNER (GmbH)
Sternwartstrasse 4
81679 München
ALLEMAGNE

Eing. 30. Nov. 2005

Sternwartstr. 4 D-81679 München

Date of mailing (day/month/year)
24 November 2005 (24.11.2005)

Applicant's or agent's file reference
M/45174-PCT

IMPORTANT NOTICE

International application No.
PCT/EP2004/008208

International filing date (day/month/year)
22 July 2004 (22.07.2004)

Priority date (day/month/year)
24 July 2003 (24.07.2003)

Applicant

FERRER INTERNACIONAL, S.A. et al

- ATTENTION:** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does not apply, please see Form PCT/IB/308(First Notice) issued previously.
- Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93bis.1. The International Bureau has effected that communication on the date indicated below:
17 February 2005 (17.02.2005)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MZ, NA, RU, SY, TM, US

In accordance with Rule 47.1(c-bis)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

- The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93bis.1:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KZ, LC, LK, LR, LS, LT, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, SC, SD, SG, SK, SL, TJ, TN, TR, TT, UA, UZ, VC, VN, YU, ZA, ZW

In accordance with Rule 47.1(c-bis)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. TIME LIMITS for entry into the national phase

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be 30 MONTHS from the priority date.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For regular updates on the applicable time limits (30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

It is the applicant's sole responsibility to monitor all these time limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Ellen Moyse

Facsimile No.+41 22 740 14 35

Facsimile No.+41 22 338 89 75

20984

Brigard & Castro

BOGOTA - COLOMBIA

urgent 30/12/04
Colombia

PODER

Yo (nosotros) FERRER INTERNACIONAL, S.A.

domiciliado(s) en Gran Vía Carlos III nº 94
ES-08028-Barcelona, España

Nombro(amos) a: RAMIRO CASTRO DUQUE y/o CARLOS H. PALACIO EASTMAN, de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recibir de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y transacciones de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistirse a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros) intereses, con todas las demás facultades a las necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistirse, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: RAMIRO CASTRO DUQUE y/o CARLOS H. PALACIO EASTMAN, domiciliado(s) en la Carrera 7 No. 16-58 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en Barcelona (España)

hoy 6 de Octubre de 2004

Firma

Nombre Jorge Raimentol
Cargo Director General

POWER OF ATTORNEY

I (We)

domiciled in

Hereby appoint RAMIRO CASTRO DUQUE and/or CARLOS H. PALACIO EASTMAN, of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures; and in other actions or similar proceedings.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint RAMIRO CASTRO DUQUE and/or CARLOS H. PALACIO EASTMAN, domiciled in Carrera 7 No. 16-58, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Granted and signed in

this day of 200_

Signature

Name
Title



126

CERTIFICADO NOTARIAL (SOCIEDAD)

On this _____ day of _____ of _____ personally appeared before me

to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the

Hoy treinta y dos de diciembre de dos mil cuatro personalmente compareció ante mí DON JORGE RAMENTOL MASSANA, mayor de edad, casado, vecino de Barcelona, calle Lleo XIII número 2, provisto DNI número 37.648.007, a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él es Secretario del Consejo de Administración y Director General de "FERRER INTERNACIONAL, S.A.", (cargo para el que fue designado por dicho Consejo el 08.02.02 elevado a público en escritura por mí autorizada el 21 de marzo de 2002, inscripción 911, del Registro Mercantil.

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por la compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de España
con fecha 30-12-04.

y que quien confiere el presente poder es su representante.

Gabriel Suau Rosselló
Notario de Barcelona

Notario Público (seal)

**CERTIFICADO NOTARIAL
PERSONA NATURAL**

Hoy _____ de _____ de _____, compareció(eron) ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney: that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of _____
under date of _____

and that he (she) who grants the present power of attorney is its Representative.

Public Notary (Seal)

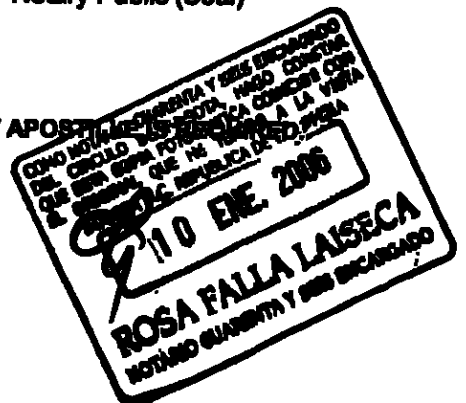
**NOTARIAL CERTIFICATE
NATURAL PERSON**

On this _____ day of _____ of _____ personally appeared before me

who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.

Notary Public (Seal)

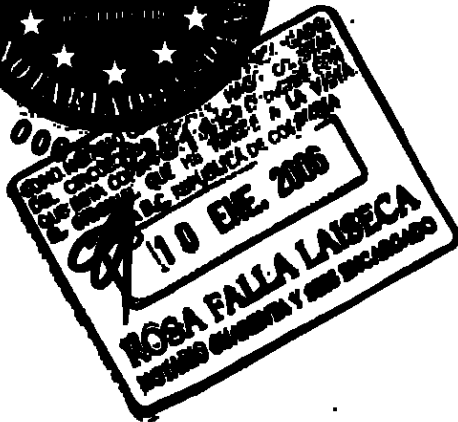
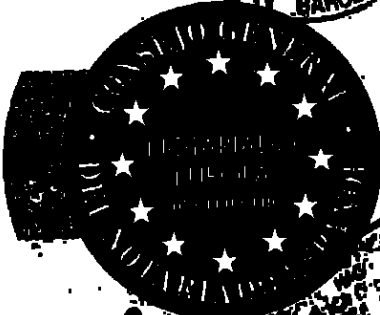
LEGALIZATION BY APOSTILLE



SELLO DE
LEGITIMACIONES Y
LEGALIZACIONES



MINI PRINCE
A10419448





5Y0077984

10/2004

RESERVA

APOSTILLE (O-legalización única)

(Convención de la Haya du 5 de octubre, 1961-Real Decreto/1978, de 2 de octubre)

1. País ESPAÑA

El presente documento público

2. ha sido firmado por D. Gabriel Suau Rosselló-----

3. Actuando en calidad de Notario, en legitimación de firma--

de D. Jorge Ramentol Massan, puesta en un poder, en repre-

sentación de Ferrer Internacional, S.A., libro indicador--

n°. 1582, de fecha 30 de diciembre de 2004.-----

4. Se halla sellado/timbrado con el de su Notaría.

C E R T I F I C A D O

5. En BARCELONA

6. El 31 de Diciembre de 2004.

7. Por DON JUAN MANUEL PERELLO FONT, Vicedecano.

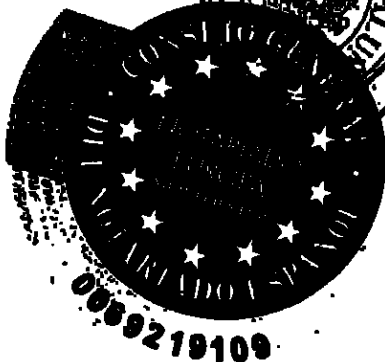
8. Con el N° : -56533-

9. Sello/timbre:

10. Firma:

SELO DE
LEGITIMACIONES Y
LEGALIZACIONES

NOT. PRIV. DE BARCELONA
A4241840



Juan Manuel Perelló Font
Vicedecano





ORGANIZACION ELECTORAL
REGISTRADURA NACIONAL DEL ESTADO CIVIL

GAVIRI A

REGISTRO CIVIL DE DEFUNCION

Indicativo
Serial

5562241



Datos de la oficina de registro									
Clase de oficina:	Registraduría	Notaría	☒	Consulado		Corregimiento		Insp. de Policía	
Código 9995									
País: Colombia Municipio: Bogotá Corregimiento: Bogotá D.C.									
COLOMBIA CUNDINAMARCA BOGOTA D.C. NOTARIA 32.									
Datos del inscrito									
Apellidos y nombres completos									
CASTRO DUQUE RAMIRO									
Documento de identificación (Clase y número)					Sexo (en Letras)				
C.C. No. 170322 DE BOGOTA					MASCULINO				
Datos de la defunción									
Lugar de la Defunción País: Colombia Departamento: Cundinamarca Municipio: Bogotá Corregimiento: Bogotá D.C.									
COLOMBIA CUNDINAMARCA BOGOTA D.C.									
Fecha de la defunción				Hora		Número de certificado de defunción			
Año	2	0	0	4	Mes	1	0	Día	3
				04:10 PM		A- 2094375.			
Presunción de muerte									
Lugar que profiere la sentencia					Fecha de la sentencia				
Año					Mes				
					Día				
Documento presentado					Nombre y cargo del declarante				
Autorización judicial ☐					Certificado Médico ☒				
					ANDRES DIAZ CAMPOS.-				
					R.M. No. 79982662				
Datos del denunciante									
Apellidos y nombres completos									
EDGAR DAVID REGINO II.									
Documento de identificación (Clase y número)					Firma				
C.C. No. 15.030.154 DE LORICA/ CORDOBA									
Primer testigo									
Apellidos y nombres completos									
Documento de identificación (Clase y número)					Firma				
Segundo testigo									
Apellidos y nombres completos									
Documento de identificación (Clase y número)					Firma				
Fecha de inscripción					Notario y firma del notario que inscribe				
Año	2	0	0	4	Mes	1	Día	0	2
					BLANCA RESTrepo				
					NOTARIO				
ESPACIO PARA NOTAS									
PADRES: ALFONSO CASTRO									
MERCEDES DUQUE.									

ORIGINAL PARA LA OFICINA DE REGISTRO

NOTARIA 32

DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

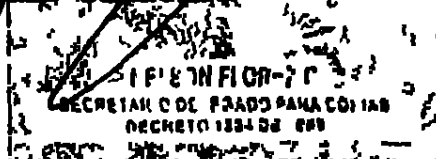
Germán Eleázar Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL
CIRCULO DE BOGOTA

CERTIFICO QUE

La presente acta es fiel copia del original tomada del registro
civil de defunciones serial indicativo número 56224
que expido en la ciudad de Bogotá D.C. hoy 05 NOV 2004

NOTARIA 32 DEL C
CIRCULO DE BOGOTA D.C.
SECRETARIO DELEGADO



REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
Indicacion de que se solicita la concesion de una patente	()	()
Datos de identificacion del solicitante o de la persona que se presenta la solicitud	()	()
Descripcion de la invencion	()	()
Dibujos de ser estos pertinentes	()	()
Comprobante de Pago de las tasas establecidas	()	()

COMPLETA () **INCOMPLETA** ()

DISEÑO INDUSTRIAL ()

- Indicacion de que se solicita el registro de Diseño Industrial () ()
- Datos de identificacion del solicitante o de la persona que presenta la solicitud () ()
- Representacion grafica o fotografica del Diseño Industrial o muestra del Material que incorpora el diseño () ()
- Comprobante de pago de las tasas establecidas () ()

COMPLETA () **INCOMPLETA** ()

ESQUEMA DE TRAZADO ()

- Indicacion de que solicita el registro de un Esquema de trazado () ()
- Datos de identificación del solicitante o de la persona que presenta la solicitud () ()
- Representación grafica del esquema de trazado () ()
- Comprobante de pago de las tasas establecidas () ()

COMPLETA () **INCOMPLETA** ()

Firma Responsable

Fecha

13-En 106

SUPERINDUSTRIA Y COMERCIO
Radicacion: 06002635 00000000 Folios: 129
Fecha (RED): 2020-01-13 15:40:57
Tramite: 011 PCT-PATENT 370 FASE INCI 411 PRESENTAR
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

PETITORIO

130

AS: 100.080

**Industria y Comercio
SUPERINTENDENCIA**

SUPERINDUSTRIA Y COMERCIO
Radicación: 05002635 00000000 Folios: 129
Fecha (GIR): 2006-01-13 15:40:57
Tramite: 011 PCT-PATENT 370 FASE NACI 411 PRESENTA
Dependencia: 2829 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL 2006-02-24

1

SOLICITUD DE:

☒ Patente de Invención.☐ Patente de Modelo de Utilidad.☒ Capítulo I.☐ Capítulo II.

2

**SOLICITANTE
(71)**

Nombre: FERRER INTERNACIONAL S.A.

Dirección: Gran Vía Carlos III, 84, E-08028,
Barcelona, España

Nacionalidad o Domicilio: España

Lugar de Constitución: España

Teléfono: Fax

E-mail

IDENTIFICACION

C.C. ☐ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número _____

3

**REPRESENTANTE
O APODERADO**Nombre: CARLOS HUMBERTO PALACIO
EASTMAN

Dirección: Cra. 7 No. 16-56 Piso 9

Teléfono: 380-2200 Fax: 380-2700

E-mail:

IDENTIFICACION

C.C. ☒ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número 79.311.882 TP 62154

4

**INVENTOR (ES)
(72)**

Nombre: Luis Anglada, Albert Palomer, Maria Princep, Antonio Guglietta

Dirección: Bruch, 111, E-08009 Barcelona, ES; Almería 23, E-08014 Barcelona, ES; Ventura
Plaza 30-32, E-08028 Barcelona, ES; Monistrol, 12, E-08870 Sant Joan Despi, España
(Respectivamente)

Nacionalidad o Domicilio: España (Respectivamente)

5 PCT (88)

Solicitud Internacional No. PCT/EP2004/008208 Fecha 22-07-2004Publicación Internacional No. WO 2005/014597 A1 Fecha 17-02-2005Título (54): N-13-(3-SUSTITUIDAS-PIRAZOLO (1,5-a) PRIMIDIN-7-IL)-FENIL-SULFONAMIDAS Y
COMPOSICIONES Y MÉTODOS RELACIONADOS7 Clasificación Internacional (51) C 07D 407/04, A 61K 31/505, A 61P 25/00, 25/22

8 Prioridad

(33) País de
Origen

(32) Fecha

(31) Número de Solicitud

SI ☒ NO ☐

ES

24-07-2003

200301746

ES

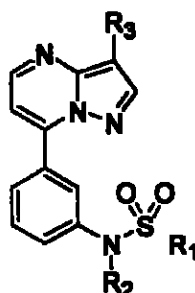
12-07-2004

200401697

REIVINDICACIONES

1) - Un compuesto de fórmula (I)

5



10

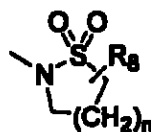
(I)

y sus sales farmacéuticamente aceptables,
donde

R₁ se selecciona entre alquil(C₁-C₆), alquenil(C₂-C₆),
15 ω,ω,ω-trifluoroalquil(C₁-C₆), cicloalquil(C₃-C₆),
cicloalquil(C₃-C₆)alquil(C₁-C₆), -O-alquil(C₁-C₆), -NH-
alquil(C₁-C₆), -N(dialquil(C₁-C₆)), alquil(C₁-C₆)-O-
alquil(C₁-C₆), alquil(C₁-C₆)-NH-alquil(C₁-C₆), alquil(C₁-C₆)-
N(dialquil(C₁-C₆)), fenil, fenil monosustituido, fenil
20 disustituido, fenilalquil(C₁-C₆), fenilalquenil(C₂-C₆),
furanil, furanil sustituido, isoxazolil, isoxazolil
sustituido, pirazolil, pirazolil sustituido, tienil, tienil
sustituido, tiazolil, tiazolil sustituido, piridil y
piridil sustituido,

25 R₂ se selecciona entre hidrógeno, alquil(C₁-C₆),
alquenil(C₂-C₆), alquinil(C₂-C₆) y cicloalquil(C₃-C₆), o bien
R₁ y R₂ forman un ciclo de estructura

30



donde n es un entero de 0 a 3 inclusive

R_3 se selecciona entre hidrógeno, halógeno, alquil(C_1-C_6), cicloalquil(C_3-C_6), alquenil(C_2-C_6), alquinil(C_2-C_6), -O-alquil(C_1-C_6), halo-alquil(C_1-C_6), -CN, -SO₂-R₄, -NH-R₄, -NR₄R₅, -COR₆, -CO-NHR₆, COOR₆, -C(NR₇)R₆, fenil, fenil sustituido, heteroaril y heteroaril sustituido;

R_4 y R_5 se seleccionan independientemente entre alquil(C_1-C_6), cicloalquil(C_3-C_6), aril y heteroaril;

R_6 se selecciona entre hidrógeno, alquil(C_1-C_6), alquenil(C_2-C_6), alquinil(C_2-C_6), cicloalquil(C_3-C_6), fenil, fenil sustituido, furanil, furanil sustituido, tienil, tienil sustituido, tiazolil, tiazolil sustituido, piridil y piridil sustituido;

R_7 se selecciona entre alquil, cicloalquil(C_3-C_6), -OH, -O-alquil(C_1-C_6), alquil(C_1-C_6)-O-alquil(C_1-C_6), alquil(C_1-C_6)-NH-alquil(C_1-C_6), alquil(C_1-C_6)-N(dialquil(C_1-C_6))), fenil, fenil monosustituido, furanil, tienil, tiazolil y piridil;

y R_8 se selecciona entre hidrógeno, alquil(C_1-C_6), cicloalquil(C_3-C_6), aril y heteroaril sustituido o no;

a condición de que:

R_1 no puede ser p-tolil y R_2 metil y R_3 benzoil simultáneamente; y

R_1 no puede ser p-tolil y R_2 etil y R_3 furanil-2-carbonil simultáneamente.

2) - Un compuesto de acuerdo con la reivindicación 1 donde R_1 y R_2 son grupos independientes y tienen los significados definidos en la fórmula (I) y R_3 es un grupo ciano.

3) - Un compuesto de acuerdo con la reivindicación 2 donde R_1 se selecciona entre metil, etil, n-propil, i-propil n-butil, fenil y 4-metoxi-fenil; y R_2 se selecciona

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133

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
PALACIO EASTMAN CARLOS HUMBERTO
Apoderado(a) y/o Representante de
FERRER INTERNACIONAL S.A.

REFERENCIA	Radicación No.	6 2635
	Solicitud internacional	EP2004/008208
	Fecha inicio fase nacional	24/02/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	2659

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud nacional no contiene la traducción de la solicitud internacional tal como fue presentada. (Numeral 5.2.5, capítulo quinto del título décimo de la Circular Única de la SIC), hacen falta las reivindicaciones: 21, 49, 50 y 51.
2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de
fecha 03 MAR. 2006
jramos