(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 November 2005 (10.11.2005)

PCT

(10) International Publication Number
WO 2005/105804 A1

(51) International Patent Classification[7]: C07D 487/04, A61K 31/4985, A61P 29/00

(21) International Application Number: PCT/HU2005/000040

(22) International Filing Date: 25 April 2005 (25.04.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P0400891 29 April 2004 (29.04.2004) HU

(71) Applicants and
(72) Inventors: **SZOLCSÁNYI, János** [HU/HU]; Hungária u. 39., H-7624 Pécs (HU). **ORFI, László** [HU/HU]; Batthányi u. 92., H-1161 Budapest (HU). **KÉRI, György** [HU/HU]; Modori u. 4., H-1021 Budapest (HU). **WÁCZEK, Frigyes** [HU/HU]; Ady Endre út 130., H-1195 Budapest (HU). **PINTÉR, Erika** [HU/HU]; Székely Bertalan u. 27., H-7624 Pécs (HU). **HELYES, Zsuzsanna** [HU/HU]; Szondi u. 10., H-7629 Pécs (HU). **SZÜTS, Tamás** [HU/HU]; Magyar Jakobinusok tere 4/a, H-1122 Budapest (HU). **NÉMETH, József** [HU/HU]; Heim Pál u.2., H-7623 Pécs (HU).

(74) Agent: **INTERINNO PATENT OFFICE**; Margit krt 73., H-1024 Budapest (HU).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: 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, KM, 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, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/105804 A1

(54) **Title:** 7H-PYRROLO[2,3-d]PYRIMIDINE DERIVATIVES, AS WELL AS THEIR THERAPEUTICALLY ACCEPTABLE SALTS, PHARMACEUTICAL PREPARATIONS CONTAINING THEM AND PROCESS FOR PRODUCTION THE ACTIVE AGENT

(57) **Abstract:** The invention relates to new 7H-pyrrolo[2,3-d]pyrimidine derivatives, as well as their therapeutically acceptable salts, pharmaceutical preparations containing them and process for producing the active agent. The pharmaceutical preparation is adventageously antiphlogistic and analgetic one, a preparation reducing neuropathic hyperalgesia and rheumatic arthritis, a preparation for hindering destruction of bones chondrus, being applicable for treatment of other diseases, which may be connected with other inflammatory processes e.g. asthma, eczema or psoriasis.

7H-pyrrolo[2,3-d]pyrimidine derivatives, as well as their therapeutically acceptable salts, pharmaceutical preparations containing them and process for producing the active agent.

The invention relates to new 7H-pyrrolo[2,3-d]pyrimidine derivatives, as well as their therapeutically acceptable salts, pharmaceutical preparations containing them and process for producing the active agent.

The compounds of general formula (I) are basic substances of pharmaceutical preparations of neurogenic and not neurogenic antiphlogistic, as well as paregoric effect, neuropathic hyperalgesia reducing ones, those for hindering rheumatic arthritis or treatment of destruction of bone or chondrus in joints, as well as for other diseases, which may be connected with other inflammatory processes e. g. asthma, eczema, psoriasis.

The compounds according to the general formula (I) are new. Their characteristic types may be described by general formulae (Ia), (Ib) and (Ic).

The compounds of 7H-pyrrolo[2,3-d]pyrimidine derivatives other than the above mentioned ones are known in the special literature as quinase inhibitors and anti-tumor agents acting in this way.

An important structural characteristic of the known active quinase inhibiting 7H-pyrrolo[2,3-d]pyrimidine derivatives is that only one from among the nitrogen atoms the one of pyrrhol in the position 7 and the other of the amine function connected to the fourth position may carry substituent (J. Med. Chem. *39* (1996) 2285-2292,Bioorg. Med. Chem. Letters *11* (2001) 849-852).

In the case of compounds according to invention both of the above indicated places carry substituents.

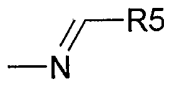
Thus, the invention relates to 7H-pyrrolo[2,3-d]pyrimidine derivatives of the general formula (I), and to their therapeutically acceptable salts.

In the general formula (I):

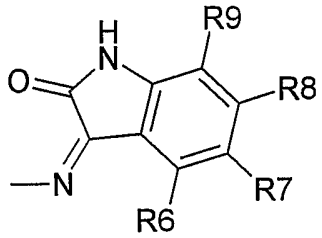
R1 is alkyl, aryl, heteroaryl or aryl-alkyl with 1-4 carbon atoms group, heteroaryl-alkyl with 1-4 carbon atoms group, morpholino-alkyl with 1-4 carbon atoms group or dialkylamino-alkyl with 1-4 carbon atoms group.

R2, R3 independently of each other are hydrogen, methyl, ethyl, propyl, isopropyl or cyclopropyl groups or R2 and R3 together are tetramethylene group.

R4 is



or



or

group,

wherein: R5 is substituted or unsubstituted aromatic or heteroaromatic ring where

R6, R7, R8 and R9 are independently hydrogen, halogen, nitro, amino, alkylamino, dialkylamino, hydroxy, methoxy, ethoxy, isopropoxy or sulfonyl group,

R10 is hydrogen or nitrile group,

R11 is hydrogen, methyl, ethyl, propyl, isopropyl, tert.- butyl group or tetramethylene ring connected to X

R12 is alkyl, aryl, heteroaryl, aryl-alkyl with 1-4 carbon atoms, heteroaryl-alkyl with 1-4 carbon atoms, morpholino-alkyl with 1-4 carbon atoms or dialkylamino-alkil with 1-4 carbon atoms group,

X is carbon if R11 is a tetramethylene ring connected to X, otherwise nitrogen, methine, methyl-methine ethyl-methine, propyl-methine, isopropyl-methine, cyclopropyil-methine, tert.- butyl-methine or phenyl-methine group.

The therapeutically acceptable salts are advantageously acid-additive ones.

The most characteristic compounds of the general formula (I) may be defined by general formula (Ia), (Ib) and (Ic) where R1, R2, R3, R5, R6, R7, R8, R9, R10, R11, R12 and X are the same as mentioned above.

The invention relates also to a pharmaceutical preparation containing the compound of general formula (I) as active substance and therapeutically acceptable additives.

The pharmaceutical preparation is advantageously antiphlogistic and analgetic one, a preparation reducing neuropathic hyperalgesia and rheumatic arthritis, a

preparation for hindering destruction of bones or chondrus, being applicable for treatment of other diseases, which may be connected with other inflammatory processes e. g. asthma, eczema or psoriasis.

The invention relates furthermore to a process for producing 7H-pyrrolo[2,3-d]pyrimidine derivatives of the general formula (I).

The process may be characterized in that a compound of general formula (II) is produced from acetoine with amine and malononitrile of molar equivalent quantities where R1, R2 and R3 are the same as mentioned above.

Formic acid of mass excess of 5 to 10 times is added, the mixture is mixed at reflux temperature for 1 hour to 2 days then the mixture is poured into icy water. The precipitated product is separated, dried then brought into reaction with phosphorus oxychloride of 5 to 10 times as much as the product at reflux temperature for 0.5 to 4 hours then the mixture is poured onto ice and the precipitated imidoyl chloride of general formula (III) where R1, R2 and R3 are the same as mentioned above is separated, dried and evaporated then

A) The imidoyl chloride of general formula (III) produced in the above mentioned way is solved in an aprotic solvent and brought into reaction with amine of general formula (II) or (IV) of equivalent quantity where R1 and R3 are the same as above in the formulas and NaH of 2 to 10 times of molar eqivalent excess is added. The reaction continues for 0.5 to 6 hours. The mixture is then poured onto ice and the precipitated product is separated and purified.

or

B) the imidoyl chloride of general formula (III) produced in the above mentioned way is brought into reaction with hydrazine hydrate of 2 to 10 times of

molar equivalent excess in a medium of polar organic solvent then the reaction product in the organic phase is separated, the organic phase is dried, evaporated then bruised with an apolar solvent. The hydrazine derivative produced in this way is mixed with a polar solvent and brought into reaction with aldehyde of equivalent quantity at 20 to 120 C° for 1 to 12 hours then the reaction product is separated.

or

C) The hydrazine derivative produced according to the process described in B) is mixed with a polar organic solvent, brought into reaction with isatin of equivalent quantity then the reaction product is separated.

The compound of general formula (II) is produced in such a way that acetoine is brought into reaction with amine and malonic acid dinitrile of molar equivalent quantities. The compounds of general formula (II) are produced in this way. The reaction can be carried out in two stages in the same reaction mixture using either acidic or alkaline catalyst.

In the first stage the acetoine is brought into reaction with the suitable amine always with acidic catalyst (concentrated HCl or toluene sulphonic acid) in aprotic solvent (advantageously in toluene or benzene) at reflux temperature using water separating additive until the whole water produced in the reaction is removed then malononitrile is added and the mixture is kept at reflux temperature until removal of water of equivalent quantity.

If amines of aniline type are used the solvent is changed to a protic one advantageously methanol, ethanol or isopropanol and they are brought into reaction with malonic acid dinitrile using alkaline medium (aqueous solution of KOH or NaOH) in inert atmosphere.

The intermediate compound of general formula (II) is filtered having cooled the mixture then mixed with formic acid of 5 to 10 mass excess (of 85 to 98 mass %) at reflux temperature for 1 hour to 2 days. The mixture is then poured onto icy water and the precipitated product is isolated either by filtering or extraction with ethyl acetate at neutral pH.

The product is thoroughly dried in both cases then brought into reaction with phosphorus oxychloride of 5 to 10 times of mass excess at reflux temperature for 0.5 to 4 hours. The mixture containing phosphorus oxychloride is poured onto ice and having set pH to neutral the precipitated imidoyl chloride of general formula (III) is either filtered or extracted with ethyl acetate, then the combined organic phase is dried and evaporated. The imidoyl chloride of general formula (III) obtained after filtering or extracting and evaporation is solved in an aprotic solvent (THF, dioxane, DMSO or DMF) or in the mixture of them.

In the version A) of the process the imidoyl chloride of the general formula (III) is brought into reaction with amine of general structure (II) or (IV) of equivalent quantity adding NaH of molar equivalent excess of 2 to 10 times for 0.5 to 6 hours. The reaction mixture is poured onto ice-water and processed, the precipitated product is filtered and the compounds of general formula (Ia) are produced by crystallizing from dioxane ethylacetate hexane mixture.

In the version B) of the process the imidoyl chloride of the general formula (III) produced in the above described way is brought into reaction with hydrazine hydrate of molar equivalent excess of 2 to 10 in a polar organic solvent (advantageously in methanol, ethanol, isopropanol, DMF, DMSO or in a mixture of any proportion of these solvents) then the solvent is removed under reduced

pressure and thereafter the product received in this way is separated between ethyl acetate and water.

The organic phase is evaporated after drying and the hydrazine derivative is received by treating the residue with an apolar solvent (advantageously with hexane or ether), which is brought into reaction with aldehydes in a polar organic solvent (advantageously in methanol, ethanol, isopropanol, DMF, DMSO solvent or in glacial acetic acid) at a temperature of 20 to 100 C° for 1 to 12 hours. If the solvent is adequately chosen the product precipitates and may be separated by filtering after cooling of the mixture.

The compounds of the general formula (Ib) are obtained after a washing with an apolar solvent (advantageously with ether or hexane).

The version C) of the process is performed similarly but the hydrazine derivative is brought into reaction with isatin.

The compounds of general formula (Ic) are produced in this way.

The intermediate compounds used in the process according to the invention are partly known as intermediate products of the above mentioned kinase inhibitor compounds, such as im2_1 to im3_3, im3_5 and im4_1 to 4, they are partly new such as the compounds given in the examples 3, 5, 6, and 8 to 11 (see Table 1).

The essence of the invention is based also on the recognition that new structures may be created by linking together the reactive intermediate products of known biologically active compounds using the process described in the Example 4 and

compounds of new structures are obtained having astoundingly different effects from those of the known compounds.

The essence of the process given in the Example 4 is that amines of general formulas (II) and (IV) solved in anhydrous dimethyl sulfoxide can be transformed into sodium salts by adding sodium hydride and the salts can be combined with imidoyl chlorides characterized by the general formula (III) at room temperature, and compounds of general structure (Ia) may be obtained in this way.

Connection of imidoyl chlorides and heterocyclic amines in presence of sodium hydride, as well as the received pyrazolyl amino and pyrrolyl amino derivatives are unknown in the literature.

Compounds having the same biological effect may be obtained also in the way that imidoyl chlorides characterized by the general formula (III) are brought into reaction first with hydrazine hydrate in a medium containing ethanol and the 4-hydrazino-7H-pyrrolo-[2,3-d]pyrimidine derivatives obtained in this way are brought into reaction with aldehydes or isatins as described in the Examples 7 and 12 to 15 and compounds of general formulas (Ib) or (Ic) are obtained in this way.

Condensation reactions of benzaldehydes and isatins in ethanol containing medium are well-known in the literature but from among the hydrazones obtainable from 4-hydrazino-7H-pyrrolo[2,3-d]pyrimidine derivatives only those having phenyl substituent in the position 5 are described up to now (J. Chem. Res. Miniprint *12* (1997) 2771-2789).

These known 5-phenyl derivatives proved to be completely ineffective in the models of inflammations described in the invention.

Table 1.

General formula	Inter-mediate compound No.	R1	R2	R3	Reference
II	Im2_1	benzyl	methyl	methyl	J. Med. Chem. 39 (1996) 2285-2292DE 2818676 (1978)
II	Im2_2	benzyl	tetramethylene		
II	Im2_3	benzyl	phenyl	phenyl	
II	Im2_4	3-chloro-phenyl	methyl	methyl	
II	Im2_5	dimethyl-amino-propyl	methyl	methyl	
III	Im3_1	benzyl	methyl	methyl	
III	Im3_2	benzyl	tetramethylene		
III	Im3_3	benzyl	phenyl	phenyl	
III	Im3_4	3-chloro-phenyl	methyl	methyl	Example 3
III	Im3_5	benzyl	tetramethine		J. Med. Chem 39 (1996) 2285-2292
IV	Im4_1	phenyl	-	tert.- butyl	Bioorg. Med. Chem.
IV	Im4_2	3-chloro-phenyl	-	tert.- butyl	
IV	Im4_3	3-nitro-phenyl	-	tert.- butyl	
IV	Im4_4	4-nitro-phenyl	-	tert.-butyl	
IV	Im4_5	3-methoxy	-	tert.- butyl	
IV	Im4_6	4-methoxy	-	tert.- butyl	

The compounds according to the invention are analgesic and antiphlogistic ones, which may be potentially orally administered.

An opportunity emerged to hinder neurogenic inflammation wherein the sensory neuronopeptides such as substance P (SP) or calcitonine gene related peptide (CGRP) released from primary afferents have important role, as well as to discover an analgesic of new type on the base of efficiency examination of heptapeptide

somatostatine analogue TT-232.

We found out on the base of our previous examinations that that the TT-232 is a potent analgesic hindering both the neurogenic and non-neurogenic inflammation, which is effective also in the neuropathic nociceptive model. As the TT-232 is a peptide structure and cannot be orally absorbed, we began simultaneously with the clinical trials examinations of the compound to examine its peptidomimetic analogues to create a compound, which may be orally absorbed and has a wide spectrum of analgetic and anti-inflammatory effects similarly to the TT-232.

The in vitro tests were performed with electric excitation of sensoric neuron elements of an isolated rat trachea. The mediator of neurogenic inflammation the P-substance is released under influence of excitation from the capsaicine sensitive neuron elements and the concentration of P-substance in the water bath may be measured by radio immunoassay. Somatostatine antagonists, as well as the TT-232 hinder the excitation of terminal nerves so the quantity of released neuropeptide becomes less in the water bath.

The antiphlogistic efficiency of TT-232 against neurogenic and non-neurogenic inflammations was formerly tested primarily on rats (such as plasm extravasation provoked by mustard-oil, dextrane oedema, chronic arthritic oedema provoked by Freund adjuvant, plasm extravasation in articulations provoked by bradyquinine, carrageenine oedema, accumulation of leucocytes under influence of carrageenine). The oedema was provoked by alcoholic solution of capsaicine onto the mouse ear in the biological tests mentioned in the patent specification, and it was quantitatively evaluated by measurement of the mass of the ear and that of Evans's blue accumulation.

The antiphlogistic effect of the TT-232 against chronic inflammation provoked by Freund's adjuvant was demonstrated formerly on Wistar's female rat. This is the experimental model of rheumatoid arthritis. The phase II clinical trials of TT-232 on patients suffering from rheumatoid arthritis was performed in 2004. Wee took into consideration that the Freund's adjuvant aggravates symptoms implying considerable deformation of articulations on rats of Lewis strain, so the effect of TT-232 was examined in addition to the swelling of articulation provoked by Freund's adjuvant also to the destruction of bone to the infiltration of synovium lymphocytes and leucocytes and to the development of mechanical hyperalgesia, as well.

The following apparatuses were used in the experiments described in the patent specification.

The NMR photos were taken by apparatus Bruker AC300.

The apparatus used for measurement of HPLC was:

Waters HPLC with a detector ZMD MS and an UV one Waters 996 DAD provided with a column Supelco Discovery RP-Amide C16 wherein the gradient of acetonitrile is 10 to 100 % (of formic acid content of 0.05 %) per 6 minutes, the flowing rate is 3 ml per minute.

The melting points were measured by the apparatus Büchi Melting Point B-540.

The compounds according to the invention, the process for producing them and experiments to determine their effects are presented in the examples below.

Example 1

Process for producing *2-amino-4,5-dimethyl-1-(3-chlorophenyl)-1H-pyrrolo-3-carbonitrile*

18 g (0.2 moles) of acetoine and 21 ml (0.2 moles) of 3-chloroaniline were solved in 300 ml of toluene then 0.2 ml of concentrated HCl was added. The reaction mixture was refluxed for two and half hours then evaporated to the half of volume at atmospheric pressure finally the whole solvent quantity was distilled in vacuum. The received material was solved in 350 ml of ethanol first 13.2 ml (0.2 moles) of malonic acid dinitrile was added then 11.2 g of KOH solved in 50 ml of water was dropped into it and cooled with ice. The mixture was refluxed for two hours then let to cool. The received crystalline product was filtered and washed with hexane (45.2 g; 92 %).

Example 2

Process for producing *5,6-dimethyl-7-(3-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-ole*

40 g of 2-amino-4,5-dimethyl-1-(3-chlorophenyl)amino-3-cyano-pyrrole (Example 1) was refluxed in 200 g of formic acid for 10 hours. The mixture was then poured onto ice and stirred for 1 hour. The precipitated material was filtered out and washed with water. The product was dried at room temperature and used in the following reaction without further purification. (27 g; 60 %).

Example 3

Process for producing *5,6-dimethyl-4-chloro-7-(3-chlorophenyl)-7H-pyrrolo[2,3-*

-d]pyrimidine

26.9 g of 4-hydroxy-5,6-dimethyl-7-((3-chlorophenyl)amino) pyrrolo[2,3-

-d]pyrimidine (Example 2) was solved in 125 ml of $POCl_3$ and the mixture was refluxed for 1 hour, then poured onto ice-water of great excess of at least ten times greater volume, then the precipitated product was filtered off after complete decomposition of $POCl_3$ then washed with water and dried. (26.28 g; 92 %).

Example 4

Process for producing *[5-tert.-butyl-2-(3-nitro-phenyl)-2H-pyrazole-3-yl]-[7-(3-chlorophenyl)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-amine.*

0.292 g (1 millimole) of 5,6-dimethyl-4-chloro-7-((3-chlorophenyl)amino) pyrrolo[2,3-d]pyrimidine (Example 3) and 0.26 g (1 millimole) of 5-tert.--butyl-2-(3-nitro-phenyl)-2H-pyrazole-3-yl-amine (im4_3) were solved in 4 ml of dimethyl sulfoxide and 200 mg of sodium hydride was added in several portions under strong mixing then the mixture was mixed at room temperature for 1 hour. The reaction mixture was processed by pouring onto ice then the precipitated deposit was filtered off and recrystallized in the mixture of ethyl acetate and hexane (0.31 g; 60 %).

Example 5

Process for producing *[7-(3-chlorophenyl)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazine*

2.92 g (10 millimoles) of 4-chloro-7-(3-chlorophenyl)-5,6-dimethyl-7H-

pyrrolo[2,3-d]pyrimidine (Example 3) was boiled together with 3 ml of hydrazine hydrate in 30 ml of ethanol for 3 hours then the solvent and the excess of hydrazine hydrate was distilled at a reduced pressure. The residue of the evaporation was separated between water and ethyl acetate. The organic phase was evaporated after drying. The residue of evaporation was bruised with ether and *[7-(3-chlorophenyl)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazine* was obtained in this way (1.9 g; 66 %).

Example 6

Process for producing *[7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazine.*

The compound was produced as described in the Example 5 with the difference that the primary substance was the known intermediate product marked as im3_1 (2.71 g of the substance).

(1.92 g; 74 %)

Example 7

Process for producing *4-{[5,6-Dimethyl-7-(3-chlorophenyl)-7H-pyrrolo[2,3-*

-d]pyrimidine-4-yl]-hydrazono-methyl}-benzene-1,2-diole.

0.287 g (1 millimole) of [7-(3-chlorophenyl)-5,6-dimethyl-7H-pyrrolo[2,3-

-d]pyrimidine-4-yl]-hydrazine (Example 5) and 0.138 g (1 millimole) of 3,4-dihydroxy-benzaldehyde were boiled in 4 ml of ethanol for 6 hours and the precipitated product i. e. 4-{[7-(3-chlorophenyl)-5,6-dimethyl-7H-pyrrolo[2,3-

d]pyrimidine-4-yl]-hydrazonomethyl}-benzene-1,2-diole was filtered and washed with ether. (0.29g; 68 %).

Example 8

Process for producing *2-amino-4,5-dimethyl-1-((3-morpholine-4-yl-propyl)-1H-pyrrol-3-carbonitrile.*

8.8 g (0.1 moles) of acetoine, 2-hydroxy-3-butanone and 14.4 ml (0.1 moles) of 4-(3-aminopropyl) morpholine were solved in 170 ml of toluene in an apparatus containing water separator attachment then 0.1 ml of concentrated hydrochloric acid was added, the mixture was then refluxed, until it boiled at 110 C° then let to cool for a short time then 6.6 ml of malonitrile was added. The mixture was then refluxed until it boiled at 110 C° then filtered through Cellit then cooled. The precipitated crystals were filtered (17.31 g; 66 %).

Example 9

Process for producing *5,6-Dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-*

-d]pyrimidine-4-ol.

3.761 g (14.33 millimoles) of 2-amino-4,5-dimethyl-1-(3-morpholine-4-yl-propyl)-1H-pyrrolo-3-carbonitrile) (Example 8) was refluxed in 38 ml of formic acid for 1 night. The mixture was diluted with water during the process and neutralized with NaHCO3 shaken out with ethyl acetate, then the organic phase was evaporated, the precipitated crystals were processed with hexane then filtered (3.265 g; 78.5 %).

Example 10

Process for producing *5,6-dimethyl-4-chloro-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine.*

3 g (10.33 millimoles) of 5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine-4-ole (Example 9) was refluxed in 15 ml of POCl3 for an hour. The mixture was then poured onto ice, neutralized with $NaHCO_3$, shaken out with ethyl acetate and evaporated. A brown oil was obtained (2.71 g; 85 %).

Example 11

Process for producing *[5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-*
-d]pyrimidine-4-yl]-hydrazine.

1.785 g (5.78 millimoles) of 5,6-dimethyl-4-chloro-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine (Example 10)was solved in so much of ethanol just enough for solution (120 ml) then 17.8 ml of hydrazine hydrate was added. The mixture was refluxed for about 15 minutes then evaporated and separated between water and ethyl acetate. The organic phase was dried and evaporated. The crystals precipitated during evaporation were bruised with hexane then filtered (1.07 g; 61 %).

Example 12

Process for producing *4-{[5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazonomethyl}-katechole.*

304.4 mg (1 millimole) of [5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-

pyrrolo-[2,3-d]pyrimidine-4-yl]-hydrazine (Example 11) and 138.1 mg (1 millimole) of 3,4-dihydroxy-benzaldehyde were solved in 6 ml of ethanol then refluxed for half an hour. The precipitated crystals were filtered out then washed with ethanol and hexane (45 %).

Example 13

Process for producing *4-{[5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]hydrazonomethyl}-2-nitro-phenol.*

304 mg (1 millimole) of [5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo-[2,3-d]pyrimidine-4-yl-hydrazine (Example 11) and 169 mg (1 millimole) of 3-nitro-4-hydroxy-benzaldehyde were refluxed in 6 ml of ethanol for 4 hours then let to cool then filtered and washed in ethanol and hexane (176 mg; 36 %).

Example 14

Process for producing *4-{[5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazonomethyl}-2-methoxy-phenol.*

304 mg (1 millimole) of [5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazine (Example 11) with 152 mg (1 millimole) of vanillin were refluxed in 6 ml of ethanol the precipitated crystals were filtered out then washed with ethanol and hexane (221.37 mg; 50 %).

Example 15

Process for producing *4,6-dichloro-3-{[5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo-[2,3-d]pyrimidine-4-yl]-hydrazono}-1,3-dihydro-indole-2-on.*

108 mg (0.5 millimole) of 4,6-dichloro-isatin was added to 152.2 mg (0.5 millimole) of [5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazine (Example 11) and the mixture was refluxed in 4 ml of ethanol. The precipitated orange yellow crystals were filtered then washed with ethanol and hexane (102 mg; 40 %).

Example 16

Process for producing *[5-tert.--butyl-2-(3-nitro-phenyl)-2H-pyrazole-3-yl]-[5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-amine.*

650 mg (2.5 millimoles) of 5-tert.--butyl-2-(3-nitro-phenyl)-2H-pyrazole-3-yl-amine and 772 mg (2.5 millimoles) of 5,6-dimethyl-4-chloro-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine (Example 10) were solved in 4 ml of DMSO then 200 mg of NaH was added, and the mixture was stirred at room temperature for half an hour then the mixture was poured onto ice. The mixture was extracted with EtOAc dried and evaporated. The received brown oil was separated in a column, evaporated then bruised with hexane, the precipitated yellow crystals were filtered (272.2 mg; 20 %).

Examples 17 to 91

The formulas of the compounds according to examples and the methods of production are given in the Table 2, the physical and chemical characteristics of the compounds are given in the Table 3.

Example 92

Process for producing *[5-tert.--Butyl-2-(4-methoxy-phenyl)-2H-pyrazole-3-yl]-*

[5,6-dimethyl-7-(6-methyl-pyridine-2-yl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-amine hydrochloride.

48 mg of the compound according to Example 91 was solved in 1 ml of anhydrous dioxane and 0.2 ml of 4M hydrochloric acid in ether was added to the mixture. The precipitated yellow deposit was filtered and washed with ether (36 mg; 70 %), melting point is 97 to 98 C°.

Table 2.

Example No	Chemical name	Formula	M. w.	Used preparation process (Example No)	Used intermediate products (Example No)	Used commercial and literary starting materials	Yield (%)
1	2-amino-1-4,5-dimethyl-(3-chloro-phenyl)-1H-pyrrolo-3-carbonitrile	C13H12ClN3	245.7137	1		malonitrile, acetoine and 3--chloro-aniline	92
2	5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-ol	C14H12ClN3O	273.7242	2	1		60
3	5,6-dimethyl-4-chloro-7-(3-chloro-phenyl)-7H-pyrrolo[2,3--d]pyrimidine	C14H11Cl2N3	292.1699	3	2		92
4	[5-terc-buthyl-2-(3-nitro-phenyl)-2H-pyrazole-3-yl]-[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-amine	C27H26ClN7O2	516.007	4		im3_4 és im4_3	60
5	[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazine	C14H14ClN5	287.7542	5	3		66
6	(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-hydrazine	C15H17N5	267.3362	6		im3_1	74

7	4-{[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazonomethyl}-pyrokatechine	C21H18ClN5O2	407.8629	7	5	3,4-dihydroxy--benzaldehyde	68
8	2-amineo-4,5-dimethyl-1-(3-morpholine-4-yl-propyl)-1H-pyrrol-3-carbonitrile	C14H22N4O	262.3576	8			66
9	5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine-4-ol	C15H22N4O2	290.3682	9	8		79
10	5,6-dimethyl-4-chloro-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine	C15H21ClN4O	308.8138	10	9		85
11	[5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3--d]pyrimidine-4-yl]-hydrazine	C15H24N6O	304.3981	11	10		61
12	4-{[5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazonomethyl}-pyrokatechine	C22H28N6O3	424.5069	12		3,4-dihydroxy-benzaldehyde	45
13	4-{[5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazonomethyl}-2-nitro-phenol	C22H27N7O4	453.505	13	11	4-hydroxy-3-nitro-benzaldehyde	36
14	4-{[5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazonomethyl}-2-methoxy-phenol	C23H30N6O3	438.534	14	11	4-hydroxy-3-methoxy-benzaldehyde	50

15	4,6-dichloro-3-{[5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazono}-1,3-dihydro-indole-2-on	C23H25Cl2N7O2	502.4074	15	11	4,6-dichloroisatin	41
16	[5-tert.-butyl-2-(3-nitro-phenyl)-2H-pyrazole-3-yl]-[5,6-dimethyl-7-(3-morpholine-4-yl-propyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-amine	C28H36N8O3	532.6509	16	10	im4_3	20
17	N-(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-N'-(2-methoxy-benzylidene)-hydrazine	C23H23N5O	385.4727	7	6	2-methoxy-benzaldehyde	54
18	4-[(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-hydrazonomethyl]-pyrokatechine	C22H21N5O2	387.445	7	6	3,4-dihydroxy-benzaldehyde	62
19	N-[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-N'-naphthalene-1-yl-methylene-hydrazine	C25H20ClN5	425.9247	7	5	naphtyl-1-carbaldehyde	35
20	N-[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-N'-(4-trifluoro-methyl-benzylidene)-hydrazine	C22H17ClF3N5	443.8625	7	5	4-trifluoromethyl-benzaldehyde	62
21	4-{[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazonomethyl}-2-nitro-phenol	C21H17ClN6O3	436.861	7	5	4-hydroxy-3-nitro-benzaldehyde	33

22	N-(3,4-Bis-benzyloxi-benzylidene)-N'-[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazine	C35H30ClN5O2	588.1147	7	5	3,4-dibenzyloxi-benzaldehyde	58
23	N-[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-N'-(3-nitro-benzylidene)-hydrazine	C21H17ClN6O2	420.8616	7	5	3-nitro-benzaldehyde	72
24	4-{[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazonomethyl}-2-methoxy-phenol	C22H20ClN5O2	421.89	7	5	4-hydroxy-3-methoxy-benzaldehyde	35
25	N-(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-N'-naftalén-1-ylmethylene-hydrazine	C26H23N5	405.5067	7	6	naphtyl-1-carbaldehyde	58
26	N-(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-N'-(4-trifluoromethyl-benzylidene)-hydrazine	C23H20F3N5	423.4446	7	6	4-trifluoromethyl-benzaldehyde	81
27	N-(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-N'-thiophene-2-yl-methylene-hydrazine	C20H19N5S	361.4719	7	6	thiophene-2-carbaldehyde	57
28	4-[(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-hydrazonomethyl]-2-nitro-phenol	C22H20N6O3	416.4431	7	6	4-hydroxy-3-nitro-benzaldehyde	95

29	4-[(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-hydrazonomethyl]-2,6-dimethyl-phenol	C24H25N5O	399.4998	7	6	3,5-dimethyl-4-hydroxy-benzaldehyde	91
30	N-(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-N'-(3,4-bis-benzyloxi-benzylidene)-hydrazine	C36H33N5O2	567.6967	7	6	3,4-dibenzyloxy-benzaldehyde	67
31	[4-[(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-hydrazonomethyl]-phenyl]-dimethyl-amine	C24H26N6	398.515	7	6	4-dimethylamino-benzaldehyde	21
32	N-(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-N'-(3-nitro-benzylidene)-hydrazine	C22H20N6O2	400.4437	7	6	3-nitro-benzaldehyde	25
33	4-[(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-hydrazonomethyl]-2-methoxy-phenol	C23H23N5O2	401.4721	7	6	4-hydroxy-3-methoxy-benzaldehyde	20
34	N-(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-N'-(4-izopropyl-benzylidene)-hydrazine	C25H27N5	397.5274	7	6	4-isopropyl-benzaldehyde	58
35	4-[(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-hydrazonomethyl]-benzonitrile	C23H20N6	380.4561	7	6	4-cyano-benzaldehyde	69
36	4-{[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3--d]pyrimidine-4-yl]-hydrazonomethyl}-2,6-dimethyl-phenol	C23H22ClN5O	419.9177	7	5	3,5-dimethyl-4-hydroxy-benzaldehyde	47

37	4-{[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3--d]pyrimidine-4-yl]-hydrazonomethyl}-benzonitrile	C22H17ClN6	400.874	7	5	4-cyano-benzaldehyde	62
38	5-bromo-3-{[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazono}-1,3-dihydro-indole-2-on	C22H16BrClN6O	495.7694	7	5	5-bromo-isatin	50
39	3-{[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazono}-1,3-dihydro-indole-2-on	C22H17ClN6O	416.8734	7	5	isatin	33
40	5-chloro-3-{[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazono}-1,3-dihydro-indole-2-on	C22H16Cl2N6O	451.3184	7	5	5-chloro-isatin	63
41	4,7-dichloro-3-{[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazono}-1,3-dihydro-indole-2-on	C22H15Cl3N6O	485.7635	7	5	4,7-chloro-isatin	78
42	3-{[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazono}-5-methyl-1,3-dihydro-indole-2-on	C23H19ClN6O	430.9005	7	5	5-methyl-isatin	63
43	3-{[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazono}-5-fluoro-1,3-dihydro-indole-2-on	C22H16ClFN6O	434.8638	7	5	5-fluoro-isatin	72
44	3-{[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-hydrazono}-5-trifluoromethoxy-1,3-dihydro-indole-2-on	C23H16ClF3N6O2	500.8712	7	5	5-trifluoromethoxy-isatin	69

45	3-[(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-hydrazono]-5-bromo-1,3-dihydro-indole-2-on	C23H19BrN6O	475.3515	7	6	5-bromo-isatin	46	
46	3-[(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-hydrazono]-1,3-dihydro-indole-2-on	C23H20N6O	396.4555	7	6	isatin	47	
47	3-[(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-hydrazono]-2-oxo-2,3-dihydro-1H-indole-5-sulphonic acid	C23H20N6O4S	476.5177	7	6	isatin-5-sulphonic acid	15	
48	3-[(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-hydrazono]-5-chloro-1,3-dihydro-indole-2-on	C23H19ClN6O	430.9005	7	6	5-chloro-isatin	55	
49	3-[(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-hydrazono]-4,6-dichloro-1,3-dihydro-indole-2-on	C23H18Cl2N6O	465.3455	7	6	4,6-dichloro-isatin	81	
50	3-[(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-hydrazono]-4,7-dichloro-1,3-dihydro-indole-2-on	C23H18Cl2N6O	465.3455	7	6	4,6-dichloro-isatin	48	
51	(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-(5-terc-buthyl-2-phenyl-2H-pyrazole-3-yl)-amine	C28H30N6	450.5915	4		im3_1 és im4_1	33	
52	(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-[5-tert.-buthyl-2-(4-nitro-phenyl)-2H-pyrazole-3-yl]-amine	C28H29N7O2	495.589	4		im3_1 és im4_4	71	

53	(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-[5-tert.-buthyl-2-(3-nitro-phenyl)-2H-pyrazole-3-yl]-amine	C28H29N7O2	495.589	4		im3_1 és im4_3	72
54	(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl)-[5-tert.-buthyl-2-(3-fluoro-phenyl)-2H-pyrazole-3-yl]-amine	C28H29FN6	468.5819	4		im3_1 és im4_2	81
55	(5-tert.-buthyl-2-phenyl-2H-pyrazole-3-yl)-[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-amine	C27H27ClN6	471.0094	4		im3_4 és im4_1	57
56	[5-tert.-buthyl-2-(3-fluoro-phenyl)-2H-pyrazole-3-yl]-[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-amine	C27H26ClFN6	488.9999	4		im3_4 és im4_2	95
57	[5-tert.-buthyl-2-(4-nitro-phenyl)-2H-pyrazole-3-yl]-[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl]-amine	C27H26ClN7O2	516.007	4		im3_4 és im4_4	91
58	(9-benzyl-6,7,8,9-tetrahydro-5H-1,3,9-triaza-fluoren-4-yl)-[5-tert.-buthyl-2-(3-fluoro-phenyl)-2H-pyrazole-3-yl]-amine	C30H31FN6	494.6202	4		im3_2 és im4_2	67
59	(9-benzyl-6,7,8,9-tetrahydro-5H-1,3,9-triaza-fluoren-4-yl)-(5-tert.-buthyl-2-phenyl-2H-pyrazole-3-yl)-amine	C30H32N6	476.6297	4		im3_2 és im4_1	59
60	5,6-dimethyl-1-(3-chloro-phenyl)-2-[7-(3-chloro-phenyl)-7H-pyrrolo-[2,3-d]pyrimidine-4--yl-amino]-4,5-dimethyl-1H-pyrrol-3-carbonitrile	C27H22Cl2N6	501.4226	4		im2_4 és im3_4	69

61	1-benzyl-2-[7-(3-chloro-phenyl)-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl-amino]-4,5,6,7-tetrahidro-1H-indole-3-carbonitrile	C30H27ClN6	507.0429	4		im2_2 és im3_4	66
62	1-benzyl-2-[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl-amino]-4,5-diphenyl-1H-pyrrol-3-carbonitrile	C38H29ClN6	605.148	4		im2_3 és im3_4	60
63	1-benzyl-2-[5,6-dimethyl-7-(3-chloro-phenyl)-7H-pyrrolo[2,3-d]pyrimidine-4-yl-amino]-4,5-dimethyl-1H-pyrrol-3-carbonitrile	C28H25ClN6	481.0047	4		im2_1 és im3_4	74
64	2-(9-benzyl-9H-1,3,9-triaza-fluorene-4-yl-amino)-1-(3-chloro-phenyl)-4,5-dimethyl-1H-pyrrol-3-carbonitrile	C30H23ClN6	503.011	4		im2_4 és im3_5	69
65	1-benzyl-2-(9-benzyl-9H-1,3,9-triaza-fluorene-4-yl-amino)-4,5,6,7-tetrahidro-1H-indole-3-carbonitrile	C33H28N6	508.6313	4		im2_2 és im3_5	68
66	1-benzyl-2-(9-benzyl-9H-1,3,9-triaza-fluorene-4-yl-amino)-4,5-diphenyl-1H-pyrrol-3-carbonitrile	C41H30N6	606.7365	4		im2_3 és im3_5	70
67	1-benzyl-2-(9-benzyl-9H-1,3,9-triaza-fluorene-4-yl-amino)-4,5-dimethyl-1H-pyrrol-3-carbonitrile	C31H26N6	482.5931	4		im2_1 és im3_5	73
68	2-(9-benzyl-6,7,8,9-tetrahidro-5H-1,3,9-triaza-fluorene-4-yl-amino)-4,5-dimethyl-1-(3-chloro-phenyl)-1H-pyrrol-3-carbonitrile	C30H27ClN6	507.0429	4		im2_4 és im3_2	68

69	1-benzyl-2-(9-benzyl-6,7,8,9-tetrahidro-5H-1,3,9-triaza-fluorene-4-yl-amino)-4,5,6,7-tetrahidro-1H-indole-3-carbonitrile	C33H32N6	512.6632	4		im2_2 és im3_2	48
70	1-benzyl-2-(9-benzyl-6,7,8,9-tetrahidro-5H-1,3,9-triaza-fluorene-4-yl-amino)-4,5-diphenyl-1H-pyrrol-3-carbonitrile	C41H34N6	610.7683	4		im2_3 és im3_3	55
71	1-benzyl-2-(9-benzyl-6,7,8,9-tetrahidro-5H-1,3,9-triaza-fluorene-4-yl-amino)-4,5-dimethyl-1H-pyrrol-3-carbonitrile	C31H30N6	486.625	4		im2_1 és im3_2	81
72	2-(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl-amino)-1-(3-chloro-phenyl)-4,5-dimethyl-1H-pyrrol-3-carbonitrile	C28H25ClN6	481.0047	4		im2_4 és im3_1	91
73	1-benzyl-2-(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamineo)-4,5,6,7-tetrahydro-1H-indole-3-carbonitrile	C31H30N6	486.625	4		im2_2 és im3_1	67
74	1-benzyl-2-(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl-amino)-4,5-diphenyl-1H-pyrrol-3-carbonitrile	C39H32N6	584.7301	4		im2_3 és im3_1	81
75	1-benzyl-2-(7-benzyl-5,6-dimethyl-7H-pyrrolo[2,3-d]pyrimidine-4-yl-amino)-4,5-dimethyl-1H-pyrrol-3-carbonitrile	C29H28N6	460.5867	4		im2_1 és im3_1	49

Table 3. Physical-chemical characters

Example No	M. w.	LC t_R	MS $[M+H]^+$ or $[M-H]^-$	NMR methode	NMR spectrum	Melting point (°C)
1	245.71	3,17	246	1H NMR, 300 MHz, DMSO-d6 (ppm) :	7.52 (d, 2 H), 7.38 (s, 1 H), 7.23 (m, 1 H), 5.46 (s, 2 H), 1.91 (s, 3 H), 1.74 (s, 3 H)	148-150
2	273.72	2,97	274	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.83 (s, 1 H), 7.71 (s, 1 H), 7.55 (m, 3 H), 7.36 (m, 1 H), 2.29 (s, 3 H), 2.07 (s, 3 H)	288-291
3	292.17	3,32	292	1H NMR, 300 MHz, DMSO-d6 (ppm) :	7.60 (m, 4 H), 7.44 (m, 1 H), 2.43 (s, 3 H), 2.23 (s, 3 H)	158-161
4	516.01	3.60	514	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.54(s, 1H), 8.07(d, 1H), 7.95(s, 1H), 7.71-7.47(m, 5H), 7.36(d, 1H), 6.48(s, 1H), 2.40(s, 3H), 2.17(s, 3H), 1.34(s, 9H)	189-190
5	287.75	2.52	288	1H NMR, 300 MHz, DMSO-d6 (ppm) :	7.71 (m, 4 H), 7.52 (m, 1 H), 7.20(m, 3H), 2.49 (s, 3 H), 2.27 (s, 3 H)	169-171
6	267.34	2.32	268	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.15(s, 1H), 7.77(s, 1H), 7.23(m, 3H), 7.01(d, 2H), 5.35(s, 2H), 4.44(s, 2H), 2.29(s, 3H), 2.13(s, 3H)	195-198
7	407.86	2.76	406	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.2, 10.47 (bs, 1H), 9(bs, 2H), 8.17-6.76(m, 9H), 2.54, 2.36(s, 3H), 2.19, 2.09(s, 3H)	105-107
8	262.36	1.91	262	1H NMR, 300 MHz, DMSO-d6. (ppm) :	5.74 (s, 2 H), 3.62 (t, 2 H), 3.55 (m, 4 H), 2.30 (bs, 4 H), 2.17 (t, 2 H), 1.96 (s, 3 H), 1.83 (s, 3 H), 1.66 (m, 2 H)	135-138
9	290.37	1,63	290	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.67 (s, 1 H), 7.72 (s, 1 H), 4.05 (t, 2 H), 3.52 (m, 4 H), 2.23 (m, 12 H), 1.76 (m, 2 H)	192,5-195,3
10	308.81			1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.28(s, 1H), 4.11(t, 2H), 3.50(t, 4H), 2.25(m, 12H), 1.77(m, 2H)	olaj
11	304.40	0,55	304	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.11 (s, 1 H), 7.67 (s, 1 H), 4.40 (s, 2 H), 4.09 (t, 2 H), 3.53 (m, 4 H), 2.23 (m, 12 H), 1.78 (m, 2 H)	115-117

12	424.51	1,92	424	1H NMR, 300 MHz, DMSO-d6 (ppm) :	10.30, 9.05 (bs, 1 H) , 8.13, 8.06 (s, 1 H) , 7.63-6.74 (m, 4 H) , 4.16, 4.04 (t, 2 H) , 3.53 (bs, 4 H) , 2.49 (s, 3 H) , 2.34 (bs, 6 H) , 2.20 (s, 3H) , 1.80 (m, 2 H)	219,4-222,4
13	453.50	2,17	453	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.50 (bs, 1 H), 8.24-7.80 (m, 4 H), 7.13 (d, 1 H), 4.10 (t, 2 H), 3.55 (bs, 6 H), 2.29 (s, 3 H), 2.27 (s, 3 H), 1.81 (m, 2 H)	158,8-161,5
14	438.53	2,54	438	1H NMR, 300 MHz, DMSO-d6 (ppm) :	10.45, 9.20 (bs 1 H) , 8.20-6.78 (m, 5 H) , 4.16, 4.05 (t, 2 H) , 3.86 (s, 3 H) , 3.81 (s, 3 H) , 3.55 (bs, 4 H) , 2.46 (s, 3 H) , 2.29 (bs, 6 H) , 2.21 (s, 3 H) , 1.18 (m, 2 H)	201,3-205
15	502.41	2,78	501	1H NMR, 300 MHz, DMSO-d6 (ppm) :	13.35 (bs, 1 H), 8.42 (s, 1 H), 7.17 (s, 1 H), 6.97 (s, 1 H), 4.25 (t, 2 H), 3.55 (bs, 4 H), 2.51, (bs, 6 H), 2.40 (s, 3 H), 2.31 (s, 3 H), 1.90 (m, 2 H)	265,6-268,5
16	532.65	3.10	532	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.44(s, 1H), 8.38(s, 1H), 8.02(m, 3H), 7.63(t, 1H), 6.43(s, 1H), 4.09(t, 2H), 3.49(t, 4H), 2.31-2.18(m, 12H), 1.77(m, 2H), 1.32(s, 9H)	120,9-125,3
17	385.47	2.84	386	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.61, 10.76(s, 1H), 8.60-6.97(m, 11H), 5.43, 5.31(s, 2H), 3.86(s, 3H), 2.39, 2.31(s, 3H), 2.21, 2.10(s, 3H),	214-216
18	387.44	2.73	386	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.48, 10.63(s, 1H), 9.39(bs, 2H), 8.24-6.80(m, 10), 5.45, 530(s, 2H), 3.89, 3.83(s, 3H), 2.48, 2.30(s, 3H), 2.22, 2.10(s, 3H)	257-259
19	425.92	2.97	426	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.72, 10.77(s, 1H), 9.13-7.40(m, 13H), 2.53, 2.42(s, 3H), 2.20, 2.13(s, 3H)	133-140
20	443.86	2.98	442	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.89, 11.02(s, 1H), 8.42-7.40(m, 10H), 2.45, 2.40(s, 3H), 2.20, 2.12(s, 3H)	238-239
21	436.86	2.85	437	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.92, 11.03(s, 1H), 8.70-7.41(m, 10H), 2.53, 2.39(s, 3H), 2.20-2.11(s, 3H)	204,2-206,5
22	588.11	3.07	586	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.60, 10.73(s, 1H), 8.27-7.12(m, 18H), 5.19(s, 4H), 2.43, 2.38(s, 3H), 2.19, 2.10(s, 3H)	101-109
23	420.86	2.91	421	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.94, 11.05(s, 1H), 8.76-7.42(m, 10H), 2.53, 2.40(s, 3H), 2.21-2.12(s, 3H)	218-219

24	421.89	2.77	420	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.53, 10.65(s, 1H), 9.40(bs, 1H), 8.25-6.80(m, 9H), 3.86, 3.82(s,3H), 2.53, 2.50(s, 3H), 2.19,2.09(s, 3H)	146-187
25	405.51	2.95	404	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.66, 10.71(s, 1H), 9.11-7.07(m, 14H), 5.45, 5..33(s, 2H), 2.43, 239(s, 3H), 2.22, 2.12(s, 3H)	121-125
26	423.44	2.93	422	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.83, 10.96(s, 1H), 8.40-7.06(m, 11H), 5.44, 5.33(s, 2H), 2.40, 2.33(s, 3H), 2.23, 2.12(s, 3H)	165-166
27	361.47	2.80	362	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.30, 10.83(s, 1H), 8.50-7.05(m, 10H), 5.43, 5.30(s, 2H), 2.44, 2.30(s, 3H), 2.22, 1.98(s, 3H)	170-172
28	416.44	2.83	415	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.70(bs, 1H), 10.9(bs, 1H), 8.27-7.05(m, 11H), 5.36(s, 2H), 2.34(s, 3H), 2.14(s, 3H)	202-205
29	399.50	2.86	398	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.43, 10.46(s, 1H), 8.7(bs, 1H), 8.17-7.05(m, 9H), 5.42, 5.29(s, 2H), 2.43, 2.30(s, 3H), 2.21(s, 6H), 2.19, 2.09(s, 3H)	237-240
30	567.70	3.04	566	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.53, 10.67(s, 1H), 8.24-7.05(m, 20H), 5.43, 5.31(s, 2H), 5.18(s, 4H), 2.38, 2.31(s, 3H), 2.21, 2.09(s, 3H)	159-160
31	398.52	2.87	397	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.43, 10.43(s, 1H), 8.20-6.72(m, 11H), 5.42, 5.29(s, 2H), 2.96(s, 6H), 2.43, 2.29(s, 3H), 2.21, 2.08(s, 3H)	219-221
32	400.44	2.84	399	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.88, 10.99(s, 1H), 8, 75-7.06(m, 11H), 5.45, 5.33(s, 2H), 2.43, 2.33(s, 3H), 2.24, 2.12(s, 3H)	103-109.5
33	401.47	2.76	400	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.47, 10.61(s, 1H), 9.38(bs, 1H), 8.23-6.79(m, 10), 5.42, 530(s, 2H), 3.86, 3.81(s, 3H), 2.47, 2.30(s, 3H), 2.21, 2.09(s, 3H)	220-221
34	397.53	2.93	398	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.60, 10.69(s, 1H), 8.30-7.05(m, 11H), 5.43, 5.31(s, 2H), 2.91(m, 1H), 2.42, 2.31(s, 3H), 2.22, 2.10(s, 3H), 1.22(d, 6H)	196-197
35	380.46	2.83	381	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.87, 11.0(s, 1H), 8.35-7.06(m, 11H), 5.36(s, 2H), 2.35(s, 3H), 2.15(s, 3H)	223.5-225
36	419.92	2.86	420	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.50, 10.52(s, 1H), 8.62(bs, 1H), 8.18-7.26(m, 8H), 2.54, 2.37(s, 3H), 2.20(s, 6H), 2.20, 2.09(s, 3H)	139-212

37	400.87	2.92	399.	1H NMR, 300 MHz, DMSO-d6 (ppm) :	12(ds, 1H), 8.38-7.39(m, 10H), 2.41(s, 3H), 2.14(s, 3H)	226-227.5
38	495.77	3.45 (46.65 %), 3.75 (45.64 %)	493	1H NMR, 300 MHz, DMSO-d6 (ppm) :	12.45(s, 1H), 10.58(s, 1H), 8.69(s, 1H), 7.98(s, 1H), 7.60(m, 3H), 7.42(m, 2H), 6.83(d, 1H), 2.57(s, 3H), 2.19(s, 3H)	292-294.5
39	416.87	3.20 (70.73 %), 3.43 (29.27 %)	415	1H NMR, 300 MHz, DMSO-d6 (ppm) :	12.31(s, 1H), 10.46(s, 1H), 8.44(d, 1H), 7.94(s, 1H), 7.60(m, 3H), 7.46(s, 1H), 7.25(t, 1H), 7.00(t, 1H), 6.87(d, 1H), 2.50(s, 3H), 2.18(s, 3H)	281-293
40	451.32	3.42 (36.77 %), 3.69 (53.69)	449	1H NMR, 300 MHz, DMSO-d6 (ppm) :	12.3(bs, 1H), 10.58(s, 1H), 8.53(s, 1H), 7.98(s, 1H), 7.60(m, 3H), 745(s, 1H), 7.28(d, 1H), 6.87(d, 1H), 2.58(s, 3H), 219(s, 3H)	314-315
41	485.76	3.52	483	1H NMR, 300 MHz, DMSO-d6 (ppm) :	13.89(s, 1H), 11.81(bs, 1H), 8.41(s, 1H), 7.61(m, 3H), 7.43(m, 2H), 7.14(d, 1H), 2.58(s, 3H), 2.24(s, 3H)	284-285
42	430.90	3.28 (68.85 %), 3.55 (31.15 %)	431	1H NMR, 300 MHz, DMSO-d6 (ppm) :	12.32(bs, 1H), 10.35(s, 1H), 8.37(s, 1H), 7.93(s, 1H), 7.60(m, 3H), 7.44(dd, 1H), 7.06(d, 1H), 6.75(d, 1H), 2.59(s, 3H), 2.28(s, 3H), 2.18(s, 3H)	302-303
43	434.86	3.29 (67.04 %), 3.51 (31.34 %)	435	1H NMR, 300 MHz, DMSO-d6 (ppm) :	12.2(bs, 1H), 10.65(s, 1H), 8.44(s, 1H), 8.00(s, 1H), 7.60(m, 3H), 7.46(s, 1H), 7.26(d, 1H), 6.94(d, 1H), 2.54(s, 3H), 2.19(s, 3H)	271-279
44	500.87	3.45 (71.15 %), 3.67 (28.85 %)	499	1H NMR, 300 MHz, DMSO-d6 (ppm) :	12.2(bs, 1H), 10.65(s, 1H), 8.44(s, 1H), 8.00(s, 1H), 7.60(m, 3H), 7.46(s, 1H), 7.26(d, 1H), 6.94(d, 1H), 2.54(s, 3H), 2.19(s, 3H)	262-276
45	475.35	3.27 (28.50 %), 3.64 (66.65 %)	473	1H NMR, 300 MHz, DMSO-d6 (ppm) :	12.3(bs, 1H), 10.56(s, 1H), 8.67(s, 1H), 8.06(s, 1H), 7.32(m, 4H), 7.09(d, 2H), 6.82(d, 1H), 5.42(s, 2H), 2.50(s, 3H), 2.21(s, 3H)	288-290
46	396.46	3.00 (27.06 %), 3.35 (71.55 %)	397	1H NMR, 300 MHz, DMSO-d6 (ppm) :	12.26(bs, 1H), 10.43(s, 1H), 8.42(s, 1H), 8.02(s, 1H), 735-6.84(m, 8H), 5.41(s, 2H), 2.50(s, 3H), 2.20(s, 3H)	292-293
47	476.52	3.19 (26.81 %), 5.68	475	1H NMR, 300 MHz, DMSO-d6 (ppm) :	12.23(bs,1H), 10.44(s, 1H), 8.81(s, 1H), 8.00(s, 1H), 7.49(dd, 1H), 7.29(m, 3H), 7.09(d, 2H), 6.76(d, 1H), 5.42(s, 2H), 2.49(s,	bomlik

		(65.39 %)			3H), 2.20(s, 3H)	
48	430.90	3.24 (27.04 %), 3.59 (66.89 %)	429	1H NMR, 300 MHz, DMSO-d6 (ppm) :	12.3(bs, 1H), 10.55(bs, 1H), 8.51(s, 1H), 8.06(s, 1H), 7.28(m, 4H), 7.07(m, 2H), 6.86(d, 1H), 5.42(s, 2H), 4.99(s, 3H), 2..49(s, 3H), 2.21(s, 3H)	302-303
49	465.35	3.38	465	1H NMR, 300 MHz, DMSO-d6 (ppm) :	13.79(s, 1H), 12(bs,1H), 8.46(s, 1H), 7.26(m, 4H), 7.08(d, 2H)., 6.96(s, 1H), 5.46(s, 2H), 2.50(s, 3H), 2.26(s, 3H)	299
50	465.35	3.34	465	1H NMR, 300 MHz, DMSO-d6 (ppm) :	13.86(s, 1H), 11.82(s, 1H), 8.48(s, 1H), 7,40-7.07(m, 7H), 5.46(s, 2H), 2.49(s, 3H), 2.26(s, 3H)	298
51	450.59	3.49	449	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.23(s, 1H), 8.05(s, 1H), 7.62(d, 2H), 7.40-7.22(m, 6H), 7.03(d, 2H), 6.44(s, 1H), 5.36(s, 2H), 2.26(s, 3H), 2.16(s, 3H), 1.33(s, 9H)	165-168
52	495.59	3.57	494	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.4(bs, 1H), 8.24(d, 2H), 8.02(d, 2H), 7.99(s, 1H), 7.25(m, 3H), 7.04(d, 2H), 6.50(s, 1H), 5.36(s, 2H), 2.36(s, 3H), 2.18(s, 3H), 1.33(s, 9H)	219.5-221
53	495.59	3.53	494	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.51(s, 1H), 8.05(d, 1H), 7.98(s, 1H), 7.65(t, 1H), 7.26(m, 3H), 7.00(m, 2H), 6.46(s, 1H), 5.36(s, 2H), 2.34(s, 3H), 2.16(s, 3H), 1.34(s, 9H)	>200 decompo-sition
54	468.5	3.54	467	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.34(s, 1H), 8.35(s, 1H), 8.47-7.20(m, 6H), 7.05(m, 3H), 6.44(s, 1H), 5.37(s, 2H), 2.36(s, 3H), 2.17(s, 3H), 1.32(s, 9H)	153-156
55	471.0	3.57	471	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.33(s, 1H), 8.00(s, 1H), 7.65-7.52(m, 4H), 7.37(m, 6H), 7.25(t, 1H), 6.44(s, 1H), 2.34(s, 3H), 2.15(s, 3H)	169-176
56	489.0	3.62	489	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.43(s, 1H), 7.98(s, 1H), 7.60-7.36(m, 7H), 7.09(t, 1H), 6.45(s, 1H), 2.38(s, 3H), 2.17(s, 3H), 1.33(s, 9H)	189-191.5
57	516.0	3.64	514.2	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.60(s, 1H), 8.27(d, 2H), 7.95(m, 3H), 7.56(m, 3H), 7.38(m, 1H), 6.50(s, 1H), 2.42(s, 3H), 2.18(s, 3H), 1.34(s, 9H)	195-198
58	494.6	3.51	495.21	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.32(s, 1H), 8.07(s, 1H), 7.42(m, 3H), 7.26(m, 3H), 7.07(m, 3H), 6.43(s, 1H), 5.31(s, 2H), 2.69(bs, 2H), 2.49(bs, 2H), 1.71(bs, 4H), 1.32(s,9H)	147-153
59	476.6	3.47	475.26	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.21(s, 1H), 8.09(s, 1H), 7.59(d, 2H), 7.41-7.20(m, 6H), 7.08(d, 2H), 6.41(s, 1H), 5.30(s, 2H), 2.63(bs, 2H), 2.49(bs, 2H), 1.70(bs, 4H), 1.32(s, 9H)	188-190
60	501.4	2.92		1H NMR,	10.10; 9.80 (s, 1H, NH),	234,3-237,2

				CDCl3 ppm	7.51-7.19 (m, 9H, aromatic-H), 2.55 (s, 3H, CH3), 2.36 (s, 3H, CH3) , 2.30 (s, 3H, CH3), 2.24 (s, 3H, CH3)	
61	507.0	2,98	507	1H NMR, CDCl3 ppm	10.06; 9.84 (s, 1H, NH), 7.50-7.22 (m, 10H, aromatic-H), 5.38 (s,.2H, CH2), 3.09; 2.90 (bs, 2H, 1'''- H2), 2.61; 2.59 (s, 3H, CH3) , 2.57 (bs, 2H, 4'''- H2), 2.27; 2.24 (s, 3H, CH3),1.88; 1.80 (bs, 4H, 2'''-, 3'''- H2)	203,7-204,7
62	605.1	3,06	605	1H NMR, CDCl3 ppm	10.10 (bs, 1H, NH), 7.53-7.04 (m, 10H, aromatic-H), 5.43 (s, 2H, CH2),2.60 (s, 2H, CH2),2.27 (s, 3H, CH3)	187,4-189,3
63	481.0	2,94	481	1H NMR, CDCl3 ppm	10.10 (s, 1H, NH), 7.50-7.18 (m, 10H, aromatic-H), 5.46 (s, 2H, CH2), 2.60 (s, 3H, CH3), 2.46 (s, 3H, CH3), 2.28 (s, 3H, CH3), 2.26 (s, 3H, CH3)	228,1-229,0
64	503.0	3,06	502	1H NMR, CDCl3 ppm	10.45 (s, 1H, NH), 8.20 (d, 1H, 7-H, 3J=7.8 Hz), 7.61-7.25 (m, 13H, aromatic-H), 5.72 (s, 2H, CH2), 2.56 (s, 3H, CH3), 2.28 (s, 3H, CH3)	252,2-253,1
65	508.6	2,97	509	1H NMR, CDCl3 ppm	10.64 (s, 1H, NH), 8.55 (d, 1H, 7-H, 3J=7.8 Hz), 7.55-7.21 (m, 14H, aromatic-H), 5.75 (s, 2H, CH2), 5.50 (s, 2H, CH2), 4.93 (bs, 2H, 1'- H2), 2.61 (bs, 2H, 4'-H2), 1.91 (bs, 2H, 2'-,3'- H2),	254,6-255,6
66	606.7	3,03	607	1H NMR, CDCl3 ppm	10.43 (s, 1H, NH), 8.56 (d, 1H, 7-H, 3J=7.8 Hz), 7.50-7.13 (m, 24H, aromatic-H), 5.76 (s, 2H, CH2), 5.53 (s, 2H, CH2)	decomposi-tion >90
67	482.5	2,89	483	1H NMR, CDCl3 ppm	10.47; 10.20 (s, 1H, NH), 8.54; 8.42 (d, 1H, 7-H, 3J=7.8 Hz), 7.60-7.16 (m, 14H, aromatic-H), 5.73 (s, 2H, CH2), 5.69; 5.53 (s, 2H, CH2), 2.46 (s, 3H, CH3), 2.23 (s, 3H, CH3)	decomposi-0tion >90
68	507.0	3,01	507	1H NMR, CDCl3 ppm	10.05; 9.87 (s, 1H, NH), 7.54-7.00 (m, 10H, aromatic-H), 5.41; 5.40 (s, 2H, CH2), 2.86 (bs, 2H, 7- H2), 2.63 (bs, 2H, 10- H2), 2.50 (s, 3H, CH3), 2.49 (s, 3H, CH3), 1.78 (bs, 4H, 8-,9- H2)	220,1-221,5
69	512.6	3,02	513	1H NMR, CDCl3 ppm	10.10; 9.92 (s, 1H, NH), 7.33-7.11 (m, 11H, aromatic-H), 5.41 (s, 2H, CH2), 5.33 (s, 2H,	216,219,9

					CH2), 3.06; 2.90 (bs, 4H, 1'-,1"-H2), 2.57 (bs, 4H, 4'-,4"- H2), 1.86 (bs, 8H, 2'-,2"-,3'-,3"- H2)	
70	610.7	3,08	611	1H NMR, CDCl3 ppm	10.2 (bs, 1H, NH), 7.33-7.03 (m, 21H, aromatic-H), 5.46 (s, 2H, CH2), 5.40 (s, 2H, CH2), 2.93 (bs, 2H, 7- H2), 2.58 (bs, 2H, 10- H2),1.77 (bs, 4H, 8-,9- H2)	191,0-191,7
71	486.6	2,99	487	1H NMR, DMSO d6 ppm	9.67 (s, 1H, NH), 7.35-7.07 (m, 11H, aromatic-H), 5.42 (s, 2H, CH2), 5.32 (s, 2H, CH2) , 2.92 (bs, 2H, 7-H2), 2.50 (bs, 5H, 10- H2, CH3), 2.49 (s, 3H, CH3), 1.74 (bs, 4H, 8-, 9- H2)	225-229,5
72	481.0	2,88	481	1H NMR, CDCl3 ppm	9.98 (s, 1H, NH), 7.51-7.03 (m, 10H, aromatic-H), 5.46 (s, 2H, CH2), 2.51 (s, 3H, CH3), 2.29 (s, 3H, CH3), 2.24 (s, 3H, CH3), 2.19 (s, 3H, -CH3)	237,9-240,5
73	486.6	3,06	487	1H NMR, CDCl3 ppm	10.00; 9.90 (s, 1H, NH), 7.32-7.06 (m, 11H, aromatic-H), 5.48; 5.45(s, 2H, CH2), 5.35; 5.32(s,2H, CH2), 3.12; 2.90 (bs,2H, 1"- H2), 2.55 (bs, 2H, 4"- H2),2.52(s, 3H, CH3) , 2.24(s, 3H, CH3), 1.86 (bs, 4H, 2"-, 3"- H2)	248,9-249,6
74	584.7	3,11	585.29	1H NMR, CDCl3 ppm	10.01 (bs, 1H, NH), 7.31-7.04 (m, 21H, aromatic-H), 5.50 (s, 2H, CH2), 5.41 (s, 2H, CH2), 2.53 (s, 3H, CH3) , 2.26 (s, 3H, CH3)	197,1-197,6
75	460.5	2,88	461	1H NMR, CDCl3 ppm	10.11; 9.90 (s, 1H, NH), 7.33-7.09 (m, 11H, aromatic-H),5.50; 5.46 (s, 2H, CH2), 5.40 (s, 2H, CH2), 2.51(s, 3H, CH3) , 2.44 (s, 3H, CH3), 2.25 (s, 3H, CH3) , 2.22 (s, 3H, CH3)	236,0-239,1

76	248.3306	1.56	249	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.63(s, 1H), 7.74(s, 1H), 4.05(t, 2H), 2.22(s, 3H), 2.21(s, 3H), 2.18(t, 2H), 2.11(s, 6H), 1.74(q, 2H)	165-166.5
77	266.7762	2.22	267	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.47(s, 1H), 4.23(t, 2H), 2.40(s, 3H), 2.36(s, 3H), 2.21(t, 2H), 2.13(s, 6H), 1.80(q, 2H)	oil
78	262.3605	0.56	263	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.86(bs, 1H), 8.12, 7.67(s, 1H), 4.39, 4.11(bs, 2H), 4.07(t, 2H), 2.27(s, 3H), 2.25(s, 3H), 2.17(t, 2H), 2.10(s, 6H), 1.77-1.71(q, 2H)	90-92
79	396.4963	2.02	397	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.36, 10.47(s, 1H), 9.27(bs, 1H), 8.19-6.76(m, 5H), 4.13, 4.01(t, 2H), 3.84, 3.79(s, 3H), 2.48-2.11(m, 14H), 1.76(q, 2H)	195.6-196.4
80	382.4692	1.91	383	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.30, 10.25(bs, 1H), 9.11(bs, 2H), 8.12-6.73(m, 5H), 4.13, 4.01(t, 2H), 2.48-2.11(m, 14), 1.76(q, 2H)	185
81	475.6422	2.92	476	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.04(s, 1H), 7.99(s, 1H), 7.46(d, 2H), 6.92(d, 2H), 6.36(s, 1H), 4.07(t, 2H), 3.71(s, 3H), 2.26(s, 3H), 2.21(s, 3H), 2.16(t, 2H), 2.09(s, 6H), 1.72(q, 2H), 1.30(s, 9H)	91.7-93.6
82	475.6422	2.99	476	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.12(s, 1H), 8.03(s, 1H), 7.26(t, 1H), 7.16(m, 2H), 6.80(d, 1H), 6.39(s, 1H), 4.08(t, 2H), 3.60(s, 3H), 2.27(s, 3H), 2.24(s, 3H), 2.15(t, 2H), 2.09(s, 6H), 1.72(q, 2H), 1.30(s, 9H)	102-104

83	490.6133	3.04	491	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.61-7.64(m, 6H), 6.45(s, 1H), 4.08(t, 2H), 2.32(s, 3H), 2.28(s, 3H), 2.16(t, 2H), 2.10(s, 6H), 1.73(q, 2H), 1.33(s, 9H)	164.4-166
84	226.2833	3.30	227	1H NMR, 300 MHz, DMSO-d6 (ppm) :	7.86(t, 1H), 7.29(d, 1H), 7.17(d, 1H), 5.67(s, 2H), 2.49(s, 3H), 1.92(s, 3H) 1.87(s, 3H)	oil
85	254.2939	2.59	255	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.82(s, 1H), 7.88(t, 1H), 7.71(s, 1H), 7.33(d, 2H), 2.49(s, 3H), 2.28(s, 3H), 2.14(s, 3H)	298.5-300
86	272.7395	3.79	273	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.47(s, 1H), 7.97(t, 1H), 7.49(d, 1H), 7.44(d, 1H), 2.53(s, 3H), 2.45(s, 3H), 2.34(s, 3H)	198.3-198.7
87	268.3238	2.05	269	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.10(s, 1H), 7.89(t, 1H), 7.86(bs, 1H), 7.41(d, 1H), 7.31(d, 1H), 4.47(s, 2H), 2.50(s, 3H), 2.35(s, 3H), 2.23(s, 3H)	214.3-215.5
88	388.4326	2.60	389	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.50, 10.45(s, 1H), 9.1(bs, 2H), 8.18-6.77(m, 8H), 2.54, 2.36(s, 3H), 2.28(s, 3H), 2.17(s, 3H)	264.2-264.8
89	417.4307	2.88	418	1H NMR, 300 MHz, DMSO-d6 (ppm) :	11.74(s, 1H), 11.27, 10.74(bs, 1H), 8.38-7.16(m, 8H), 2.45, 2.27(s, 3H), 2.4(s, 3H), 2.19(s, 3H)	216.5-217
90	496.5766	4.65	497	1H NMR, 300 MHz, DMSO-d6	8.6-7.26(m, 9H), 6.51(s, 1H), 2.53(s, 3H), 2.40(s, 3H), 2.26(s, 3H), 1.34(s, 9H)	108-110

				d6 (ppm) :		
91	481.6056	4.49	482	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.23(s, 1H), 8.04(s, 1H), 7.89(t, 1H), 7.52(d, 2H), 7.41(d, 1H), 7.32(d, 1H), 6.95(d, 2H), 6.41(s, 1H), 3.73(s, 3H), 2.53(s, 3H), 2.31(s, 3H), 2.24(s, 3H), 1.32(s, 9H)	221.5-222.4
92	517	4.49	482	1H NMR, 300 MHz, DMSO-d6 (ppm) :	8.23(s, 1H), 8.04(s, 1H), 7.89(t, 1H), 7.52(d, 2H), 7.41(d, 1H), 7.32(d, 1H), 6.95(d, 2H), 6.41(s, 1H), 3.73(s, 3H), 2.53(s, 3H), 2.31(s, 3H), 2.24(s, 3H), 1.32(s, 9H)	97-98

Example 93. (Study of pharmaceutical effect)

Examination of active substances inhibiting release of substance P (SP) by radio immuno-assay (RIA) method in vitro on rat trachea

The influence of active substances on the SP release (of 500 nanomoles) was examined in in vitro environment on rat trachea in biological bath (Wistar's rats of 200 to 250 g weight were used). Samples were taken three times in periods of 8 minutes after perfusion with oxygenated Krebs's solution for 1 hour. The organ was excited with electric current of 10 Hz, 40 V, 0.1 ms, 120 s in the middle period of 8 minutes. The SP content of the samples were measured by a specific radio immuno-assay method. The values are represented in the diagram in the following way: the value before electric excitation with empty column, the one measured immediately after excitation with black and the one measured at 8 minutes after excitation with shaded columns. The following radio immuno-assay method was used: 5000 cpm of mono-iodized SP marked with I^{125} iodine isotope was used as RIA tracer. Synthetic SP was used as standard in the concentration range of 0 to 100 phento moles per ml. The neuropeptide concentrations related to the weight of humid tissues of the samples were expressed in units "phento moles per mg". The Figure 8 shows the inhibiting effect of TT-232 as reference substance and 8 compounds in concentration of 500 nM to the release of P-substance under electric excitation (see the black columns). The significant values related to the control ones received on prepared organs treated only with solvent are shown.

Example 94. (Study of pharmaceutical effect)

Examination of the in vivo neurogenic inflammation inhibiting effect.

(Swelling and plasm protein extravasation provoked by capsaicine in the mouse ear).

BALB/c male mice of 18 to 20 g were anesthetized with ketamine (100 mg/kg according to the invention) and xylazine (10 mg/kg i. m.). Having measured the ear thickness at the base the examined substances were applied according to the invention in quantities of 0.1 ml per 10 g. 10 minutes later Evans blue stain of 125 mg per kg (solution of 2.5 %, 0.05 ml per 10 g) was injected into tail veins then 5 minutes later 10 μl of alcohol of 96 % was applied on the left ear and 10 μl of capsaicine solution of 2.5 % was applied on the right ear of each animal. The Evans blue marker stain connects itself to the plasma albumin in the circulation. The surfaces become blue where the plasma albumin leaves blood vessels because of inflammation. The thickness of ears was measured again after 30 minutes and the swelling was defined as per cents of the initial thickness. The animals were killed thereafter by bleeding to death, their ears were cut and the mass of the ears was measured. The stain accumulated in the tissue pieces was extracted with 1.5 ml of formamide at 20 C° for 72 hours. The optical densities of the solutions were determined by spectrophotometry (with microplate reader) at the wavelength of 620 nm. The quantity of extravased stain (indicating the plasma albumin quantity) was defined in units of mg per humid tissue The values measured in the ears treated in alcohol were subtracted from the ones measured in the ears treated with capsaicine at both animals. The animals treated with solvent served as control. The Figure 9 shows accumulation of Evans blue quantity in the control group pre-treated with solvent (black column) after administering TT-232 as reference

substance and dosing of 100 μg/kg of 11 compounds according to the invention. Non-parametric Mann-Whitney test was used to the statistical evaluation of the results. *$p < 0.05$; **$p < 0.01$.

Example 95. (Study of pharmaceutical effect)

Examination of vasodilatation and extravasation of plasma protein in mouse's ear provoked by mustard oil.

Balb/c male mice were anesthetized with ketamine (100 mg/kg according to the invention) and xylazine (5 mg/kg i. m.) then albumin (30 kBq activity per mouse) marked with 0.1 ml of iodine isotope I^{125} was dosed i. v. 10 μl of mustard oil of1 % was dribbled onto both sides of the left ear of each mouse and smeared. The radioactivity was measured in each minute for 50 minutes with gamma ray counter above the ear. The increase of activity indicates vasodilatation and extravasation of the plasma protein. 20 μg/kg of TT-232 and non peptide following molecule 11527 (10 and 100 μg/kg) were dosed according to the invention 30 minutes before the treatment with mustard oil. A solvent was used in the control group.

Bonferroni's modified test after ANOVA was used for statistical evaluation, *$p < 0.05$, **$p < 0.01$; n=7 per group (see Figure 10).

Example 96. (Study of pharmaceutical effect)

Examination of neuropathic hyperalgesia

The partial unilateral ligation of n. ishiadicus causes diminution of the mechanonociceptive threshold of the extremity (Seltzer's operation). The mechanonociception was examined with Ugo Basile's analgesimeter (Randall-

Selitto test). The foot of the animal was put under a teflon cone with rounded end and gradually increasing force was exerted onto middle region of the beck of foot. The pain threshold is the value when the animal pulls its leg out. It may be read out in grams by the hand moving before linear scale. The change of the mechanical threshold was expressed in per cents of the own initial threshold. The nervus ischiadus of the thigh of male Sprague-Dawley rats was prepared on the one side in pentobarbital narcosis after control measurements then 1/3 to 1/2 part of the nerves were carefully detached, tightly bound with non-traumatic thread (Mersilene, Ethicon) of 6/0 size, then the incision was closed. The mechanonociceptive thresholds were measured again on the 7^{th} day after the operation. Only the animals were involved in the following examination, which showed reduction of thresholds of at least 20 % related to the control results. The measurements were repeated 20 minutes after dosing of 18 according to invention. The results were expressed in per cents related to the initial values measured before dosing (shown by white column) and compared to the control group with solvent. Non-parametric Mann-Whitney tests were used to determine statistically significant differences. *$p < 0.05$, **$p < 0.1$, $n = 6$ to 8 per group (see Figure 11).

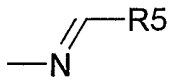
CLAIMS

1 7H-pyrrolo[2,3-d]pyrimidine derivatives of the general formula (I), as well as their pharmaceutically acceptable salts characterized by that in the formula

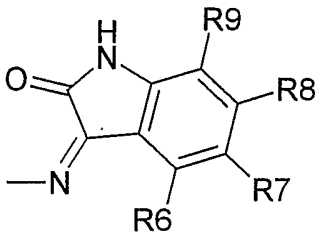
R1 is alkyl, aryl, heteroaryl, aryl-alkyl with 1-4 carbon atoms, heteroaryl-alkyl with 1-4 carbon atoms, morpholino-alkyl with 1-4 carbon atoms or dialkylamino-alkyl with1-4 carbon atoms,

R2, R3 independently of each other are hydrogen, methyl, ethyl, propyl, isopropyl or cyclopropyl groups or R2 and R3 are together a tetramethylene group

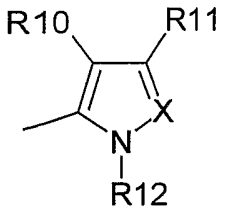
R4 is



or



or



group, wherein

R5 is a substituted or unsubstituted aromatic or heteroaromatic ring where

R6, R7, R8 and R9 independently of each other are hydrogen, halogen, nitro, amino, alkylamino, dialkylamino, hydroxy, methoxy, ethoxy, isopropoxy or sulfonyl group,

R10 is hydrogen or nitrile group,

R11 is hydrogen, methyl, ethyl, propyl, isopropyl, tert.-butyl group or tetramethylene ring connected to X,

R12 is alkyl, aryl, heteroaryl, aryl-alkyl with 1-4 carbon atoms, morpholino-alkyl with 1-4 carbon atoms, dialkylamino-alkyl with 1-4 carbon atoms,

X is carbon, if R11 is a tetramethylene ring connected to X, otherwise nitrogen, methine, methyl-methine, ethyl-methine, propyl-methine, isopropyl-methine, cyclopropyl-methine, tert.- butyl-methine or phenyl-methine.

2 The compounds of general formula (I) according to Claim 1 characterized by that their structures correspond to the general formula (Ia) wherein R1, R2, R3, R10, R11, R12 and X are the same as in the Claim 1.

3 The compounds of general formula (I) according to Claim 1

characterized by that their structures correspond to the general formula (Ib) wherein R1, R2, R3 and R5 are the same as in the Claim 1.

4 The compounds of general formula (I) according to Claim 1 characterized by that their structures correspond to the general formula (Ic) wherein R1, R2, R3, R6, R7, R8 and R9 are the same as in the Claim 1.

5 Pharmaceutical preparations characterized by that they contain compounds of general formula (I) and therapeutically acceptable additives.

6 Pharmaceutical preparations according to Claim 5 characterized by that they might be applied as antiphlogistic or analgetic medicament.

7 Pharmaceutical preparations according to Claim 5 characterized by that they might be applied as neuropathic hyperalgesia reducing medicament.

8 Pharmaceutical preparations according to Claim 5 characterized by that they might be applied as rheumatic arthritis reducing medicaments.

9 Pharmaceutical preparations according to Claim 5 characterized by that they might be applied as medicament hindering destruction of bones or chondrus.

10 Pharmaceutical preparations according to Claim 5 characterized by that they might be applied for treatment of diseases, which may be connected with inflammatory processes e. g. asthma, eczema or psoriasis.

11 Process for producing 7H-pyrrolo[2,3-d]pyrimidine derivatives of the general formula (I) characterized by that a compound of general formula (II) produced from acetoin with amine and malonic acid dinitrile of molar equivalent

quantities where R1, R2 and R3 are the same as mentioned in the formula (I),the compound is mixed with formic acid of mass excess of 5 to 10 times at reflux temperature for a time period of 1 hour to 2 days, then the mixture is poured into ice-water, the precipitated product is separated, the product is dried then brought into reaction with phosphorus oxychloride of mass excess of 5 to 10 times at reflux temperature for 0.5 to 4 hours then the mixture is poured onto ice and the precipitated imidoyl-chloride of general formula (III) where R1, R2 and R3 are the same as mentioned in the formula (I) is separated, dried and evaporated, thereafter

A) the imidoyl chloride of general formula (III) is solved in an aprotic solvent and brought into reaction with amine of general formula (II) or (IV) of equivalent quantity where R1 and R3 are the same as above adding NaH of 2 to 10 times of molar equivalent excess for 0.5 to 6 hours, the produced mixture is poured onto ice and the precipitated product is separated and purified,

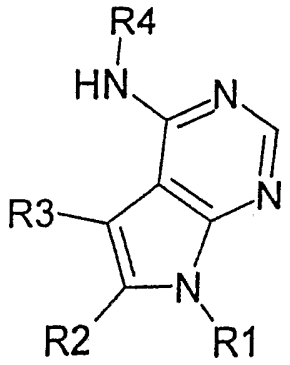
or

B) the imidoyl chloride of general formula (III) produced in this way is brought into reaction with hydrazine hydrate of molar equivalent excess of 2 to 10 times in a medium of polar organic solvent, the reaction product in the organic phase is separated from the mixture, the organic phase is dried and evaporated then bruised with an apolar solvent, the hydrazine derivative produced in this way is mixed with a polar organic solvent and brought into reaction with an aldehyd of equivalent quantity at 20 to 120 C° for 1 to 12 hours, then the reaction product is separated,

or

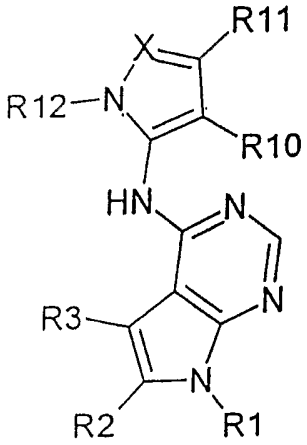
C) the hydrazine derivative produced according to version B) is mixed

with a polar organic solvent and brought into reaction with isatin of equivalent quantity then the product of reaction is separated.



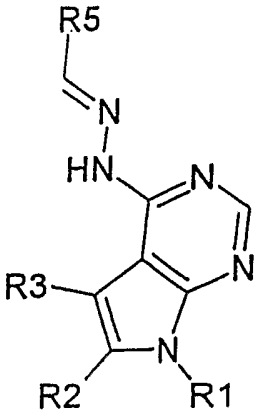
I

Fig. 1



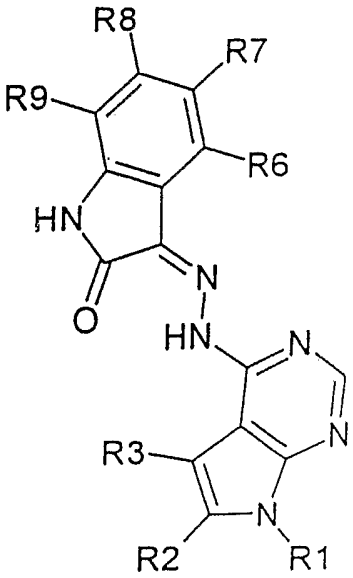
I.a

Fig. 2



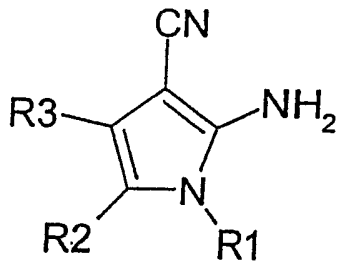
I b

Fig. 3



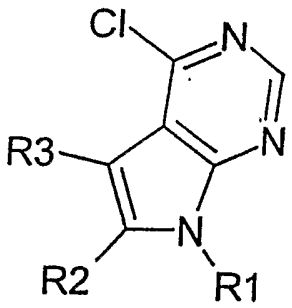
I.c

Fig 4



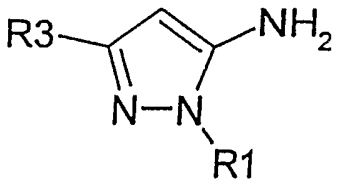
II

Fig. 5



III

Fig. 6



IV

Fig. 7

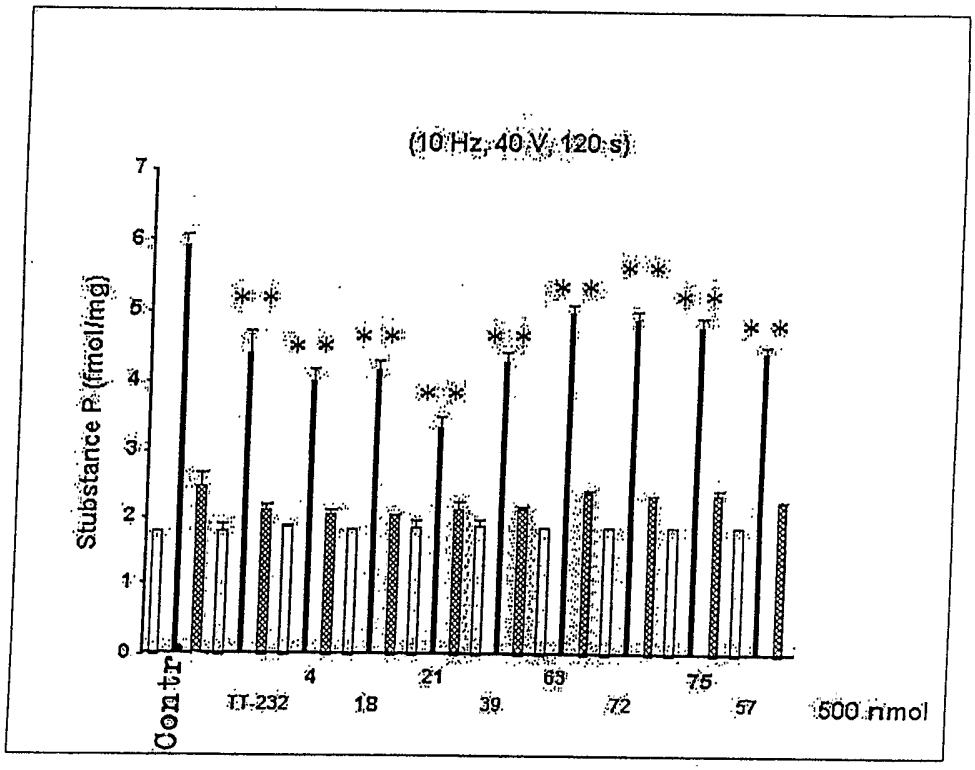

(10 Hz, 40 V, 120 s)
Substance P (fmol/mg)
0
1
2
3
4
5
6
7
Contr
TT-232
4
18
21
39
63
72
75
57
500 nmol

Fig. 8

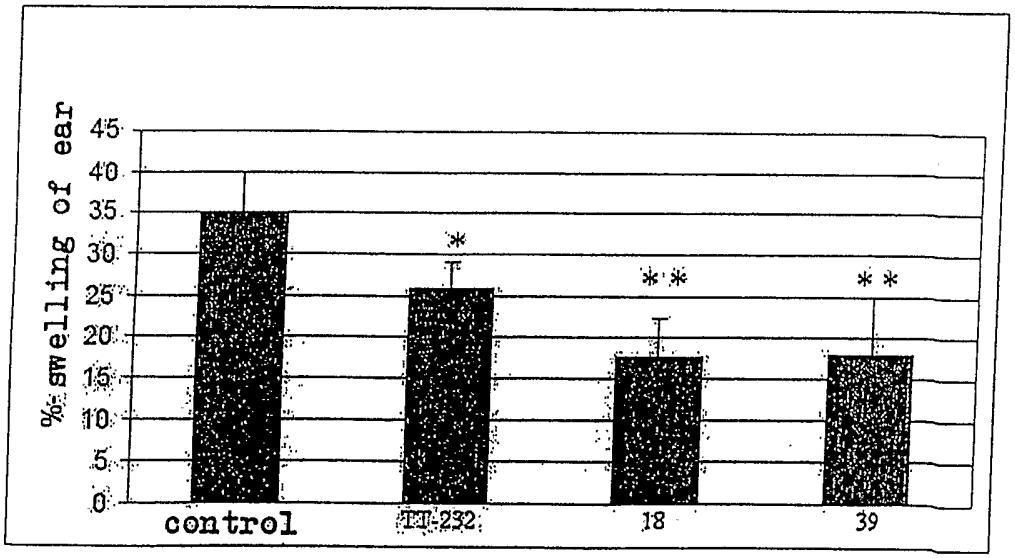

% swelling of ear
0
5
10
15
20
25
30
35
40
45
control
TT-232
18
39

Fig. 9

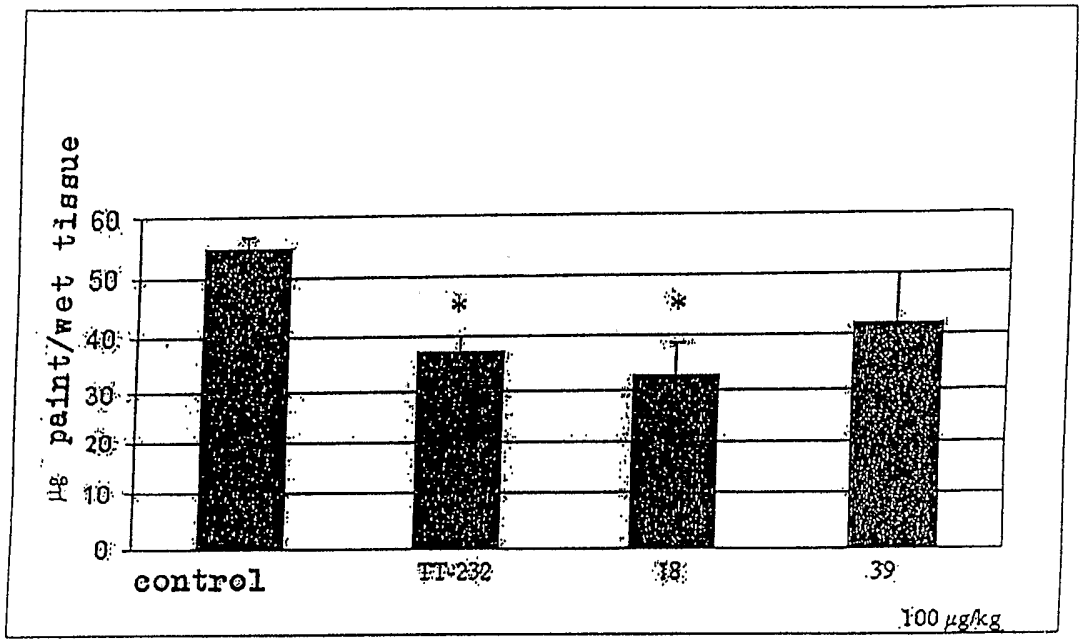

µg paint/wet tissue
60
50
40
30
20
10
0
control
FT-232
18
39
100 µg/kg

Fig. 10

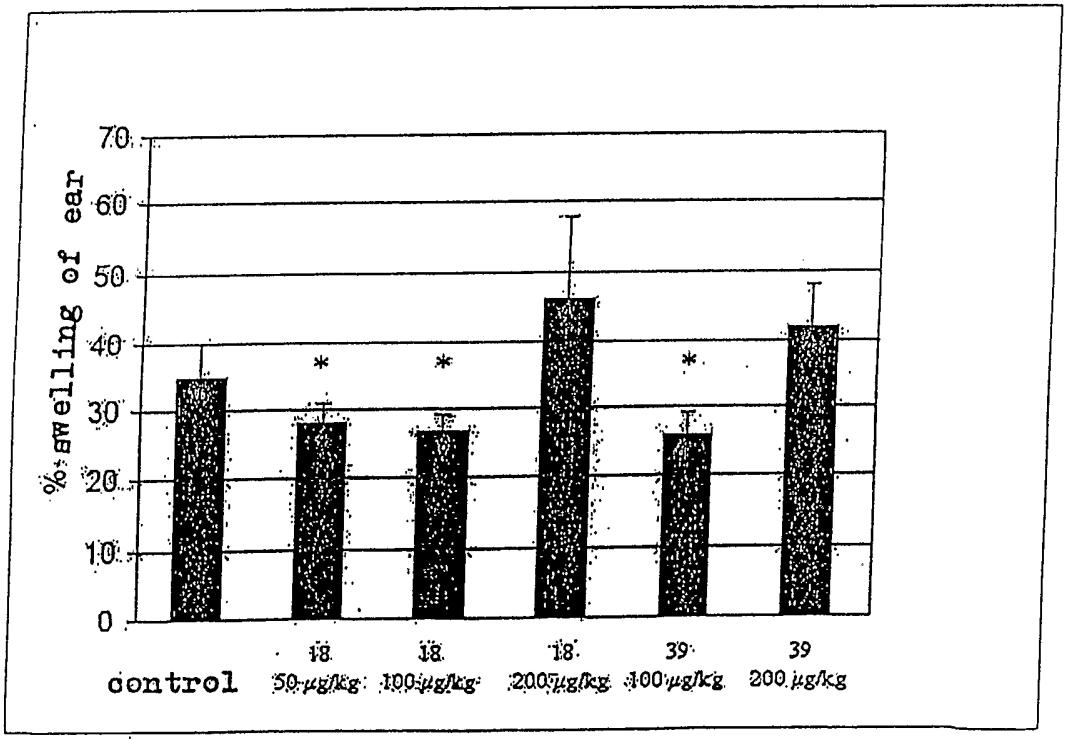

% swelling of ear
70
60
50
40
30
20
10
0
control
18
50 µg/kg
18
100 µg/kg
18
200 µg/kg
39
100 µg/kg
39
200 µg/kg

Fig. 11

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU2005/000040

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/4985 A61P29/00

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 A61P

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, WPI Data, PAJ, BIOSIS, INSPEC, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	US 4 229 453 A (ROTH ET AL) 21 October 1980 (1980-10-21) column 1, line 1 - line 50; claims 1-13	1-11
A	W.M. BASYOUNI, H.M. HOSNI, K.A.M. EL-BAYOUKI: "Pyrrolo'2,3-d!pyrimidines. Part 3: Synthesis of some novel 4-substituted pyrrolo'2,3-d!pyrimidines and their related derivatives" JOURNAL OF CHEMICAL RESEARCH, MINIPRINT, vol. 12, 1997, pages 2771-2789, XP009054934 cited in the application the whole document	1-11

-/--

[X] Further documents are listed in the continuation of box C

[X] 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.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 2005	20/10/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax. (+31-70) 340-3016	Papathoma, S

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU2005/000040

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	TRAXLER P M ET AL: "4-(PHENYLAMINO)PYRROLOPYRIMIDINES: POTENT AND SELECTIVE, ATP SITE DIRECTED INHIBITORS OF THE EGF-RECEPTOR PROTEIN TYROSINE KINASE" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, no. 12, December 1996 (1996-12), pages 2285-2292, XP002053503 ISSN: 0022-2623 cited in the application the whole document	1-11
A	WO 01/42246 A (PFIZER PRODUCTS INC; BLUMENKOPF, TODD, ANDREW; FLANAGAN, MARK, EDWARD;) 14 June 2001 (2001-06-14) abstract page 1, line 1 - page 21, line 22; claims 1,21-26	1-11
A	EP 1 081 149 A (OTSUKA PHARMACEUTICAL FACTORY, INC) 7 March 2001 (2001-03-07) abstract paragraph '0166! - paragraph '0172!	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU2005/000040

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 4229453	A	21-10-1980	AT	368501 B	25-10-1982
			AT	317679 A	15-02-1982
			DE	2818676 A1	08-11-1979
			DK	174079 A	28-10-1979
			EP	0005205 A1	14-11-1979
			ES	479970 A1	16-11-1979
			FI	791342 A	28-10-1979
			JP	54144395 A	10-11-1979
			NO	791150 A	30-10-1979
WO 0142246	A	14-06-2001	AT	257157 T	15-01-2004
			AU	777911 B2	04-11-2004
			AU	1295001 A	18-06-2001
			BG	106855 A	29-12-2002
			BR	0016263 A	13-08-2002
			CA	2393640 A1	14-06-2001
			CN	1409712 A	09-04-2003
			CZ	20021846 A3	18-06-2003
			DE	60007552 D1	05-02-2004
			DE	60007552 T2	23-09-2004
			DK	1235830 T3	29-03-2004
			EE	200200304 A	16-06-2003
			EP	1235830 A2	04-09-2002
			ES	2208433 T3	16-06-2004
			HK	1051195 A1	29-07-2005
			HR	20020509 A2	31-08-2004
			HU	0203503 A2	28-02-2003
			JP	2003516405 T	13-05-2003
			MA	26851 A1	20-12-2004
			MX	PA02005675 A	02-09-2002
			NO	20022738 A	07-06-2002
			NZ	518884 A	27-02-2004
			NZ	528905 A	24-03-2005
			PL	355907 A1	31-05-2004
			PT	1235830 T	30-04-2004
			SK	7562002 A3	05-08-2003
			TR	200201498 T2	21-01-2003
			TR	200400105 T4	23-02-2004
			UA	72290 C2	16-09-2002
			ZA	200204535 A	29-09-2003
EP 1081149	A	07-03-2001	AT	236166 T	15-04-2003
			AU	751337 B2	15-08-2002
			AU	3732099 A	06-12-1999
			CA	2331468 A1	25-11-1999
			CN	1117093 C	06-08-2003
			DE	69906511 D1	08-05-2003
			DE	69906511 T2	29-01-2004
			WO	9959998 A1	25-11-1999
			NO	20005820 A	17-11-2000
			US	6372749 B1	16-04-2002