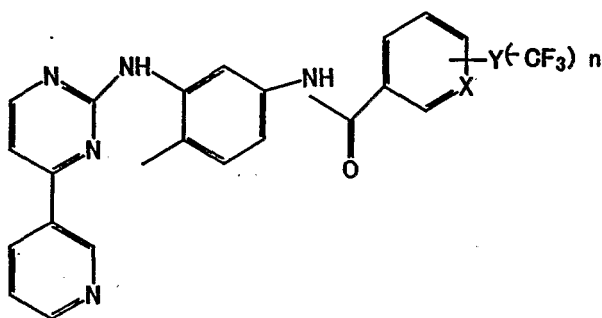


NOVEL PHENYLAMINOPYRIMIDINE DERIVATIVES AS INHIBITORS OF BCR-ABL KINASE

The present invention relates to novel intermediates useful for the preparation of novel phenylaminopyrimidine derivatives, novel phenylaminopyrimidine derivatives, pharmaceutical composition containing the novel phenylaminopyrimidine derivatives and processes for their preparation. The invention particularly relates to novel Phenyl pyrimidine amine derivatives of the general formula I given below



(I)

In the formula the symbols have the following meanings

Series A	Series B
X = CH	X = N
n = 1, 2	n = 1
R = H, Me	R = H, Me

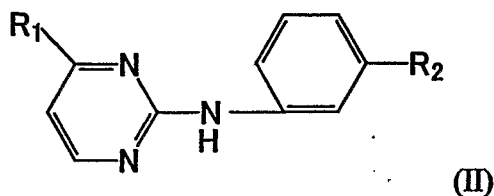
The invention also provides the pharmaceutically acceptable salts of the formula I as defined above. Further, the present invention also provides a process for the preparation of the above said novel compounds and the pharmaceutically acceptable salts thereof. The invention also provides a pharmaceutical composition containing the novel compounds of the general formula I along with usually employed pharmaceutically acceptable excipients and a process for its preparation.

The novel compounds of the formula 1 can be used in the therapy of Chronic Myeloid Leukemia (CML). Since the IC_{50} values of these molecules are in the range 0.1 to 10.0 nm, these novel compounds are potentially useful for the treatment of CML.

Background of the invention

Phenyl pyrimidine amine derivatives are known from the patents WO 9509851, WO 9509853, EP0588762, WO 9509847, WO 9903854, and EP-B-0-564 409 as effective compounds for treatment of tumors.

For example in WO 9509851 compounds of the general formula II are disclosed



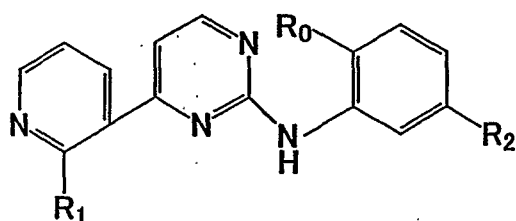
wherein

R1 is a substituted cyclic radical, the cyclic radical being bonded to a ring carbon atom in each case and being selected from phenyl, pyridyl, pyrazinyl, thiazolyl, pyrimidinyl, pyridazinyl and imidazolyl, and the substituents of the above-mentioned cyclic radical being selected from one or more of the groups halogen, cyano, carbamoyl, $-C(=O)-OR_3$, $-C(=O)-R_4$, $-SO_2-N(R_5)-$, $-N(R_7)-R_8$, $-OR_9$ and fluorine substituted lower alkyl,

wherein R_3 , R_4 , R_5 , R_6 , R_7 , R_8 and R_9 are each independently of the others hydrogen or lower alkyl that is unsubstituted or substituted by mono- or di-lower alkylamino; and

R_2 is selected from halogen, cyano, carbamoyl, $-C(=O)-OR_{10}$, $-C(=O)-R_{11}$, $-SO_2-N(R_{12})-R_{13}$, $-N(R_{14})-R_{15}$, $-OR_{16}$ and fluorine-substituted lower alkyl, wherein R_{10} , R_{11} , R_{12} , R_{13} , R_{14} , R_{15} and R_{16} are each independently of the others hydrogen or lower alkyl that is unsubstituted or substituted by mono- or di-lower alkylamino, or a salt of such a compound having at least one salt-forming group.

In WO 9509853, N-phenyl-2-pyrimidineamine derivative compounds of the general formula III are disclosed



(III)

An N-phenyl-2-pyrimidineamine derivative of formula III wherein R₀ is hydrogen, halogen, lower alkoxy or lower alkyl,

R₁ is

- a) N-(amino-lower alkyl)-carbamoyl,
- b) N-(hydroxy-lower alkyl)-carbamoyl,
- c) hydrazino,
- d) cyclohexyl-amino that is unsubstituted or substituted by amino,
- e) piperazinyl that is unsubstituted or substituted by amino-lower alkyl,
- f) morpholinyl, or
- g) lower alkylamino that is substituted by morpholinyl, hydroxy-lower alkylamino, cyano, imidazolyl, guanidyl, amino, lower alkanoylamino, lower alkylamino-carbonylamino, amidino, di-lower alkylamino-cyclohexyl, carboxy, lower alkoxy, dihydroxyphosphoryloxy, piperazinyl, lower alkanoyl-piperazinyl, formylpiperazinyl, prolylamido or by a radical of the formula H₂N-CH(R)-C(=O)-NH- wherein R is hydrogen, C₁-C₄ alkyl, benzyl, hydroxymethyl, 1-hydroxy-ethyl, mercaptomethyl, 2-methylthio-ethyl, indol-3-yl-methyl, phenyl-methyl, 4-hydroxy-phenyl-methyl, carbamoyl-methyl, 2-carbamoyl-ethyl, carboxy-methyl, 2-carboxy-ethyl, 4-amino-butyl, 3-guanidyl-propyl or R is 1H-imidazol-4-yl-methyl, and

R₂ is C₁-C₆ alkyl, C₁-C₃ alkoxy, chlorine, bromine, iodine, trifluoromethyl, hydroxy, phenyl, amino, mono(C₁-C₃ alkyl)amino, di(C₁-C₃ alkyl)amino, C₂-C₄ alkanoyl, propen-yloxy, carboxy, carboxy-methoxy, ethoxycarbonyl-methoxy, sulfanilamido, N,N-di-(C₁-C₃ alkyl)sulfanilamido, N-methyl-piperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-

benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethyl-benzyl or a radical of one of the formulae:

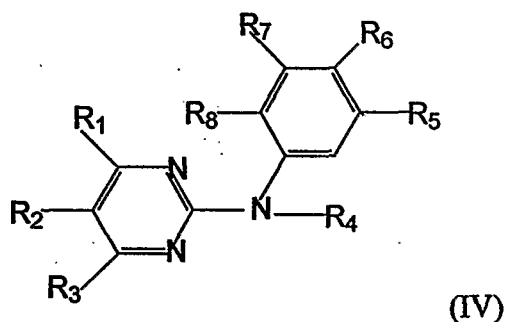
--CO₂ R₃, --NH--C(=O)--R₃, --N(R₃)--C(=O)--R₄, --O--(CH₂)_n--N(R₃)--R₄, --C(.dbd.O)--NH--(CH₂)_n--R₄@a, --C(=O)--NH--(CH₂)_n--N(R₃)--R₄, --CH(CH₃)--NH--CHO, --C(CH₃).dbd.N--OH, --C(CH₃)=N--O--CH₃, --CH(CH₃)--NH₂, --NH--CH₂--C(=O)--N(R₃)--R₄, wherein R₃ and R₄ are each independently of the other C₁-C₃ alkyl, R₄@a is hydroxy, amino or imidazolyl, X is oxygen or sulfur, m is 1, 2 or 3, n is 2 or 3, R₅ is hydrogen, C₁-C₃ alkyl, C₁-C₃ alkoxy, chlorine, bromine, iodine or trifluoromethyl, R₆ is 1H-imidazol-1-yl or morpholinyl and R₇ is C₁-C₃ alkyl or is phenyl that is unsubstituted or mono-substituted by C₁-C₃ alkyl, halogen or by trifluoromethyl, or a salt thereof. An N-phenyl-2-pyrimidineamine derivative of formula III wherein R₀ is hydrogen, halogen, lower alkoxy or lower alkyl, R₁ is

- a) N-(amino-lower alkyl)-carbamoyl,
 - b) N-(hydroxy-lower alkyl)-carbamoyl,
 - c) hydrazino,
 - d) cyclohexyl-amino that is unsubstituted or substituted by amino,
 - e) piperazinyl that is unsubstituted or substituted by amino-lower alkyl,
 - f) morpholinyl, or
 - g) lower alkylamino that is substituted by morpholinyl, hydroxy-lower alkylamino, cyano, imidazolyl, guanidyl, amino, lower alkanoylamino, lower alkylamino-carbonylamino, amidino, di-lower alkylamino-cyclohexyl, carboxy, lower alkoxy-carbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy, lower alkoxy, dihydroxyphosphoryloxy, piperazinyl, lower alkanoyl-piperazinyl, formylpiperazinyl, prolylamido or by a radical of the formula H₂ N--CH(R)--C(=O)--NH-- wherein R is hydrogen, C₁-C₄ alkyl, benzyl, hydroxymethyl, 1-hydroxy-ethyl, mercaptomethyl, 2-methylthio-ethyl, indol-3-yl-methyl, phenyl-methyl, 4-hydroxy-phenyl-methyl, carbamoyl-methyl, 2-carbamoyl-ethyl, carboxy-methyl, 2-carboxy-ethyl, 4-amino-butyl, 3-guanidyl-propyl or R is 1H-imidazol-4-yl-methyl, and
- R₂ is C₁-C₆ alkyl, C₁-C₃ alkoxy, chlorine, bromine, iodine, trifluoromethyl, hydroxy, phenyl, amino, mono(C₁-C₃ alkyl)amino, di(C₁-C₃ alkyl)amino, C₂-C₄ alkanoyl, propen-yloxy, carboxy, carboxy-methoxy, ethoxycarbonyl-methoxy, sulfanilamido, N,N-di-(C₁-C₃ alkyl)sulfanilamido, N-methyl-piperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-

benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethyl-benzyl or a radical of one of the formulae:

--CO₂ R₃, --NH--C(=O)--R₃, --N(R₃)--C(=O)--R₄, --O--(CH₂)_n--N(R₃)--R₄, --C(=O)--NH--(CH₂)_n--R₄@a, --C(=O)--NH--(CH₂)_n--N(R₃)--R₄, --CH(CH₃)--NH--CHO, --C(CH₃)=N--OH, --C(CH₃)=N--O--CH₃, --CH(CH₃)--NH₂, --NH--CH₂--C(=O)--N(R₃)--R₄, wherein R₃ and R₄ are each independently of the other C₁ -C₃ alkyl, R₄@a is hydroxy, amino or imidazolyl, X is oxygen or sulfur, m is 1, 2 or 3, n is 2 or 3, R₅ is hydrogen, C₁ -C₃ alkyl, C₁ -C₃ alkoxy, chlorine, bromine, iodine or trifluoromethyl, R₆ is 1H-imidazol-1-yl or morpholinyl and R₇ is C₁ -C₃ alkyl or is phenyl that is unsubstituted or mono-substituted by C₁ -C₃ alkyl, halogen or by trifluoromethyl, or a salt thereof.

EP0588762 *idem.*, US 5,516,775 compounds of the general formula IV are disclosed



wherein R₁ is hydrogen or C₁ -C₃ alkyl, R₂ is hydrogen or C₁ -C₃ alkyl, R₃ is 2-pyridyl, 3-pyridyl,

4-pyridyl, 2-methyl-3-pyridyl, 4-methyl-3-pyridyl, 2-furyl, 5-methyl-2-furyl, 2,5-dimethyl-3-furyl, 2-thienyl, 3-thienyl, 5-methyl-2-thienyl, 2-phenothiazinyl, 4-pyrazinyl, 2-benzofuryl, N-oxido-2-pyridyl, N-oxido-3-pyridyl, N-oxido-4-pyridyl, 1H-indol-2-yl, 1H-indol-3-yl, 1-methyl-1H-pyrrol-2-yl, 4-quinolinyl, 1-methyl-pyridinium-4-yl iodide, dimethylaminophenyl or N-acetyl-N-methylaminophenyl, R₄ is hydrogen, C₁ -C₃ alkyl, --CO--CO--O--C₂ H₅ or N,N-dimethylaminoethyl, at least one of R₅, R₆, R₇ and R₈ is C₁ -C₆ alkyl, C₁ -C₃ alkoxy, chloro, bromo, iodo, trifluoromethyl, hydroxy, phenyl, amino, mono-(C₁ -C₃ -alkyl)amino, di(C₁ -C₃ alkyl)amino, C₂ -C₄ alkanoyl, propenyloxy, carboxy, carboxymethoxy, ethoxycarbonylmethoxy,

sulfanilamido, N,N-di(C1 -C3 alkyl)sulfanilamido, N-methylpiperazinyl, piperidinyl, 1H-imidazol-1-yl, 1H-triazol-1-yl, 1H-benzimidazol-2-yl, 1-naphthyl, cyclopentyl, 3,4-dimethylbenzyl or a radical of one of the formulae:

--CO₂R, --NH--C(=O)--R, --N(R)--C(=O)--R,

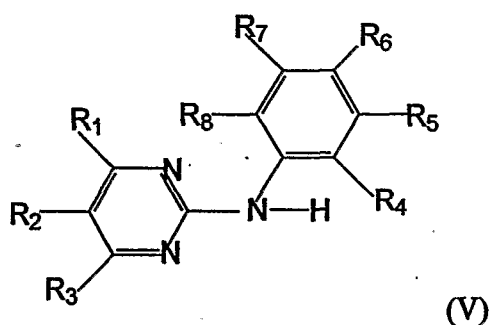
--O--(CH₂)_n--N(R)--R, --C(=O)--NH--(CH₂)_n--N(R)--R, --CH(CH₃)--NH--CHO, --C(CH₃)=N--OH,

--C(CH₃)=N--O--CH₃, --C(CH₃)--NH₂, --NH--CH₂--C(=O)--N(R)--R,

--(CH₂)_m--R₁₀, --X--(CH₂)_m--R₁₀ or wherein R is C1 -C3 alkyl, X is oxygen or sulfur, m is 1, 2 or 3,

n is 2 or 3, R₉ is hydrogen, C1 -C3 alkyl, C1 -C3 alkoxy, chloro, bromo, iodo or trifluoromethyl, R₁₀ is 1H-imidazol-1-yl or morpholinyl, and R₁₁ is C1 -C3 alkyl or unsubstituted phenyl or phenyl which is monosubstituted by C1 -C3 alkyl, halogen or trifluoromethyl, and the other substituents R₅, R₆, R₇ and R₈ are hydrogen, or a pharmaceutically acceptable salt thereof.

In EP 0564 409 compounds of the general formula V are disclosed



Wherein

R₁ is pyrazinyl, 1-methyl-1H-pyrrolyl, amino- or amino-lower alkyl-substituted phenyl wherein the amino group in each case is free, alkylated or acylated, 1H-indolyl or 1H-Imidazolyl bonded at a five-membered ring carbon atom, or unsubstituted or lower alkyl-substituted pyridyl bonded at a ring carbon atom and unsubstituted or substituted at the nitrogen atom by oxygen,

R₂, R₃ are each independently of the other hydrogen or lower alkyl, one or two of the radicals R₄, R₅, R₆, R₇ and R₈ are each nitro, fluoro-substituted lower alkoxy or a radical of the formula (Va)

--N(R₉)-C(=X)-(Y)_n-R₁₀ (Va)

Wherein

R₉ is hydrogen or lower alkyl,

X is oxo, thio, imino, N-lower alkyl-imino, hydroximino or O-lower alkyl-hydroximino,

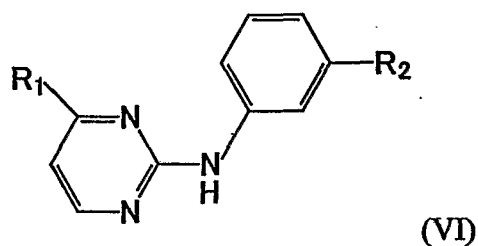
Y is oxygen or the group NH,

5 N is 0 or 1 and

R₁₀ is an aliphatic radical having atleast 5 carbon atoms, or an aromatic, aromatic-aliphatic, cycloaliphatic, cycloaliphatic-aliphatic, heterocyclic or hetero-cyclicaliphatic radical,

And the remaining radicals R₄, R₅, R₆, R₇ and R₈ are each independently of the others hydrogen, lower alkyl that is unsubstituted or substituted by free or alkylated amino, piperazinyl, piperidinyl, pyrrolidinyl or by morpholinyl, or lower alkanoyl, trifluoromethyl, free, etherified or esterified hydroxyl, free, alkylated or acylated amino or free or esterified carboxy, or a salt of such a compound having atleast one salt-forming group.

In WO 9509847, N-phenyl-2-pyrimidineamine derivative of the general formula VI are disclosed



wherein

R₁ is naphthyl, fluorenyl, anthracenyl or a substituted cyclic radical, the cyclic radical being bonded to a ring carbon atom in each case and being selected from phenyl, pyridyl, 1H-indolyl, pyrazinyl, thiazolyl, pyrimidinyl, pyridazinyl and imidazolyl, and the substituents of the above-mentioned phenyl radical being selected from hydroxy, halogen, nitro, cyano, unsubstituted or halogen-substituted lower alkoxy, from a radical of formula VIa

C(=O)-(O)_m-R₃ (VIa)

wherein m is 0 or 1 and

R3 is hydrogen, benzyl, lower alkyl or amino-lower alkyl wherein the amino group is free, lower alkylated or lower alkanoylated, from a radical of formula $m-C(=O)-N(R4)R5$ (VIb) wherein R4 and R5 are each independently of the other hydrogen or unsubstituted or amino- or hydroxy-substituted lower alkyl, from a radical of formula VIc

$-SO_2-N(R6)R7$ (VIc) wherein

R6 and R7 are each independently of the other hydrogen, lower alkyl or amino-lower alkyl, or wherein

R6 and R7 together form the bivalent radical $-(CH_2)_2-NH-(CH_2)_2-$, and from radical of formula VIId

$-N(R8)R9$ (VIId) wherein

R8 and R9 are each independently of the other lower alkyl, or wherein

R8 is hydrogen and R9 is amino or amino-cyclohexyl, or is lower alkyl that is substituted by imidazolyl, guanidyl, lower alkylamino-carbonylamino, amidino, di-loweralkylamino-cyclohexyl, piperazinyl, carboxy, lower alkoxy-carbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy, lower alkoxy, dihydroxyphosphoryloxy or by formylpiperazinyl, and the substituents of the other above-mentioned cyclic radicals being selected from hydroxy, halogen, cyano, amino-lower alkyl, unsubstituted or halogen-substituted lower alkoxy, phthalimido-substituted lower alkyl, from a radical of the above-mentioned formulae VIa, m or VIc and from a radical of formula VII

$-N(R10)R11$ (VII)

wherein R10 and R11 are each independently of the other hydrogen or lower alkyl, or wherein R10 is hydrogen and

R11 is amino or amino-cyclohexyl, or is lower alkyl substituted by amino, lower alkylamino, di-lower alkylamino, lower alkanoylamino, imidazolyl, guanidyl, lower alkylamino-carbonylamino, amidino, di-lower alkylamino-cyclohexyl, piperazinyl, formylpiperazinyl, carboxy, lower alkoxy-carbonyl, carbamoyl, N-hydroxy-carbamoyl, hydroxy, lower alkoxy, dihydroxyphosphoryloxy or by glycidamido; and

R2 is nitro, fluorine-substituted lower alkoxy or a radical of formula VIII

$-N(R12)-C(=X)-(Y)_n-R13$ (VIII)

wherein

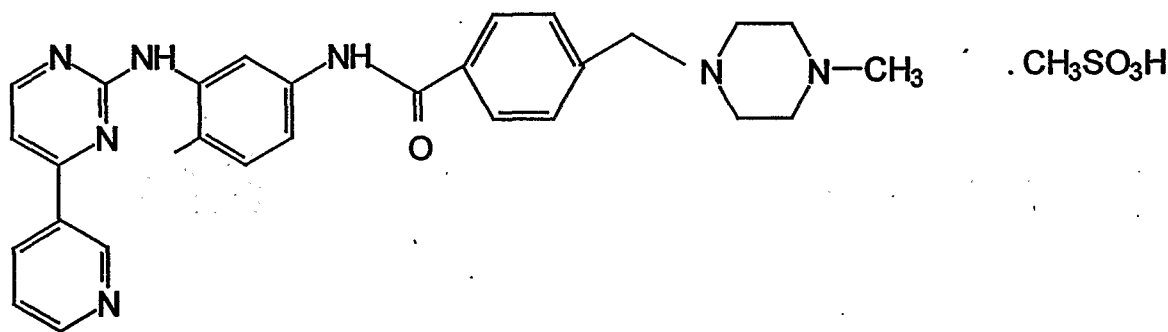
R12 is hydrogen or lower alkyl,

X is oxo, thio, imino, N-lower alkyl-imino, hydroximino or O-lower alkyl-hydroximino,

Y is oxygen or the group NH, n is 0 or 1, and

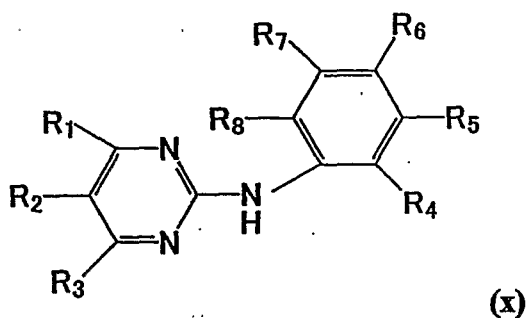
R13 is an aliphatic radical having at least 5 carbon atoms, or an aromatic, aromaticaliphatic, cycloaliphatic, cycloaliphatic-aliphatic, heterocyclic or heterocyclic-aliphatic radical, or a salt of such a compound having at least one salt-forming group.

Furthermore EP0564409 discloses the use of said compounds in the treatment of arteriosclerosis. The patent WO9903854 describes the use of pyridyl pyrimidine amine derivatives, especially of GleevecTM, the Novartis compound CGP57148 of the formula IX, as tyrosine kinase inhibitors in cancer treatment. The IC₅₀ value reported for GleevecTM is 38 nano molar (nm).



IX

In the recent patent WO 0222597 dated 11.09.2001 of Novartis, compounds of the formula (X) have been disclosed wherein :



R_i is pyrazinyl ; 1-methyl-1 H-pyrrolyl ; amino-or amino-lower alkyl-substituted phenyl, wherein the amino group in each case is free, alkylated or acylated ; 1H-indolyl or 1H -imidazolyl bonded at a five-membered ring carbon atom; or unsubstituted or lower alkylsubstituted pyridyl bonded at a ring carbon atom and unsubstituted or substituted at the nitrogen atom by oxygen, R₂ and R₃ are each independently of the other hydrogen or lower alkyl, one of the radicals R₄, R₅, R₆, R₇ and R₈ is a radical of formula $11-N(R_9)-C(=X)-(Y)_n-R_{10}$ wherein

R_g is hydrogen or lower alkyl,

X is oxo, thio, imino, N-lower alkyl-imino, hydroximino or O-lower alkyl-hydroximino,

Y is oxygen or the group NH, n is 0 or 1 and

R₁₀ is phenyl which is a) substituted by a radical selected from the group consisting of amino; mono-or di lower alkylamin ; lower alkanoylamino ; formyl ; lower alkoxy-carbonyl ; and lower alkyl which is substituted by amino, mono-or di-lower alkylamin or lower alkanoylamino, or b) substituted by an unsubstituted or substituted radical selected from the group consisting of benzylamino ; benzoylamino ; pyrrolidinyl ; piperidyl ; piperazinyl ; piperazinyl-carbonyl ; morpholinyl ; and lower alkyl substituted by benzylamino, benzoylamino, pyrrolidinyl, piperidyl, piperazinyl or morpholinyl, the substituents of said substituted radical being selected from the group consisting of cyano; lower alkyl ; hydroxy-or amino-substituted lower alkyl ; trifluoromethyl ; hydroxy; lower alkoxy ; lower alkanoyloxy ; amino; mono-or di-lower alkylamin ; lower alkanoylamino ; benzoylamino ; carboxy; lower alkoxy carbonyl and halogen, and c) optionally further substituted by one or more radicals selected from the group consisting of cyano; lower alkyl ; hydroxy-or amino-substituted lower alkyl ; trifluoromethyl ; hydroxy; lower alkoxy ; lower alkanoyloxy ; amino; mono-or di-lower alkylamin ; lower alkanoylamino ; benzoylamino ; carboxy; lower alkoxy carbonyl and halogen, with the proviso that R₁₀ is not (4-

methyl-piperazinyl)-methylphenyl, and the remaining radicals R4, R5, R6, R7 and R8 are each independently of the others hydrogen; lower alkyl that is unsubstituted or substituted by free or alkylated amino, piperazinyl, piperidyl, pyrrolidinyl or morpholinyl ; lower alkanol ; trifluoromethyl ; free, etherified or esterified hydroxy; free, alkylated oracylated amino; or free or esterified carboxy, or a salt of such a compound having at least one salt-forming group.

It is very well known that phenyl amino pyrido pyrimidines falling under the above mentioned categories are found to be very useful for the treatment of Bcr-abl positive cancer and tumor diseases, such as leukemias [especially Chronic Myeloid Leukemia (CML) and Acute Lymphoblastic Leukemia, where especially apoptotic mechanisms of action are found]. Consequently interest and attention are being given for developing more new molecules falling within above mentioned categories of compounds.

With the above objectives in view we continued our R & D in the above mentioned directions and have filed applications for patents both for new molecules as well as for the improved processes for the preparation of such molecules

Therefore, the main objective of the present invention is to provide novel phenyl amino pyrido pyrimidines of general formula (I) defined above and their pharmaceutically acceptable salts

Another objective of the present invention is to provide novel phenyl amino pyrido pyrimidines of general formula (I) defined above and their pharmaceutically acceptable salts which have IC₅₀ values in the range 0.1 to 10.0 nm

Yet another objective of the present invention is to provide novel phenyl amino pyrido pyrimidines of general formula (I) and their pharmaceutically acceptable salts which are useful for the treatment of CML

Still another objective of the present invention is to provide a process for the preparation of novel phenyl amino pyrido pyrimidines of general formula (I) defined above and their pharmaceutically acceptable salts

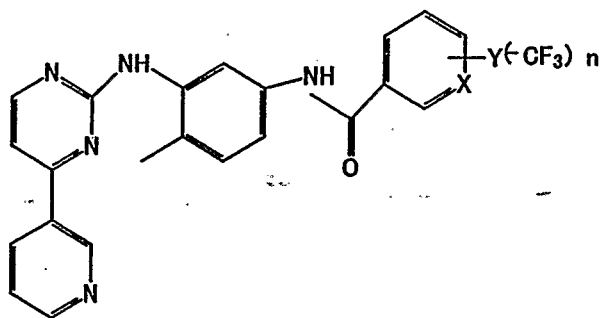
Further objective of the present invention is to provide a pharmaceutical composition containing the novel phenyl amino pyrido pyrimidines of general formula (I) and their pharmaceutically acceptable salts useful for the treatment of CML

Still another objective of the present invention is to provide a process for the preparation of pharmaceutical composition containing novel phenyl amino pyrido pyrimidines of general formula (I) defined above and their pharmaceutically acceptable salts

Still another objective of the present invention is to provide novel intermediates useful for the preparation of novel compounds of the formula I defined above

Yet another objective of the present invention is to provide processes for the preparation of novel intermediates useful for the preparation of novel compounds of the formula I defined above

Accordingly, the present invention provides phenyl amino pyrido pyrimidines of general formula (I)



(I)

Wherein the symbols have the following meanings

Series A	Series B
X = CH	X = N
n = 1, 2	n = 1
R = H, Me	R = H, Me

and the pharmaceutically acceptable salts thereof

The trifluoro methyl group in the above compounds is preferably bonded to the phenyl/pyridinyl at position 3 (when n = 1) and when two such groups are present, they are preferably bonded at positions 3,5 (when n = 2)

Special preference is given to compounds of the general formula (I) wherein R represents methyl group and the trifluoromethyl group is present in position 3 of the phenyl/pyridinyl ring (n=1, Series-A, Series-B) and when two such groups are present, bonding at position 3,5- is preferred (n=2, Series-A).

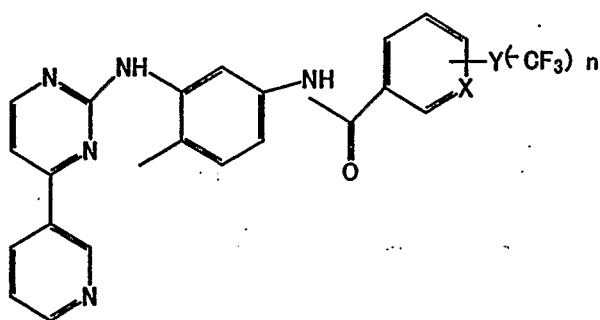
Very special preference is given to compound(s) of general formula (I) where in R represents a methyl group and the trifluoromethyl group is present in position 3 and position 3,5-of the phenyl ring (n = 1 and 2, Series-A)

The above mentioned compounds are new as they have not been reported in the literature

The compounds of the formula (I) form pharmaceutically acceptable salts. For example salts are formed with inorganic acids such as hydrochloric acid, sulfuric acid, phosphoric acid, (or) with suitable organic carboxylic (or) sulfonic acids for example aliphatic mono-(or) dicarboxylic acids, such as trifluoro acetic acid, acetic acid, propionic acid, glycolic acid, succinic acid, maleic acid, fumaric acid, hydroxymaleic acid, malic acid, tartaric acid, citric acid (or) oxalic acid (or) amino acids such as arginine (or) lysine, aromatic carboxylic acids, such as benzoic acid, 2-phenoxy benzoic acid, 2-acetoxy benzoic acid, salicylic acid, aromatic aliphatic carboxylic acids, such as nicotinic acid, aliphatic sulfonic acids, such as methane sulfonic acid and aromatic sulfonic acids like for example benzene and 4-toluene sulfonic acids.

However, only pharmaceutically acceptable non toxic salts are used for the therapeutic purposes, and those salts are therefore preferred.

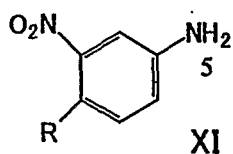
According to another embodiment of the invention there is provided a process for the preparation of novel phenyl amino pyrido pyrimidines of the formula I,



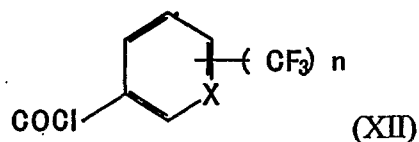
(I)

where the symbols have the meanings given below and their pharmaceutically acceptable acid addition salts which comprises

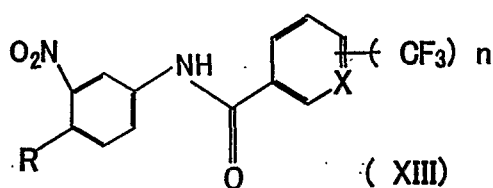
(i) - condensing 4-methyl-3-nitroaniline of the formula (XI)



wherein R represents hydrogen or methyl with trifluoro methyl aroyl chlorides of the formula (XII),

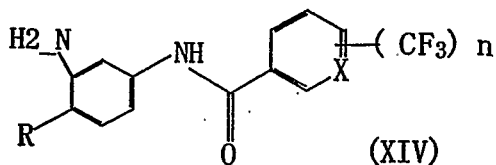


n represents 1 or 2 and x represents N or H in the presence of chloro hydrocarbon solvent and a base at a temperature in the range of 30 to 40 Deg C to yield the novel intermediate nitro trifluoromethyl aroyl amides of the formula (XIII)



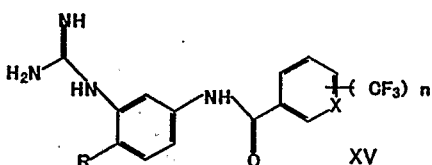
where R and n have the meanings given above

- (ii) Reducing the resulting novel compounds of the formula (XIII) using a metal - acid reducing agent at a temperature in the range of 0-5°C to yield the novel intermediate amino trifluoromethyl aryl amides of the formula (XIV) .



where R & n have the meanings given above .

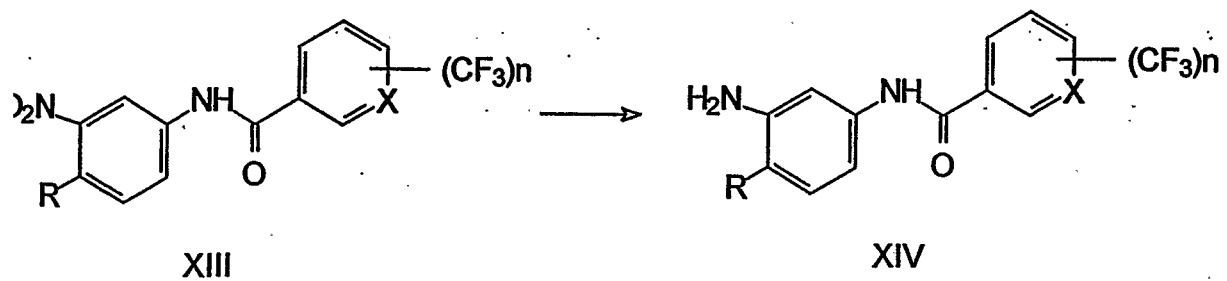
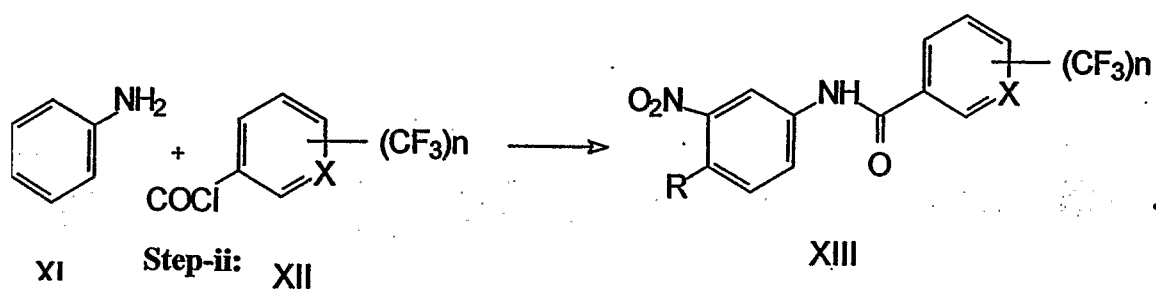
- (iii) condensing the compounds of the formula (XIV) with cyanamide (CNNH₂) at a temperature in the range of 60 to 95°C in the presence of polar solvent and an inorganic acid to yield the novel intermediate salts of guanidino trifluoromethyl aryl amides of formula (XV)

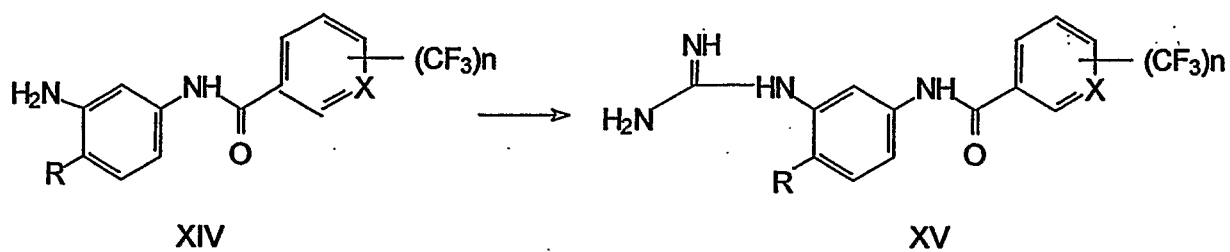
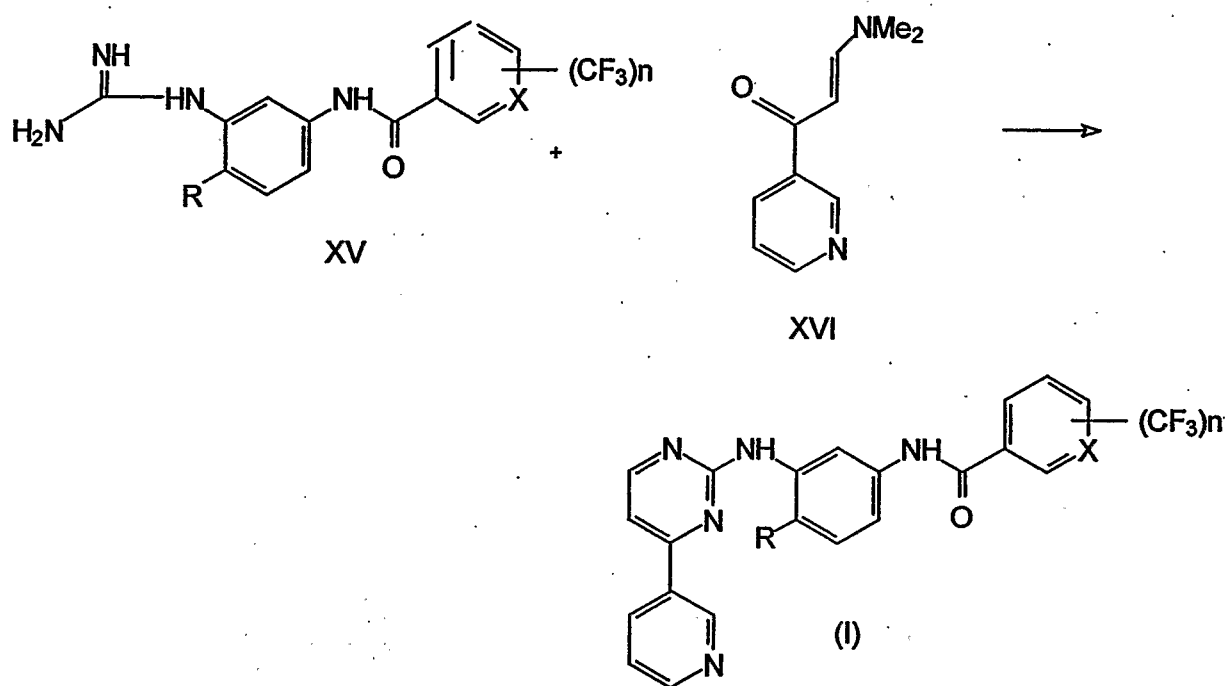


where R and n have the meanings given above and

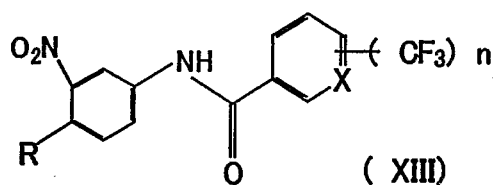
- (iv) condensing the novel compounds of the formula (XV) with a compound of formula (XVI) in the presence of a base and at a temperature in the range of 30 to 40 Deg C to yield the novel compounds of general formula (I) where R ,n ,X are as defined above and if desired converting the novel compounds of the formula I into pharmaceutically acceptable salts by conventional methods

The above defined process is shown in the Scheme I given below

Scheme I :**Step-i:**

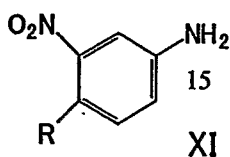
Step-iii:**Step-iv:**

According to another embodiment of the invention there is provided a process for the preparation of novel nitro trifluoromethyl aryl amides of the formula (XIII)

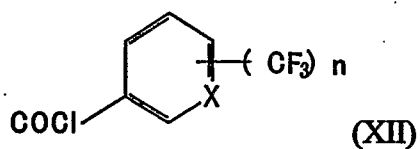


Useful as an intermediate for the preparation of novel compound of the formula I which comprises

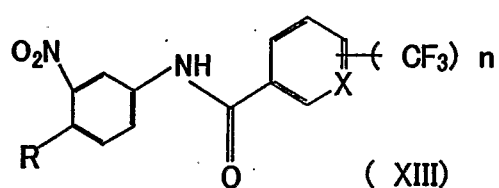
condensing 4-methyl-3-nitroaniline of the formula (XI)



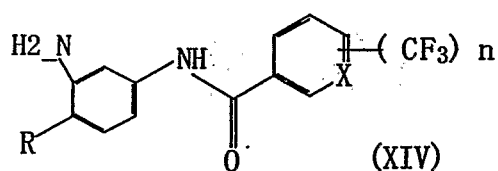
wherein R represents hydrogen or methyl with trifluoro methyl aryl chlorides of the formula (XII),



wherein n represents 1 or 2 and x represents N or H in the presence of chloro hydrocarbon solvent and a base at a temperature in the range of 30 to 40 Deg C to yield the novel intermediate nitro trifluoromethyl aroyl amides of the formula (XIII)



According to another embodiment of the invention there is provided a process for the preparation of novel amino trifluoromethyl aroyl amides of the formula (XIV)

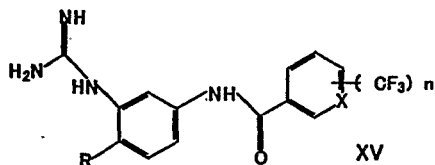


where R & n have the meanings given above .

useful for the preparation of novel compounds of the formula I which comprises

reducing the novel compounds of the formula (XIII) using a metal - acid reducing agent at a temperature in the range of 0-5°C to yield the novel compounds of the formula XIV

According to another embodiment of the invention there is provided a process for the preparation of novel salts of guanidino trifluoromethyl aroyl amides of formula (XV)



where R and n have the meanings given above, useful as an intermediate for the preparation of new compounds of the formula I which comprises condensing the compounds of the formula (XIV) with cyanamide (CNNH₂) at a temperature in the range of 60 to 95°C in the presence of polar solvent and an inorganic acid to yield the novel intermediate of formula (XV)

In a preferred embodiment of the invention, the chloro hydrocarbon solvent used in step(i) may be selected from-Chloroform, Methylene chloride or ethylene chloride, preferably chloroform

The base used may be selected from triethyl amine, dipropyl amine or diisopropyl amine preferably triethyl amine. The temperature may be preferably in the range of 30 to 40 - Deg C

In another embodiment the metal - acid reducing agent used in step (ii) for reducing the novel compound of the formula-XII may be selected from stannous chloride / Concd. HCl iron / Concd. HCl, Zinc- Concd. HCl, preferably stannous chloride / Concd. HCl

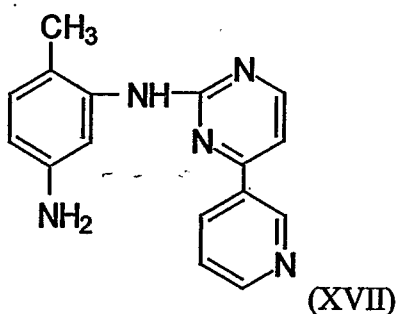
The polar solvent used in step(iii) may be selected from n-propanol, isopropanol, ethanol, n-butanol or their mixtures preferably n-butanol.

The base such as potassium hydroxide or sodium hydroxide preferably may be used in step (iv) and the temperature may be at the range of 90 – 95 deg C

According to yet another embodiment of the present invention there is provided an alternative process for the preparation of the compounds of the general formula I as defined above

Accordingly the present invention provides a process for the preparation of compounds of the general formula I as defined above which comprises

- (i) Preparing N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine amine of the formula (XVII)



by conventional methods.

- (ii) Condensing N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine amine of the formula (XVII) with trifluoro methyl aroyl chlorides of the formula (XII) to yield the novel compounds of general formula (I) where [R, n, X are as defined above]

The compounds of the formula (I) as defined above inhibit Bcr-abl Kinase and are thus, as explained above, suitable for the treatment of Bcr-abl positive cancer and tumor diseases, such as leukemias (especially Chronic Myeloid Leukemia (CML) and Acute Lymphoblastic Leukemia, where especially apoptotic mechanisms of action are found)

The invention also relates to pharmaceutical compositions comprising an effective amount, especially an amount effective in the prevention or therapy of one of the abovementioned

diseases, of the active ingredient together with pharmaceutically acceptable carriers that are suitable for topical, enteral, for example oral or rectal, or parental administration, and may be inorganic or organic, solid or liquid. In addition to the active ingredient(s), the pharmaceutical compositions of the present invention may contain one or more excipients or adjuvants. Selection of excipients and the amounts to use may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

Diluents increase the bulk of a solid pharmaceutical composition, and may make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel(R)), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrans, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit(R)), potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

Solid pharmaceutical compositions that are compacted into a dosage form, such as capsules may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel(R)), hydroxypropyl methyl cellulose (e.g. Methocel(R)), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon(R), Plasdone(R)), pregelatinized starch, sodium alginate and starch.

The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach may be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol(R), Primellose(R)), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon(R), Polyplasdone(R)), guar gum, magnesium aluminum silicate, methyl cellulose,

microcrystalline cellulose, polacrillin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab(R)) and starch.

Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that may function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc and tribasic calcium phosphate.

When a dosage form such as a capsule is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

Solid compositions may also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification

The details of the invention are provided in the Examples given below which are provided to illustrate the invention only and therefore they should not be construed to limit the scope of the invention

Example -1

Preparation of (3-trifluoromethyl)-N- [4- methyl -3- (4-pyridin-3-yl-pyrimidin-2- ylamiño)-phenyl]-benzamide of the formula (I) where R represents methyl, X represents CH and n=1 :

Step I : Preparation of novel (3- trifluoromethyl)-N- (4-methyl-3-nitro-phenyl)- benzamide of the formula (XIII) where R represents methyl, X represents CH and n=1 :

In the first instance , 3-trifluoro methyl benzoyl chloride which is used as one of the starting material is prepared as follows .

Thionyl chloride (312.0 g, 2.63mol) is added over a period of 15 min to a solution of 3- trifluoro methyl benzoic acid (100.0 g, 0.53mol) in chloroform (1000ml) at room temperature. The reaction mixture is heated to reflux temperature for 1hour. The excess of thionyl chloride is removed by co-distillation with chloroform under reduced pressure at 40° C. After the end of the distillation, the resulting trifluoro methyl benzoyl chloride is cooled down to room temperature and dissolved in 100 ml chloroform.

A solution of 4-methyl-3-nitroaniline (49.0 g, 0.32mol) in chloroform (600 ml) is cooled to -5° C and triethyl amine (161.0 g, 1.59mol) of is added. Trifluoromethyl benzoyl chloride in chloroform prepared as described above is added drop wise at -5° C over a period of 60-75 min. The resulting suspension is stirred for 1 hr at -5° C. The suspension is distilled to a residual volume of 800 ml and filtered ,washed with chilled chloroform (250ml) and dried in vacuum to give 85.0 g of novel (3- trifluoromethyl)- N- (4-methyl-3-nitro-phenyl)-benzamide of the formula (IV) where R represents methyl, X represents CH and n=1 (83%) as pale yellow crystals (98.0% purity by HPLC) MR-162-164°C

Step II : Preparation of novel (3- trifluoromethyl)- N- (3 - amino- 4 - methyl - phenyl) - benzamide of the formula (XIV) where R represents methyl, X represents CH and n=1 :

A suspension of (3-trifluoromethyl)-N- (4-methyl-3-nitro-phenyl)- benzamide of the formula (XIII) (85 g, 0.26moles) prepared by the process described in step I and stannous chloride (297.5 g, 1.3 moles) in absolute ethanol (490 ml) is heated to reflux temperature for 30 min. The resulting suspension is then cooled to room temperature and quenched into 4 L of ice cold water.

The reaction mixture P^H is adjusted to 8.0 with 2.4 L of 5% sodium hydroxide solution and extracted with 2 x 2 L of ethyl acetate. The ethyl acetate layer is washed successively with water and brine and dried over sodium sulfate. The ethyl acetate is distilled completely and 500 ml of hexane is added to the residue and filtered. The filtered cake is dried in vacuum at 60 °C to give 60.0 g of novel (3-trifluoromethyl)- N- (3- amino- 4 - methyl - phenyl)- benzamide of the formula (XIV) where R represents methyl, X represents CH and n=1 (80%) as yellow crystals (98.2% purity by HPLC) MR-145-149°C

Step III : Preparation of - (3-trifluoromethyl)- N - (3-guanidino-4-methyl-phenyl)) – benzamide of the formula (XV) where R represents methyl, X represents CH and n=1 :

A suspension of (3-trifluoromethyl)-N- (3-amino-4-methyl-phenyl)- benzamide of the formula (XIV) prepared by the process described in step (II) (60 g, 0.20 mol) in n-butanol (400 ml) is treated sequentially with concentrated nitric acid until the pH reaches 2.5 (13 g) and with a solution of cyanamide (12.6 g, 0.3 mol) in water (13 ml) over a period of 30 min. The resulting reaction mixture is stirred at reflux temperature for 6 hrs. The reaction mixture is then distilled off completely under vacuum and the residue is allowed to cool down to room temperature. A mixture of 240 ml of methanol and 240 ml of IPE is added to the reaction mass and stirred at room temperature for 1 hr. The product is filtered off with suction, washed with a mixture of methanol and IPE (3 x 50ml) and dried in vacuum at 60° C to give 43.2 g of the nitrate salt of (3-trifluoromethyl)- N - (3-guanidino-4-methyl-phenyl)) – benzamide of the formula (XV), where R represents methyl, X represents CH and n=1 53% of theory (99% area by HPLC) MR-243-245°C

Step (IV) : Preparation of (3-trifluoromethyl) -N- [4- methyl -3- (4-pyridin-3-yl-pyrimidin-2- ylamino)-phenyl]-benzamide of the formula (I) where R represents methyl, X represents CH and n=1 :

A suspension of nitrate salt of (3-trifluoromethyl)- N- (3-guanidino-4-methyl-phenyl)- benzamide nitrate prepared by the process described in step (XV) (43 g, 0.11 mol) in n-butanol (290ml) under an atmosphere of nitrogen is treated successively with sodium hydroxide flakes

(6.9 g, 0.17 mol) and 3-dimethylamino-1-pyridin-3-yl-propenone (18.6 g, 0.11mol). The resulting suspension is heated to reflux temperature for 2 hrs. The reaction mixture becomes a homogeneous deep orange solution and dimethylamine is removed by the distillation of n-butanol. Reaction mass is cooled down to RT and a mixture of water and chloroform (250 ml+250 ml) is added and chloroform layer is separated out. The chloroform layer is washed with water and distilled to a residual volume of 40 ml. Ethyl acetate (200 ml) is added to the reaction mass and filtered off with suction, the isolated solid is washed with ethyl acetate (2 x 50ml) and water (2 x 50 ml) and dried in vacuum at 60° C. Yield : 29.0 g of novel (3-trifluoromethyl) -N-[4-methyl-3- (4-pyridin-3-yl-pyrimidin -2 - ylamino)-phenyl]-benzamide of the formula (I) where R represents methyl, X represents CH and n=1 60% based on theory, as pale yellow crystals.

(99. 89% purity by HPLC). MR-211-213°C

IC₅₀ - 8 nms(Fig - 1)

¹H - NMR (400 MHz, DMSO-d₆, δ) :

2.23(s,3H);7.20-9.28(Aryl,13H);10.42(s, 1H)

Analysis : C₂₄H₁₈ F₃N₅O

Molecular weight : 449.0

IR : KBR Disc

-NH- C = O : at 3445 cm⁻¹

-NH- C = O : At 1648 cm⁻¹

Example -2

Alternative process for the Preparation of (3-trifluoromethyl) -N- [4- methyl -3- (4-pyridin-3-yl-pyrimidin-2- ylamino)-phenyl]-benzamide of the formula (I) where R represents methyl, X represents CH and n=1 :

In the first instance , 3-Trifluoro methyl benzoyl chloride which is used as one of the starting material is prepared as follows .

Thionyl chloride (2.65kg, 3.72mol) is added over a period of 15 min to a solution of

3- trifluoro methyl benzoic acid (0.848kg, 4.46mol) and D.M.F.(8.5 ml) in chloroform (9L) at room temperature. The reaction mixture is heated to reflux temperature for 1 hour. The excess of thionyl chloride is removed by co-distillation with chloroform under reduced pressure at 40° C. After the end of the distillation, the resulting 3-trifluoro methyl benzoyl chloride is cooled down to room temperature and dissolved in 600 ml chloroform.

A solution of N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine amine of the formula (XVII) (1.03kgs, 3.72mol) in chloroform (9L) is cooled to -5° C and triethyl amine (1.35kg, 13.37mol) is added. Trifluoromethyl benzoyl chloride in chloroform prepared as described above is added drop wise at -5° C over a period of 60-75 min. The resulting suspension is stirred for 1 hr at -5° C. The suspension is distilled to a residual volume of 6L and filtered, washed with D.M. water and methanol (2.5L) and dried in vacuum to give 1 kg of novel (3-trifluoromethyl)-N- [4- methyl -3- (4-pyridin-3-yl-pyrimidin-2- yl amino)-phenyl]-benzamide of the formula (I) where R represents methyl, X represents CH and n=1 (60%) as pale yellow crystals (95.0% area by HPLC) . This product is further purified by refluxing with 3 volumes of ethylacetate and filtering at 40°C [0.85 kg, 50.9%] (98.5% purity by HPLC) MR- MR-210-213°C

Example -3.

Preparation of (3,5 - Bis trifluoromethyl)-N- [4 - methyl - 3 - (4-pyridin-3-yl-pyrimidin-2-yl amino) - phenyl] - benzamide(I) where R represents methyl, X represents CH and n=2

Step I : Preparation of novel (3,5-Bis trifluoromethyl) - N- (4-methyl-3-nitro-phenyl)-benzamide(XIII) where R represents methyl, X represents CH and n=2 :

In the first instance , 3,5 -Bis trifluoro methyl benzoyl chloride which is used as one of the starting materials is prepared as follows .

Thionyl chloride (576.0 g, 4.8mol) is added over a period of 15 min to a solution of 3,5 -Bis trifluoro methyl benzoic acid (Lancaster) (250.0 g, 0.97mol) in chloroform (2.5 L) at room temperature. The reaction mixture is heated to reflux temperature for 1 hour. The excess of

thionyl chloride is removed by co-distillation with chloroform under reduced pressure at 40° C. After the end of the distillation, the resulting 3,5-Bis trifluoro methyl benzoyl chloride is cooled down to room temperature and dissolved in 400 ml chloroform. A solution of 4-methyl-3-nitroaniline (92.0 g, 0.60mol) in chloroform (1.2 L) is cooled to -5° C and triethyl amine (304.8 g, 3.0mol) of is added. 3,5-Bis trifluoro methyl benzoyl chloride in chloroform is added drop wise at -5° C over a period of 60-75 min. The resulting suspension is stirred for 1 hr at -5° C. The suspension is distilled to a residual volume of 800 ml and filtered, washed with chilled chloroform (200ml) and dried in vacuum to give 160.0 g of novel (3,5-Bis trifluoromethyl) - N-(4-methyl-3-nitro-phenyl)-benzamide(XIII) where R represents methyl, X represents CH and n=2 (68%) as cream colored crystals (98.2% purity by HPLC) MR-123-130°C.

Step (II) : Preparation of (3,5-Bis trifluoromethyl) - N- (3-amino-4-methyl-phenyl)-benzamide(XIV) where R represents methyl, X represents CH and n=2 :

A suspension of novel (3,5-Bis trifluoromethyl)- N- (4-methyl-3-nitro-phenyl)- benzamide(XIII) (160 g, 0.41moles) and stannous chloride (460.8 g, 2.0 moles) in absolute ethanol (850 ml) is heated to reflux temperature for 40 min. The resulting suspension is then cooled to room temperature and quenched into 5 L of ice cold water. The reaction mixture P^H is adjusted to 8.0 with 4.3 L of 5% sodium hydroxide solution and extracted with 2 x 2 L of ethyl acetate. The ethyl acetate layer is washed successively with water and brine and dried over sodium sulfate. The ethyl acetate is distilled completely and 500 ml of hexane is added to the residue and filtered. The filtered cake is dried in vacuum at 60 °C to give 96.0 g of novel (3,5-Bis trifluoromethyl) - N- (3-amino-4-methyl-phenyl)-benzamide(XIV) where R represents methyl, X represents CH and n=2 of the formula (V) (65%) as yellow crystals. (98.5% purity by HPLC) MR-153-156°C

Step (III) : Preparation of (3,5-Bis-trifluoromethyl) - N - (3-guanidino - 4 - methyl - phenyl) -benzamide(XV) where R represents methyl, X represents CH and n=2 :

A suspension of (3,5-Bis-trifluoromethyl)-N- (3-amino-4-methyl-phenyl)- benzamide (90 g, 0.20 mol) in n-butanol (500 ml) is treated sequentially with concentrated nitric acid until the pH reaches 2.5 (15.9 g) and with a solution of cyanamide (15.7 g, 0.37 mol) in water (15 ml) over a period of 30 min. The resulting reaction mixture is stirred at reflux temperature for 6 hrs. The reaction mixture is then distilled off completely under vacuum and the residue is allowed to cool down to room temperature. A mixture of 180 ml of methanol and 180 ml of IPE is added to the reaction mass and stirred at room temperature for 1 hr. The product is filtered off with suction, washed with a mixture of methanol and IPE (3 x 50ml) and dried in vacuum at 60° C to give 72.0 g of the nitrate salt of novel (3,5-Bis-trifluoromethyl) - N - (3-guanidino - 4 - methyl - phenyl) - benzamide of the formula (XV) where R represents methyl, X represents CH and n=2 62% of theory (99.2% purity by HPLC), MR-285-287°C

Step (IV) : Preparation of (3,5 - Bis trifluoromethyl)-N- [4 - methyl - 3 - (4-pyridin-3-yl-pyrimidin-2- ylamino) - phenyl] - benzamide(I) where R represents methyl, X represents CH and n=2 :

A suspension of (3,5-Bis-trifluoromethyl)-N- (3-guanidino-4-methyl-phenyl)- benzamide nitrate (70 g, 0.15 mol) in n-butanol (470 ml) under an atmosphere of nitrogen is treated successively with sodium hydroxide flakes (7.0 g, 0.18 mol) and 3-dimethylamino-1-pyridin-3-yl-propenone (28.0 g, 0.16mol). The resulting suspension is heated to reflux temperature for 2 hrs. The reaction mixtures becomes a homogeneous deep orange solution and dimethylamine is removed by the distillation of n-butanol. Reaction mass is cooled down to RT and a mixture of water and chloroform (300 ml + 300 ml) is added and chloroform layer is separated out. The chloroform layer is washed with water and distilled to a residual volume of 70 ml. Ethyl acetate (350 ml) is added to the reaction mass and filtered off with suction, the isolated solid is washed with ethyl acetate (2 x 50ml) and water (2 x 50 ml) and dried in vacuum at 60° C. Yield : 48.0 g of (3,5 - Bis trifluoromethyl)-N- [4 - methyl - 3 - (4-pyridin-3-yl-pyrimidin-2- ylamino) - phenyl] - benzamide of the formula I where R represents methyl, X represents CH and n=2 62% based on theory, as pale yellow crystals. (99.9% purity by HPLC)

MR-248-250°C, IC₅₀ - 0.7 nms (Fig - 2)

¹H - NMR (400 MHz, DMSO-d₆, δ) :

2.24(s, 3H); 7.22-9.28(Aryl, 12H); 10.61(s, 1H)

Analysis : $C_{25}H_{17}F_6N_5O$

Molecular weight : 517.0

IR : KBR Disc

-NH- C=O : at 3445.3 cm^{-1}

-NH- C=O : At 1651.6 cm^{-1}

Example -4

Alternative process for the Preparation of (3,5 - Bis trifluoromethyl)-N- [4 - methyl - 3 - (4-pyridin-3-yl-pyrimidin-2- yl amino) - phenyl] - benzamide(I) where R represents methyl, X represents CH and n=2

In the first instance, 3,5 -Bis trifluoro methyl benzoyl chloride which is used as one of the starting material is prepared as follows :

Thionyl chloride (2.04 kg, 17.2mol) is added over a period of 15 min to a solution of 3,5 -Bis trifluoro methyl benzoic acid (855.0 g, 3.3mol) and D.M.F.(9 ml) in chloroform (9 L) at room temperature. The reaction mixture is heated to reflux temperature for 1 hour. The excess of thionyl chloride is removed by co-distillation with chloroform under reduced pressure at 40°C . After the end of the distillation, the resulting 3,5-Bis trifluoro methyl benzoyl chloride is cooled down to room temperature and dissolved in 700 ml chloroform.

A solution of N-(5-amino-2-methylphenyl)-(3-pyridyl)-2-pyrimidine amine of the formula (XVII) (0.73kgs, 2.64mol) in chloroform (9L) is cooled to -5°C and triethyl amine (1.03 kg, 10.2mol) of is added. 3,5-Bis trifluoro methyl benzoyl chloride in chloroform is added drop wise at -5°C over a period of 60-75 min. The resulting suspension is stirred for 1 hr at -5°C . The suspension is filtered, washed with D.M. water and methanol vacuum to give 1.3 kg of wet crude title compound which on recrystallization from methanol yielded 0.82 kgs (60%) of

(3,5 - Bis trifluoromethyl)-N- [4 - methyl - 3 - (4-pyridin-3-yl-pyrimidin-2- yl-amino) - phenyl] - benzamide(I) where R represents methyl, X represents CH and n=2 as cream colored crystals (99.9% purity by HPLC) MR-248-250°C

Example -5

Preparation of (2-trifluoromethyl) - N - [4-methyl -3- (4-pyridin-3-yl-pyrimidin-2-yl-amino)-phenyl]-benzamide (I) where R represents methyl, X represents CH and n=1 :

Step I : Preparation of novel (2- trifluoromethyl) - N- (4-methyl-3-nitro-phenyl)-benzamide of the formula (XIII) where R represents methyl, X represents CH and n=1 :

In the first instance, trifluoro methyl benzoyl chloride which is used as one of the starting material is prepared as follows :

Thionyl chloride (62.4 g, 0.53mol) is added over a period of 15 min to a solution of 2- trifluoro methyl benzoic acid (Aldrich) (20.0 g, 0.106mol) in chloroform (200ml) at room temperature. The reaction mixture is heated to reflux temperature for 1 hour. The excess of thionyl chloride is removed by co-distillation with chloroform under reduced pressure at 40° C. After the end of the distillation, the resulting trifluoro methyl benzoyl chloride is cooled down to room temperature and dissolved in 100 ml chloroform. A solution of 4-methyl-3-nitroaniline (9.80 g, 0.06mol) in chloroform (120 ml) is cooled to -5° C and triethyl amine (32.2 g, 0.32mol) of is added. Trifluoromethyl benzoyl chloride in chloroform prepared as described above is added drop wise at -5° C over a period of 30-45 min. The resulting suspension is stirred for 1 hr at -5° C. The suspension is distilled to a residual volume of 150 ml and filtered, washed with chilled chloroform and dried in vacuum to give 19.0 g of novel (2-trifluoromethyl) -N - (4-methyl-3-nitro-phenyl)-benzamide of the formula (XIII) where R represents methyl, X represents CH and n=1 (92%) as pale yellow crystals (97.50% purity by HPLC) MR-120-130°C

Step II : Preparation of novel (2 - trifluoromethyl N- (3 - amino- 4 - methyl - phenyl)) - benzamide of the formula (XIV) where R represents methyl, X represents CH and n=1 :

A suspension of (2-trifluoromethyl)-N- (4-methyl-3-nitro-phenyl)- benzamide of the formula (XIII) (19 g, 0.058 moles) prepared by the process described in step I and stannous chloride (59.5 g, 0.26 moles) in absolute ethanol (100 ml) is heated to reflux temperature for 30 min. The resulting suspension is then cooled to room temperature and quenched into 1 L of ice cold water. The reaction mixture P^H is adjusted to 8.0 with 0.5 L of 5% sodium hydroxide solution and extracted with 2 x 0.5 L of ethyl acetate. The ethyl acetate layer is washed successively with water and brine and dried over sodium sulfate. The ethyl acetate is distilled completely and 100 ml of hexane is added to the residue and filtered. The filtered cake is dried in vacuum at 60 °C to give 14.0 g of novel (2-trifluoromethyl) - N- (3- amino- 4 - methyl - phenyl) – benzamide of the formula (XIV) where R represents methyl, X represents CH and n=1 (83%) as yellow crystals (98.4% purity by HPLC) MR-128-135°C

Step III : Preparation of (2-trifluoromethyl) -N - (3-guanidino-4-methyl-phenyl) – benzamide of the formula (XV) where R represents methyl, X represents CH and n=1 :

A suspension of (2-trifluoromethyl)-N- (3-amino-4-methyl-phenyl)- benzamide of the formula (XIV) prepared by the process described in step (II) (14 g, 0.047 mol) in n-butanol (100 ml) is treated sequentially with concentrated nitric acid until the pH reaches 2.5 (2.6 g) and with a solution of cyanamide (2.5 g, 0.06 mol) in water (3 ml) over a period of 10 min. The resulting reaction mixture is stirred at reflux temperature for 4-6 hrs. The reaction mixture is then distilled off completely under vacuum and the residue is allowed to cool down to room temperature. A mixture of 50 ml of methanol and 50 ml of IPE is added to the reaction mass and stirred at room temperature for 1 hr. The product is filtered off with suction, washed with a mixture of methanol and IPE (3 x 20ml) and dried in vacuum at 60° C to give 8.6 g of the nitrate salt of (2-trifluoromethyl) - N - (3-guanidino-4-methyl-phenyl) -benzamide of the formula (XV), where R represents methyl, X represents CH and n=1 52% of theory (99.1% purity by HPLC) MR-160-165°C

Step (IV) : Preparation of (2-trifluoromethyl) -N- [4- methyl -3- (4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide of the formula (I) where R represents methyl, X represents CH and n=1 :

A suspension of nitrate salt of N- (3-guanidino-4-methyl-phenyl)- (2-trifluoromethyl)-benzamide nitrate prepared by the process described in step (XV) (8.6 g, 0.02 mol) in n-butanol (60ml) under an atmosphere of nitrogen is treated successively with sodium hydroxide flakes (1.4 g, 0.03 mol) and 3-dimethylamino-1-pyridin-3-yl-propenone (3.72 g, 0.02mol). The resulting suspension is heated to reflux temperature for 2 hrs. The reaction mixture becomes a homogeneous deep orange solution and dimethylamine is removed by the distillation of n-butanol. Reaction mass is cooled down to RT and a mixture of water and chloroform (50 ml+50 ml) is added and chloroform layer is separated out. The chloroform layer is washed with water and distilled to a residual volume of 10 ml. Ethyl acetate (40 ml) is added to the reaction mass and filtered off with suction, the isolated solid is washed with ethyl acetate (2 x 10ml) and water (2 x 10 ml) and dried in vacuum at 60° C. Yield : 6.2 g of novel (2-trifluoromethyl) -N- [4-methyl-3- (4-pyridin-3-yl-pyrimidin -2 - ylamino)-phenyl]-benzamide of the formula (I) where R represents methyl, X represents CH and n=1 64% based on theory, as off white crystals. MR – 206-207°C

¹H – NMR (400 MHz, DMSO-d₆, δ) :

2.2(s,3H);7.20-9.28(Aryl,13H);10.4(s, 1H)

Analysis : C₂₄H₁₈F₃N₅O

Molecular weight : 449.0

IR : KBR Disc

-NH- C=O : at 3431.2 cm⁻¹

-NH- C=O : At 1655.9 cm⁻¹

Example – 6

Alternative process for the Preparation of (2-trifluoromethyl) – N - [4-methyl -3- (4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide (I) where R represents methyl, X represents CH and n=1 :

In the first instance, 2-trifluoro methyl benzoyl chloride which is used as one of the starting material is prepared as follows :

Thionyl chloride (156 g, 1.3mol) is added over a period of 15 min to a solution of 2- trifluoro methyl benzoic acid (50.0 g, 0.26mol) in chloroform (250ml) at room temperature. The reaction mixture is heated to reflux temperature for 1 hour. The excess of thionyl chloride is removed by co-distillation with chloroform under reduced pressure at 40° C. After the end of the distillation, the resulting trifluoro methyl benzoyl chloride is cooled down to room temperature and dissolved in 100 ml chloroform.

A solution of N-(5-amino-2-methylphenyl)-(3-pyridyl)-2-pyrimidine amine of the formula (XVII)(55 g,0.20) in chloroform (440 ml) is cooled to -5° C and triethyl amine (79.6 g, 0.788mol) is added. Trifluoromethyl benzoyl chloride in chloroform prepared as described above is added drop wise at -5° C over a period of 30-45 min. The resulting suspension is stirred for 1 hr at -5° C. The suspension is filtered, washed with D.M.water and methanol and dried in vacuum to give 51.9g (58%) of novel 4 - (2-trifluoromethyl) - N - [4-methyl -3- (4-pyridin-3-yl-pyrimidin-2- ylamino)-phenyl]-benzamide (I) where R represents methyl, X represents CH and n=1 as pale yellow crystals (99.50% purity by HPLC)

Example - 7

Preparation of (6-trifluoromethyl)-N- [4-methyl- 3 - (4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-Nicotinamide (I) where R represents methyl, X represents N and n=1 :

Step I : Preparation of novel (6- trifluoromethyl) - N- (4-methyl-3-nitro-phenyl)-benzamide of the formula (XIII) where R represents methyl, X represents N and n=1 :

In the first instance , 6- trifluoromethyl Nicotinoyl chloride which is used as one of the starting material is prepared as follows .

Thionyl chloride (15.6 g, 0.13mol) is added over a period of 15 min to a solution of 6- trifluoromethyl Nicotinic acid (GEORGANICS, consortinum, slovak Republic)

(5.0 g, 0.026mol) in chloroform (100ml) at room temperature. The reaction mixture is heated to reflux temperature for 1 hour. The excess of thionyl chloride is removed by co-distillation with chloroform under reduced pressure at 40° C. After the end of the distillation, the resulting 6-trifluoromethyl Nicotinoyl chloride is cooled down to room temperature and dissolved in 10 ml chloroform. A solution of 4-methyl-3-nitroaniline (2.4 g, 0.016mol) in chloroform (50 ml) is cooled to -5° C and triethyl amine (8.0 g, 0.08mol) is added. 6- trifluoromethyl Nicotinoyl chloride in chloroform prepared as described above is added drop wise at -5° C over a period of 30 min. The resulting suspension is stirred for 1 hr at -5° C. The suspension is filtered, washed with chilled chloroform and dried in vacuum to give 3.6g of novel (6-trifluoromethyl) - N- (4-methyl-3-nitro-phenyl)- Nicotinamide of the formula (XIII) where R represents methyl, X represents N and n=1 (70%) as pale yellow crystals

(98.0% purity by HPLC)

MR-167-171°C

Step II : Preparation of novel (6 – trifluoromethyl) - N- (3 - amino- 4 - methyl - phenyl) Nicotinamide – of the formula (XIV) where R represents methyl, X represents N and n=1 :

A suspension of (6-trifluoromethyl)- N- (4-methyl-3-nitro-phenyl)- nicotinamide of the formula (XIII) (3.6 g, 0.011moles) prepared by the process described in step I and stannous chloride (12.4 g, 0.055 moles) in absolute ethanol (25 ml) is heated to reflux temperature for 30 min. The resulting suspension is then cooled to room temperature and quenched into 0.28 L of ice cold water. The reaction mixture P^H is adjusted to 8.0 with 5% sodium hydroxide solution and extracted with 2 x 50 ml of ethyl acetate. The ethyl acetate layer is washed successively with water and brine and dried over sodium sulfate. The ethyl acetate is distilled completely and 10 ml of hexane is added to the residue and filtered. The filtered cake is dried in vacuum at 60 °C to give 3.0g of novel (3-trifluoromethyl) - N- (3- amino- 4 - methyl - phenyl) – benzamide of the formula (XIV) where R represents methyl, X represents N and n=1 (92%) as yellow crystals.(98% purity by HPLC) MR – 174-180.5 Deg C

Step III : Preparation of(6-trifluoromethyl) - N - (3-guanidino-4-methyl-phenyl) – Nicotinamide of the formula (XV) where R represents methyl, X represents N and n=1 :

A suspension of (6-trifluoromethyl)-N-(3-amino-4-methyl-phenyl)-Nicotinamide of the formula (XIV) prepared by the process described in step (II) (3.0 g, 0.01 mol) in n-butanol (20 ml) is treated sequentially with concentrated nitric acid until the pH reaches 2.5 (0.65 g) and with a solution of cyanamide (0.64 g, 0.015 mol) in water (1 ml) over a period of 5 min. The resulting reaction mixture is stirred at reflux temperature for 5 hrs. The reaction mixture is then distilled off completely under vacuum and the residue is allowed to cool down to room temperature. A mixture of 12 ml of methanol and 12 ml of IPE is added to the reaction mass and stirred at room temperature for 1 hr. The product is filtered off with suction, washed with a mixture of methanol and IPE (3 x 10ml) and dried in vacuum at 60° C to give 1.70 g of the nitrate salt of (6-trifluoromethyl)-N-(3-guanidino-4-methyl-phenyl)-Nicotinamide of the formula (XV), where R represents methyl, X represents N and n=1 50% of theory (99.1% purity by HPLC) MR- 287.6-292.4 °C

Step (IV) : Preparation of (6-trifluoromethyl)-N-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-yl amino)-phenyl]-Nicotinamide of the formula (I) where R represents methyl, X represents N and n=1

A suspension of nitrate salt of (6-trifluoromethyl)-N-(3-guanidino-4-methyl-phenyl)-nicotinamide nitrate prepared by the process described in step (XV) (1.7g, 0.005 mol) in n-butanol (12ml) under an atmosphere of nitrogen is treated successively with sodium hydroxide flakes (0.22g, 0.005 mol) and 3-dimethylamino-1-pyridin-3-yl-propenone (0.85 g, 0.005mol). The resulting suspension is heated to reflux temperature for 2 hrs. The reaction mixture becomes a homogeneous deep orange solution and dimethylamine is removed by the distillation of n-butanol. Reaction mass is cooled down to RT and a mixture of water and chloroform (50 ml+50 ml) is added and chloroform layer is separated out. The chloroform layer is washed with water and distilled to a residual volume of 5 ml. Ethyl acetate (25 ml) is added to the reaction mass and filtered off with suction, the isolated solid is washed with ethyl acetate and water and dried in vacuum at 60° C. Yield : 1.4g of novel (6-trifluoromethyl)-N-[4-methyl-3-(4-pyridin-3-yl-pyrimidin-2-yl amino)-phenyl]-Nicotinamide of the formula (I) where R represents methyl, X represents N and n=1 62% based on theory, as pale yellow crystals. (99.9% purity by HPLC). MR-243-244°C

^1H – NMR (400 MHz, DMSO- d_6 , δ) :

2.2(s,3H);7.20-9.28(Aryl,12);10.7(s, 1H)

Analysis : $\text{C}_{23}\text{H}_{17}\text{F}_3\text{N}_6\text{O}$

Molecular weight : 450.0

IR : KBR Disc

-NH- C=O : at 3444 cm^{-1}

-NH- C=O : At 1648 cm^{-1}

Example – 8

Alternative process for the Preparation of (6-trifluoromethyl)-N- [4-methyl- 3 - (4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-Nicotinamide (I) where R represents methyl, X represents N and $n=1$:

In the first instance , 6- trifluoromethyl Nicotinoyl chloride which is used as one of the starting material is prepared as follows .

Thionyl chloride (15.6 g, 0.13mol) is added over a period of 15 min to a solution of 6- trifluoromethyl Nicotinic acid (GEORGANICS, consortium, slovak Republic)

(5.0 g, 0.026mol) in chloroform (100ml) at room temperature. The reaction mixture is heated to reflux temperature for 1 hour. The excess of thionyl chloride is removed by co-distillation with chloroform under reduced pressure at 40°C . After the end of the distillation, the resulting 6-trifluoromethyl Nicotinoyl chloride is cooled down to room temperature and dissolved in 10 ml chloroform. A solution of N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine amine of the formula (XVII) (4.8 g, 0.016mol) in chloroform (50 ml) is cooled to -5°C and triethyl amine (8.0 g, 0.08mol) of is added. 6- trifluoromethyl Nicotinoyl chloride in chloroform prepared as described above is added drop wise at -5°C over a period of 30 min. The resulting suspension is stirred for 1 hr at -5°C . The suspension is filtered ,washed with D.M.water and methanol and dried in vacuum to give 4.3g of novel (6-trifluoromethyl)-N- [4-methyl- 3 - (4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-Nicotinamide (I) where R represents methyl, X represents N and $n=1$ (60%) as cream coloured crystals (98.0% purity by HPLC)
MR-242-244°C

Example – 9

Preparation of (5-trifluoromethyl)-N- [4-methyl- 3 - (4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-Nicotinamide (I) where R represents methyl, X represents N and n=1 :

Step I : Preparation of novel (5- trifluoromethyl) - N- (4-methyl-3-nitro-phenyl)-Nicotinamide of the formula (XIII) where R represents methyl, X represents N and n=1 :

In the first instance , 5- trifluoromethyl Nicotinoyl chloride which is used as one of the starting material is prepared as follows .

Thionyl chloride (15.6 g, 0.13mol) is added over a period of 15 min to a solution of 5- trifluoromethyl Nicotinic acid (GEORGANICS, consortium, slovak Republic) (5.0 g, 0.026mol) in chloroform (100ml) at room temperature. The reaction mixture is heated to reflux temperature for 1 hour. The excess of thionyl chloride is removed by co-distillation with chloroform under reduced pressure at 40° C. After the end of the distillation, the resulting 6-trifluoromethyl Nicotinoyl chloride is cooled down to room temperature and dissolved in 10 ml chloroform. A solution of 4-methyl-3-nitroaniline (2.4 g; 0.016mol) in chloroform (50 ml) is cooled to -5° C and triethyl amine (8.0 g, 0.08mol) of is added. 6- trifluoromethyl Nicotinoyl chloride in chloroform prepared as described above is added drop wise at -5° C over a period of 30 min. The resulting suspension is stirred for 1 hr at -5° C. The suspension is filtered ,washed with chilled chloroform and dried in vacuum to give 3.6g of novel (5-trifluoromethyl)- N- (4-methyl-3-nitro-phenyl)- Nicotinamide of the formula (XIII) where R represents methyl, X represents N and n=1 (70%) as pale yellow crystals

(98.0% purity by HPLC)

MR-167-171°C

Step II : Preparation of novel (5-trifluoromethyl)- N- (3 - amino- 4 - methyl - phenyl) - Nicotinamide -of the formula (XIV) where R represents methyl, X represents N and n=1 :

A suspension of (5-trifluoromethyl)- N- (4-methyl-3-nitro-phenyl)- nicotinamide of the formula (XIII) (3.6 g, 0.011moles) prepared by the process described in step I and stannous chloride

(12.4 g, 0.055 moles) in absolute ethanol (25 ml) is heated to reflux temperature for 30 min. The resulting suspension is then cooled to room temperature and quenched into 0.28 L of ice cold water. The reaction mixture P^H is adjusted to 8.0 with 5% sodium hydroxide solution and extracted with 2 x 50 ml of ethyl acetate. The ethyl acetate layer is washed successively with water and brine and dried over sodium sulfate. The ethyl acetate is distilled completely and 10 ml of hexane is added to the residue and filtered. The filtered cake is dried in vacuum at 60 °C to give 3.0g of novel (5-trifluoromethyl) - N- (3- amino- 4 - methyl - phenyl) - nicotinamide of the formula (XIV) where R represents methyl, X represents N and n=1 (92%) as yellow crystals.(98% purity by HPLC) -MR – 174-180.5 Deg C

Step III : Preparation of (5-trifluoromethyl)-N - (3-guanidino-4-methyl-phenyl) – Nicotinamide of the formula (XV) where R represents methyl, X represents N and n=1 :

A suspension of (5-trifluoromethyl)- N- (3-amino-4-methyl-phenyl) - Nicotinamide of the formula (XIV) prepared by the process described in step (II) (3.0 g, 0.01 mol) in n-butanol (20 ml) is treated sequentially with concentrated nitric acid until the pH reaches 2.5 (0.65 g) and with a solution of cyanamide (0.64 g, 0.015 mol) in water (1 ml) over a period of 5 min. The resulting reaction mixture is stirred at reflux temperature for 5 hrs. The reaction mixture is then distilled off completely under vacuum and the residue is allowed to cool down to room temperature. A mixture of 12 ml of methanol and 12 ml of IPE is added to the reaction mass and stirred at room temperature for 1 hr. The product is filtered off with suction, washed with a mixture of methanol and IPE (3 x 10ml) and dried in vacuum at 60° C to give 1.70 g of the nitrate salt of (5-trifluoromethyl) - N - (3-guanidino-4-methyl-phenyl) - Nicotinamide of the formula (XV), where R represents methyl, X represents N and n=1 50% of theory (99.1% purity by HPLC) MR- 287.6-292.4°C

Step (IV) : Preparation of (5-trifluoromethyl) -N- [4- methyl -3- (4-pyridin-3-yl-pyrimidin-2- yl amino)-phenyl] - Nicotinamide of the formula (I) where R represents methyl, X represents N and n=1

A suspension of nitrate salt of (5-trifluoromethyl) - N- (3-guanidino-4-methyl-phenyl)-nicotinamide nitrate prepared by the process described in step (XV) (1.7g, 0.005 mol) in n-

butanol (12ml) under an atmosphere of nitrogen is treated successively with sodium hydroxide flakes (0.22g, 0.005 mol) and 3-dimethylamino-1-pyridin-3-yl-propenone (0.85 g, 0.005mol). The resulting suspension is heated to reflux temperature for 2 hrs. The reaction mixture becomes a homogeneous deep orange solution and dimethylamine is removed by the distillation of n-butanol. Reaction mass is cooled down to RT and a mixture of water and chloroform (50 ml+50 ml) is added and chloroform layer is separated out. The chloroform layer is washed with water and distilled to a residual volume of 5 ml. Ethyl acetate (25 ml) is added to the reaction mass and filtered off with suction, the isolated solid is washed with ethyl acetate and water and dried in vacuum at 60° C. Yield : 1.4g of novel (5-trifluoromethyl) -N- [4-methyl-3- (4-pyridin-3-yl-pyrimidin -2 - yl amino)-phenyl]- Nicotinamide of the formula (I) where R represents methyl, X represents N and n=1 62% based on theory, as pale yellow crystals. (99.9% purity by HPLC). MR-243-244°C

¹H – NMR (400 MHz, DMSO-d₆, δ) :

2.2(s,3H);7.20-9.28(Aryl,12);10.7(s, 1H)

Analysis : C₂₃ H₁₇ F₃ N₆ O

Molecular weight : 450.0

IR : - KBR Disc

-NH- C=O : at 3444 cm⁻¹

-NH- C=O : At 1648 cm⁻¹

Example – 10

Alternative process for the Preparation of (5-trifluoromethyl)-N- [4-methyl- 3 - (4-pyridin-3-yl-pyrimidin-2- yl amino)-phenyl]-Nicotinamide (I) where R represents methyl, X represents N and n=1 :

In the first instance , 5- trifluoromethyl Nicotinoyl chloride which is used as one of the starting material is prepared as follows .

Thionyl chloride (15.6 g, 0.13mol) is added over a period of 15 min to a solution of

5- trifluoromethyl Nicotinic acid (5.0 g, 0.026mol) in chloroform (100ml) at room temperature. The reaction mixture is heated to reflux temperature for 1 hour. The excess of thionyl chloride is removed by co-distillation with chloroform under reduced pressure at 40° C. After the end of the distillation, the resulting 6- trifluoromethyl Nicotinoyl chloride is cooled down to room temperature and dissolved in 10 ml chloroform.

A solution of N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine amine of the formula (XVII) (4.8 g, 0.016mol) in chloroform (50 ml) is cooled to -5° C and triethyl amine (8.0 g, 0.08mol) of is added. 6- trifluoromethyl Nicotinoyl chloride in chloroform prepared as described above is added drop wise at -5° C over a period of 30 min. The resulting suspension is stirred for 1 hr at -5° C. The suspension is filtered, washed with D.M.water and methanol and dried in vacuum to give 4.3g of novel (5-trifluoromethyl)-N- [4-methyl- 3 - (4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-Nicotinamide (I) where R represents methyl, X represents N and n=1 (60%) as cream coloured crystals (98.0% purity by HPLC)

MR-242-244°C

Example-11

Capsules containing 25 mg and 50 mg of the compounds prepared by the process described in the Example-1(3-trifluoromethyl) -N- [4-methyl-3- (4-pyridin-3-yl-pyrimidin-2-ylamino)-phenyl]-benzamide and Example-3(3,5 - Bis trifluoromethyl)-N- [4 - methyl - 3 - (4-pyridin-3-yl-pyrimidin-2-ylamino) - phenyl] - benzamide having the following composition are prepared in customary manner

	<u>Compound of formula-I</u> (3,5 - Bis trifluoromethyl)- N- [4 - methyl - 3 - (4- pyridin-3-yl-pyrimidin-2- ylamino) - phenyl] - benzamide	<u>Compound of formula-I</u> (3-trifluoromethyl) -N- [4- methyl-3- (4-pyridin-3-yl- pyrimidin -2 - ylamino)- phenyl]-benzamide
Ingredient	mg/ capsule*	mg/ capsule*
	25.0	50.0

PVP	25.0	50.0
Lactose	127.0	77.0
Talc	0.5	0.5
Crospovidone	20.0	20.0
Magnesium stearate	0.5	0.5
SLS	2.0	2.0

In Vitro Studies :

Compounds of the formula – I prepared by the process described in (Example-1 and Example-3) are dissolved in cell culture medium DMSO at a concentration of 10mM for *in vitro* studies. The stock solution is further diluted with the same cell culture medium and used in concentrations of 0.1-10 μ m for the experiments.

For the study the results of which are disclosed here the BCR-abl positive cell line K562 (the continuous cell line established by Lozzio and Lozzio (1975) from the pleural effusion of a 53 year old female with Chronic Myeloid Leukemia in terminal blast crisis) and D32p210 cell line (a BCR-abl transfected cell-line) were used. The K562 and D32p210 cells were grown in RPMI medium supplemented with 10% fetal calf serum at 37°C and 5% CO₂ and 95% air. The cells were sub-cultured for every 24 hours. Cell proliferation by MTT assay was done as follows 5x10³ cells were seeded per well in 96- well plate and different concentrations of the compounds of formula(I) ranging from 1nM to 100 μ M were added in quadruplets. After incubating the cells with the compounds for the required time period (24hrs), 20 μ l of 5 mg/ml MTT was added (final concentration 100 μ g /ml) and incubated for additional 3 hrs at 37°C and 5% CO₂. After 3 hrs, formazan crystals were dissolved in lysis buffer (10% SDS, 5% Isobutanol, 12mmol/L HCl) over night at 37°C. Absorbance was measured on ELISA reader at dual wavelength of 570-630nm. By MTT assay the IC₅₀ values of the compounds of formula (I) are computed. The observed values are 8 nms and 0.7 nms respectively as shown in Fig-1 & Fig-2 of the drawings accompanying this specification

DNA fragmentation assay was done as follows. Cells were treated with compounds of the formula(I) for 24 hrs and the fragmented DNA was isolated using SDS/Proteinase K/Rnase A extraction method, which allows the isolation of only fragmented DNA without contaminating genomic DNA (Nucleic acids Res 22: 5506-5507, 1994). The cells were washed in cold Phosphate Buffered Saline (PBS) and lysed in a buffer containing 50mM Tris HCl (pH 8.0), 1mM EDTA, 0.2% triton X-100 for 20 min at 4°C. After centrifugation at 14,000 g for 15 minutes, the supernatant was treated with proteinase K (0.5 mg/ml) and 1% Sodium Dodecyl sulphate (SDS) for 1 hour at 50°C. DNA was extracted twice with buffered phenol and precipitated with 140mM NaCl and 2 volumes of ethanol at -20°C overnight. DNA precipitates were washed twice in 70% ethanol, dissolved in Tris-EDTA (TE) and treated for 1 hr at 37°C with Rnase. Protein microlitres (µl) of DNA was mixed with 3 µl of DNA sample buffer (0.25% bromophenol blue, 0.25% xylene cyanol and 30% glycerol) and was resolved in 1% agarose gel in TBE (44.6 mM Tris, 445 mM boric acid and 1mM EDTA) DNA fragmentation was visualized upon staining gel with ethidium bromide (0.5 mg/ml) and exposed to UV light. The presence of apoptosis was indicated by the appearance of ladder of oligonucleosomal DNA fragments that are approximately 180-200 bp multiples. The DNA fragments in the gel clearly indicated that compounds of the formula (I) as specified above induce apoptosis in Bcr-Abl positive cell line K562 as shown in Fig-3.

FACS Analysis :

The Fluorescence Activated Cell Sorter (FACS) analysis was done as follows:

To quantitate apoptosis in D32p210 cells, treated with compounds of formula (I) prepared by the process described in (Example-1- Example-3) a flow cytometric analysis using Propidium Iodide (PI) was performed. D32p210 cells were treated with compounds of formula (I) for 24 hrs. After treatment, the cells were washed twice with ice cold PBS and were fixed with 1 ml of ice-cold 70% ethanol gradually and maintained at 4°C overnight. The cells were harvested by centrifugation at 500X g for 10 min, washed with PBS twice and re-suspended in 1 ml of DNA staining solution containing 0.1% triton X-100, 0.1 mM EDTA, RNase A (50 µg/ml) and 50 µg/ml Propidium Iodide (PI) and incubated for 1 hr in dark at room temperature. The red fluorescence of individual cells was measured with a fluorescence activated cell sorter (FACS) caliber flow cytometer (Becton Dickinson, san Jose,CA,USA). Minimums of 10,000 events

were collected per sample. The relative DNA count per cell was obtained by measuring the fluorescence of PI that bound stoichiometrically to DNA as shown in Fig – 4.

Inhibition constants K_i (binding constant of the inhibitor to enzyme) or IC_{50} (Inhibiting concentration at which growth or activity is inhibition by 50%) values derived from the above mentioned *in vitro* assays and studies provide a measure of the inhibition capacity of the compounds of formula (I) as specified above is shown in Fig-5

The *In Vitro* Kinase assay was done as follows :

The inhibition of the kinase activity of the bcr-abl tyrosine kinase by the compounds of the formula – I (Example -1)was quantified by western blot and densitometric analysis. Briefly, 5×10^6 32Dp210 cells were treated with different concentrations of compounds of the formula – I (Example -1, Stage-IV) for 30 min. At the end of the incubation, cells were pelleted, washed with PBS and lysed in 50 μ l of lysis buffer containing 10mM Tris-HCl (pH 8.0), 150 mM NaCl, 1% Triton X-100, 1% Na-deoxycholate, 0.1mM Na-orthovanadate, 50mM β -glycerophosphate, 50mM NAF, 1mM PMSF, 10 μ g/ml leupeptin and 10 μ g/ml pepstatin. Control was cells without the drug. Equal amount of proteins were resolved on 6% SDS gel and transferred onto nitrocellulose membrane. After blocking with 5% nonfat milk powder, primary antibody(anti-phosphotyrosine antibody) was added. Blot was developed using secondary antibody conjugated to alkaline phosphatase. The band intensity of the bcr-abl kinase was quantified by Densitometric analysis.

The apoptosis induced by compounds of the formula – I (Example -1, Stage-IV)was observed through the phase contrast microscopy. The percentage of apoptosis was 53.3% . compounds of the formula – I prepared by the process described in Example -1 inhibited kinase activity of bcr-abl kinase in 32Dp210 cells in a dose dependent manner and the IC_{50} value was 4nM as calculated by densitometric analysis.

The *Ex-vivo* study was done as follows :

Lymphocytes were extracted from the peripheral blood collected from CML patients and normal persons using Ficoll Histopaque. Briefly, the blood was diluted with 1:1 ratio with 0.96%

NaCl(saline) and was overlaid on Ficoll histopaque gradient carefully. The buffy coat of lymphocytes was extracted by centrifugation at 1000 rpm for 20 min at room temperature. The lymphocytes were carefully taken out from the interface using Pasteur pipette and were washed once with RPMI medium.

The lymphocytes isolated as above were cultured in RPMI medium containing 10% FBS at 37°C and 5% CO₂. The cells were subcultured for every 48 hours.

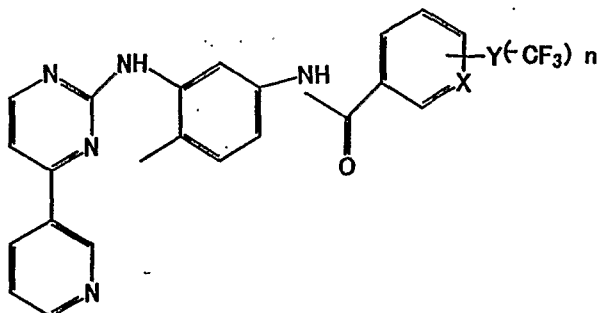
After 48 hrs of the culture, the cells (from CML patients and normal persons) were seeded into 96-well plate at a density of 5×10^3 cells/well. The compounds of formula (I) prepared by the process described in (Example-1 and Example -3)were added at different concentrations to the cells and were incubated for 24hrs. After the incubation period, MTT was added to the cells and incubated for additional 3hrs. The formazan crystals formed were dissolved in lysis buffer and the absorbance was read at a dual wavelength of 570-630 nm. The percent inhibition of cell proliferation was calculated in relation to unreacted cells. The percentage inhibition in cell proliferation obtained from the MTT assay is tabulated in the table (Fig – 6).

Advantages of the invention :

1. Novel compounds of formula- I and novel intermediates are disclosed.
2. Novel compounds of formula-I have been found to be potentially useful therapeutic agents for treatment of CML as evidenced by *in vitro* and *ex- vivo* studies.

We Claim

1. Novel phenyl amino pyrido pyrimidines of general formula (I)



Wherein the symbols have the following meanings

Series A	Series B
X = CH	X = N
n = 1, 2	n = 1
R = H, Me	R = H, Me

and the pharmaceutically acceptable salts thereof

2. Novel compounds of the formula I as claimed in claim 1 wherein the trifluoro methyl group is bonded to the phenyl / pyridinyl at position 3 (when n = 1) and when two such groups are present, they are bonded at positions 3,5 (when n = 2)

3. Novel compound of the formula I as claimed in claims 1 & 2 wherein R represents methyl group and the trifluoromethyl group present in position 3 of the phenyl / pyridinyl ring (n=1, Series-A, Series-B) and when two such groups are present, bonding at position 3,5- is preferred (n=2, Series-A).

4. Novel compounds of the formula I as claimed in claims 1 to 3 wherein R represents a methyl group and the trifluoromethyl group is present in position 3 and position 3,5-of the phenyl ring (n = 1 and 2, Series-A)
5. Novel (3-trifluoromethyl)-N- [4-methyl-3- (4-pyridin-3-yl-pyrimidin-2- ylamino)-phenyl]-benzamide of the formula (I) where R represents methyl, X represents CH and n=1,
6. Novel . (3,5 - Bis trifluoromethyl)-N- [4 - methyl - 3 - (4-pyridin-3-yl-pyrimidin-2- ylamino) - phenyl] – benzamide of the formula I where R represents methyl, X represents CH and n=2 of novel compounds of the formula defined in claim 1
7. Novel . (2-trifluoromethyl)-N- [4-methyl-3- (4-pyridin-3-yl-pyrimidin-2- ylamino)-phenyl]-benzamide of the formula (I) where R represents methyl, X represents CH and n=1 of novel compounds of the formula defined in claim 1
8. Novel (6-trifluoromethyl)-N- [4-methyl- 3 - (4-pyridin-3-yl-pyrimidin-2- ylamino)-phenyl]-Nicotinamide of the formula (I) where R represents methyl, X represents N and n=1 of novel compounds of the formula defined in claim 1
9. Novel . (5-trifluoromethyl)-N- [4-methyl- 3 – (4-pyridin-3-yl-pyrimidin-2- ylamino)-phenyl]-Nicotinamide of the formula (I) where R represents methyl, X represents N and n=1 of novel compounds of the formula defined in claim 1
10. Novel intermediate (3- trifluoromethyl)-N- (4-methyl-3-nitro-phenyl)- benzamide of the formula (XIII) where R represents methyl, X represents CH and n=1 ,useful for then preparation of novel compounds of the formula defined in claim 1
11. Novel (3,5-Bis trifluoromethyl) -N- (4-methyl-3-nitro-phenyl)-benzamide(XIII) where R represents methyl, X represents CH and n=2 ,useful for the preparation of novel compounds of the formula defined in claim 1

12. Novel intermediate (2- trifluoromethyl)-N- (4-methyl-3-nitro-phenyl)- benzamide of the formula (XIII) where R represents methyl, X represents CH and $n=1$ useful for the preparation of novel compounds of the formula defined in claim 1
13. Novel (6-trifluoromethyl) -N- (4-methyl-3-nitro-phenyl)- Nicotinamide of the formula (XIII) where R represents methyl, X represents N and $n=1$ useful for the preparation of novel compounds of the formula defined in claim 1
14. Novel (5-trifluoromethyl) -N- (4-methyl-3-nitro-phenyl)- Nicotinamide of the formula (XIII) where R represents methyl, X represents N and $n=1$ useful for the preparation of novel compounds of the formula defined in claim 1
15. Novel (3- trifluoromethyl) -N- (3-amino-4-methyl-phenyl)-benzamide of the formula (XIV) where R represents methyl, X represents CH and $n=1$,useful for the preparation of novel compounds of the formula defined in claim 1
16. Novel (3,5-Bis trifluoromethyl)-N- (3-amino-4-methyl-phenyl))-benzamide(XIV) where R represents methyl, X represents CH and $n=2$ useful for the preparation of novel compounds of the formula defined in claim 1
17. Novel (2-trifluoromethyl) -N- (3-amino-4-methyl-phenyl)-benzamide of the formula (XIV) where R represents methyl, X represents CH and $n=1$ useful for the preparation of novel compounds of the formula defined in claim 1
18. Novel (6 - trifluoromethyl) -N- (3 - amino- 4 - methylphenyl) - Nicotinamide of the formula (XIV) where R represents methyl, X represents N and $n=1$ useful for the preparation of novel compounds of the formula defined in claim 1
19. Novel (5 - trifluoromethyl) - N- (3 - amino- 4 - methyl - phenyl) - Nicotinamide of the formula (XIV)where R represents methyl, X represents N and $n=1$ useful for the preparation of novel compounds of the formula defined in claim 1

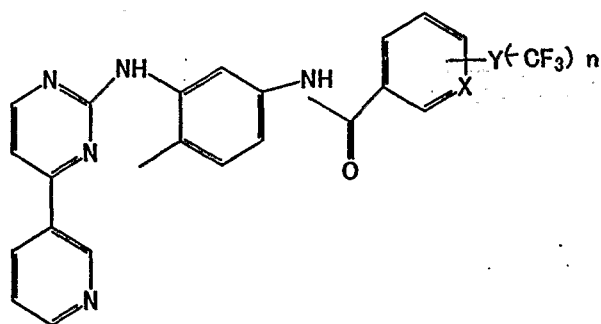
20. Novel (3,5-Bis-trifluoromethyl) - N - (3-guanidino - 4 - methyl - phenyl) - benzamide(XV) where R represents methyl, X represents CH and n=2 useful for the preparation of novel compounds of the formula defined in claim 1

21. Novel (3-trifluoromethyl) - N - (3-guanidino-4-methyl-phenyl) - 4 - benzamide of the formula (XV), where R represents methyl, X represents CH and n=1 ,useful for the preparation of novel compounds of the formula defined in claim 1

22. Novel (2-trifluoromethyl) - N - (3-guanidino-4-methyl-phenyl) -) – benzamide of the formula (XV), where R represents methyl, X represents CH and n=1 useful for the preparation of novel compounds of the formula defined in claim 1

23. Novel (6-trifluoromethyl) - N - (3-guanidino-4-methyl-phenyl) - Nicotinamide of the formula (XV), where R represents methyl, X represents N and n=1 useful for the preparation of novel compounds of the formula defined in claim 1

24. Novel (5-trifluoromethyl) - N - (3-guanidino-4-methyl-phenyl) -Nicotinamide of the formula (XV), where R represents methyl, X represents N and n=1 useful for the preparation of novel compounds of the formula defined in claim 1

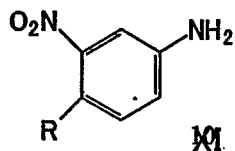


25. A process for the preparation of novel phenylamino pyrimidines of the formula I ,
Wherein the symbols have the meaning given below

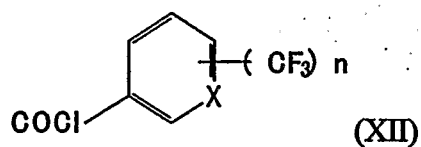
Series A	Series B
X = CH	X = N
n = 1, 2	n = 1
R = H, Me	R = H, Me

where the symbols have the meanings given below and their pharmaceutically acceptable acid addition salts which comprises

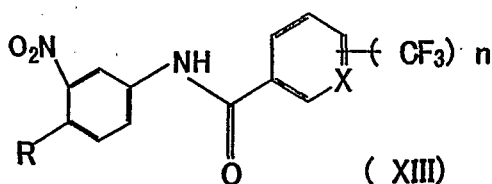
- (i) condensing 4-methyl-3-nitroaniline of the formula (XI)



wherein R represents hydrogen or methyl with trifluoro methyl aroyl chlorides of the formula (XII),

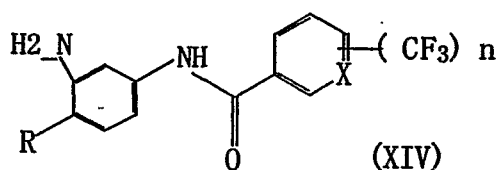


n represents 1 or 2 and x represents N' or H in the presence of chloro hydrocarbon solvent and a base at a temperature in the range of 30 to 40 Deg C to yield the novel intermediate nitro trifluoromethyl aroyl amides of the formula (XIII)



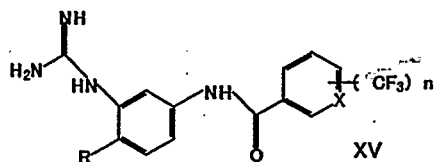
where R and n have the meanings given above

(ii) Reducing the resulting novel compounds of the formula (XIII) using a metal - acid reducing agent at a temperature in the range of 0-5°C to yield the novel intermediate amino trifluoromethyl aroyl amides of the formula (XIV)



where R & n have the meanings given above .

(iii) condensing the compounds of the formula (XIV) with cyanamide (CNNH₂) at a temperature in the range of 60 to 95°C in the presence of polar solvent and an inorganic acid to yield the novel intermediate salts of guanidino trifluoromethyl aroyl amides of formula (XV)

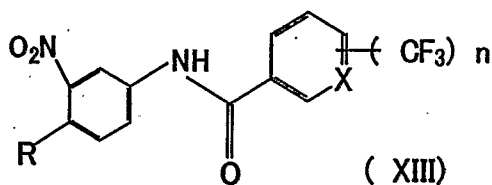


where R and n have the meanings given above and

- (iv) condensing the novel compounds of the formula (XV) with a compound of formula (XVI) in the presence of a base and at a temperature in the range of 30 to 40 Deg C to yield the novel compounds of general formula (I) where R, n, X are as defined above

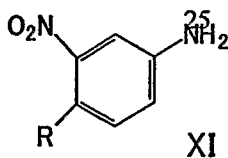
and if desired converting the novel compounds of the formula I into pharmaceutically acceptable salts by conventional methods.

26. A provided a process for the preparation of novel nitro trifluoromethyl aroyl amides of the formula (XIII)



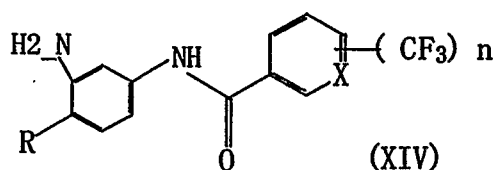
Useful as an intermediate for the preparation of novel compound of the formula I which comprises

condensing 4-methyl-3-nitroaniline of the formula (XI)



wherein R represents hydrogen or methyl with trifluoro methyl aroyl chlorides of the formula (XII), n represents 1 or 2 and x represents N or H in the presence of chloro hydrocarbon solvent and a base at a temperature in the range of 30 to 40 Deg C to yield the novel intermediate nitro trifluoromethyl aroyl amides of the formula (XIII)

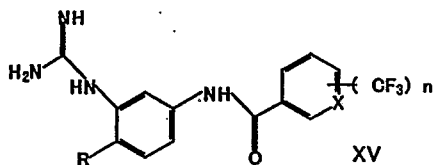
27. A process for the preparation of novel amino trifluoromethyl aroyl amides of the formula (XIV)



where R & n have the meanings given above .

useful for the preparation of novel compounds of the formula I which comprises reducing the novel compounds of the formula (XIII) using a metal - acid reducing agent at a temperature in the range of 0-5°C to yield the novel compounds of the formula XIV

28. A process for the preparation of novel salts of guanidino trifluoromethyl aroyl amides of formula (XV)



where R and n have the meanings given above , useful as an intermediate for the preparation of new compounds of the formula I which comprises condensing the compounds of the formula (XIV) with cyanamide (CNNH₂) at a temperature in the range

of 60 to 95°C in the presence of polar solvent and an inorganic acid to yield the novel intermediate of formula (XV)

29. A process as claimed in claims 25 to 28 wherein the chloro hydrocarbon solvent used in step(i) is selected from-Chloroform, Methylene chloride or ethylene chloride, preferably chloroform

30. A process as claimed in claims 25 to 29 wherein the base used is selected from triethyl amine, dipropyl amine or diisopropyl amine preferably triethyl amine and the temperature may be preferably in the range of 30 to 40 - Deg C

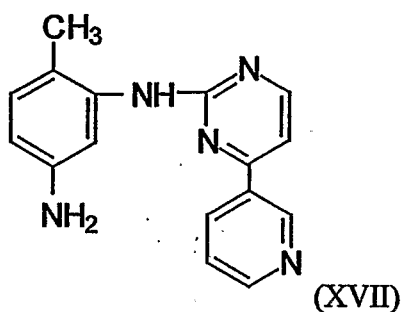
31. A process as claimed in claims 25 to 30 wherein the metal – acid reducing agent used in step (ii) for reducing the novel compound of the formula-XII is selected from stannous chloride / Concd. HCl iron / Concd. HCl, Zinc- Concd. HCl, preferably stannous chloride / Concd. HCl

32. A process as claimed in claims 25 to 31 wherein the polar solvent used in step(iii) is selected from n-propanol, isopropanol, ethanol, n-butanol or their mixtures preferably n-butanol.

33. A process as claimed in claims 25 to 22 wherein the base such as potassium hydroxide or sodium hydroxide, preferably is used in step (iv) & the temperature is in the range of 90 – 95 deg C.

34. A process for the preparation of compounds of the general formula I as defined above which comprises

(i) Preparing N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine amine of the formula (XVII)



by conventional methods.

- (ii) Condensing N-(5-amino-2-methylphenyl)-4-(3-pyridyl)-2-pyrimidine amine of the formula (XVII) with trifluoro methyl aroyl chlorides of the formula (XII) to yield the novel compounds of general formula (I)

35. Novel pharmaceutical composition containing compounds of the formula I as defined in claim 1 along with pharmaceutically acceptable carriers that are suitable for topical, enteral, for example oral or rectal, or parental administration.

36. Novel pharmaceutical composition as claimed in claim 35 wherein the pharmaceutically acceptable carriers are selected from inorganic or organic, solid or liquid.

37. Novel pharmaceutical composition as claimed in claims 35 & 36 wherein the composition contains one or more excipients or adjuvants.

38. Novel pharmaceutical composition as claimed in claims 35 to 37 wherein the composition contains diluents, such as microcrystalline cellulose, microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates, potassium chloride, powdered cellulose, sodium chloride, sorbitol and talc.

39. Novel pharmaceutical composition as claimed in claims 35 to 38 wherein the composition contains binders such as acacia, alginic acid, carbomer, carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, liquid glucose, magnesium

aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon(R), Plasdone(R)), pregelatinized starch, sodium alginate and starch.

40. Novel pharmaceutical composition as claimed in claims 35 to 39 wherein the composition contains Flavoring agents and flavor enhancers such as maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

41. Novel pharmaceutical composition as claimed in claims 35 to 40 wherein the composition contains pharmaceutically acceptable colors.

42. Novel intermediates of the formulae (XIII) to (XV) useful for the preparation of novel compounds of the formula I as defined in claim 1 substantially as herein described with reference to the Examples 1,3,5,7 & 9

43. A process for the preparation of novel intermediates of the formulae (XIII) to (XIV) useful for the preparation of novel compounds of the formula I as defined in claim 1 substantially as herein described with reference to the Examples 1,3,5,7 & 9

44. Novel compounds of the formula I defined above substantially as herein described with reference to the Examples 1 to 10.

45. A process for the preparation of novel compounds of the formula I defined above substantially as herein described with reference to the Examples 1 to 10

46. Novel pharmaceutical composition substantially as herein described with reference to Example 11.