The present invention relates to novel 3-substituted (7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo) [4,5-d] pyrimidin-6-yl of formula 1 wherein R is selected from a group consisting of hydrogen, alkyl having carbon no up to 10, allyl, cyanoalkyl, aromatic, substituted aromatics (halogen, OH, COOH, OC\textsubscript{2}, alkyl, etc.). pyridyl, piperidine, piprazine, morphine. R\textsubscript{1} is selected from a group consisting of NH\textsubscript{2}, NHAr, N(R)\textsubscript{2} (wherein R could be aliphatic or olefinic group up to 10 carbon), heterocycles such as furan, thiophene, pyrrole, pyridyl, piprazine, morphine and R\textsubscript{2} is O and S separately. Particularly the present invention relates to (7-imino-3-substituted -2-thioxo-3,7-dihydro-2H-thiazolo[4,5-d] pyrimidin-6-yl)urea (15-21) and Furan-2-carboxylic acid (7-imino-3 -substituted -2-thioxo-3,7- dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)amide. The compounds of present invention are useful in the treatment of central nervous disorders including, Parkinson disease, Huntington's disease, attention disorder, cognition, Alzheimer disease, depression and hypertension.
"A NOVEL 3-SUBSTITUTED 7-IMINO-2-THIOXO-3, 7-DIHYDRO-2H-THIAZOLO
[4,5-D1 PYRIMIDIN-6-YL - AND PROCESS FOR PREPARATION THEREOF"

FIELD OF THE INVENTION

The present invention relates to novel 3-substituted (7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl. Particularly the present invention relates to (7-Imino-3-substituted -2-thioxo-3,7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-urea and Furan-2-carboxylic acid (7-imino-3-substituted -2-thioxo-3,7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-amide.

The compounds of present invention are useful in the treatment of central nervous disorders including, Parkinson disease, Huntington's disease, attention disorder, cognition, Alzheimer disease, depression and hypertension.

BACKGROUND OF THE INVENTION

Adenosine is an endogenous purine nucleoside that modulates a variety of physiological processes. At present, four adenosine receptor subtypes belonging to the family of G protein-coupled receptors (GPCRs) have been cloned and characterized (A1, A2A, A2B, and A3). Among four adenosine receptors, A2A Receptors (A2ARS) appear to play the most important role in the control of motor behavior and in the modulation of dopamine-mediated responses (Pinna, A.; Wardas, J.; Simola, N.; Morelli, M.; Life Sci. 2005, 77, 3259-3267). These observations support therapeutic use of A2A antagonists for neurodegenerative disorders such as Parkinson's disease (PD) and Alzheimer's disease.

PD is a neurodegenerative disorder characterized by the loss of motor coordination manifested as tremor and rigidity of the limbs and trunk (Jenner, P.; Neurology 2003, 61, S32-S38). These symptoms are due to the deterioration and loss of dopaminergic neurons in the pars compacta region of the substantia nigra, which result in a decrease of dopamine in the striatum (Gillespie, et al. Neurology 2003, 61, 293-296.)

The finding revealed that the A2AR is primarily located in the striatum and is co-expressed with the dopamine D2 receptor which supports the role for A2A in motor activity (Shih-Jen, T. Medical
hypotheses 2005, 64, 197-200). Results from different studies showed that $A_2A$R S exert an excitatory
influence on striatopallidal neurons, which is partially related to their antagonistic effect on dopamine
D$_2$ receptor activation (Cieslak, M.; Komoszynsk, M.; A Wojtczak Purinergic Signalling 2008, 4, 305—
312) This functional interaction has suggested new therapeutic approaches for PD, based on the use of
selective $A_2A$R antagonists. Therefore, antagonists of the $A_2A$ subtype of adenosine receptor have emerged as a leading candidate class of nondopaminergic antiparkinsonian agents (Kashe, H.; Biosci, Biotechnol, Bichem 2001, 65, 1447-1457). The effects of $A_2A$ antagonists have also been reported to afford neuroprotection in animal models of PD (Chen et al. Progress in Neurology, 2007, 83, 310-331)

\[
\begin{align*}
\text{SCH 58261} & \quad \text{KW 6002} \\
\end{align*}
\]

$A_2A$ antagonists SCH 5826 and KW 6002.

In the past ten years, great efforts have been devoted to identify potent and selective $A_2A$ adenosine
antagonists. Recently, there has been much progress made in the discovery of small molecules as $A_2A$
antagonists and compounds such as KW-60021 has been the subject of clinical evaluation. These
xanthine-based compounds have been reported to possess efficacy in models of the Parkinson’s disease
without inducing hyperactivity or inducing dyskinesias. (Kanda, T.; Jackson, M. J.; Smith, L. A.;
Pearce, R. K. B.; Nakamura, J.; Kase, H.;

Kuwana, Y.; Jenner, P. Exp. Neurol. 2000, 162, 321). More recently, the compound has been the subject
of clinical evaluation, but failed to meet primary endpoints in two of the three essential trials
compound such as SCH58261 have been reported and widely studied (Baraldi et al. J. Med. Chem.
2002, 45, 115) However, SCH 58261 suffered from several drawbacks including lower selectivity, poor
solubility and pharmacokinetic profile.
In view of the limitation as described above for the use of known A\textsubscript{2A} antagonist for the treatment of the central nervous system disorder such as Parkinson disease, there is need to develop novel compounds as A\textsubscript{2A} antagonist, free from the above said drawbacks.


In view of the limitation as described above for the use of known A\textsubscript{2A} antagonist for the treatment of the central nervous system disorder such as Parkinson disease, there is need to develop novel compounds as A\textsubscript{2A} antagonist, free from the above said drawbacks.

Thiazolo[4,5-d]pyrimidine derivatives, which can be considered as thiole-analogues of the natural purine bases such as adenine and guanine, have acquired a growing importance in the field of medicinal chemistry because of their biological potential (Zhi, H.; Chen, L.M.; Zhang, L.L.; Liu, S. J.; WanD. C. Cheong.; Lin, H. Q.; Hu. C. ARKIVOC-2008 (xiii) 266-277). Furthermore, the recently demonstrated adenosine A\textsubscript{2A} receptor antagonistic activities of certain thiazoles with a urea moiety (Slee, D.; Lanier M.; Vong, B.G.; Chen, Y.; Zhang, X.; Lin, E.; Moorjani., M.; Castro, P.; Laria J.C; US Patent 20,080,275,064, 06 November 2008) and thiazolopyrimidines (Sugihara, Y.; Kawakita, Y.; US Patent 20,080,269,238, 30 October 2008) for the development of a suitable approach to the treatment of PD.

In the present invention, novel thiazolo-pyrimidine pharmacophore was constructed with urea and furonamide moiety possessing aliphatic flexible groups, and aromatic planer structures as side chains as a potential A\textsubscript{2A} receptor antagonist.

**OBJECTIVES OF THE INVENTION**

The main objective of the invention is to provide novel (7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl - as potential Adenosine A\textsubscript{2A}Receptor antagonist.

Another object of the part of invention is to provide a process of preparation of (7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl - as potential Adenosine A\textsubscript{2A} Receptor antagonist.

Further object of invention is to provide a compound having better binding affinity, selectivity and
antagonistic capability compared to known antagonist SCH58261 with adenosine $A_{2A}$ receptor.

**SUMMARY OF THE INVENTION**

Accordingly the present invention provides a novel compound of formula 1.

![Formula 1]

wherein $R$ is selected from a group consisting of hydrogen, alkyl having carbon no up to 10, allyl, cycloalkyl, aromatic, substituted aromatics selected from the group consisting of halogen, OH, COOH, OCH$_3$, alkyl, pyridyl, piperidine, piprazine, morphine. $R_i$ is selected from a group consisting of NH$_2$, NHR, N(R)$_2$ (where $R$ is aliphatic or olefinic group having up to 10 carbon), hetrocycles such as furan, thiophene, pyrole, pyridyl, piprazine, morphine and $R_2$ is O or S separately.

In an embodiment of the present invention is disclosed the formula la comprising compounds No 15-21.

![Formula la]

Wherein $R$ is selected from a group consisting of ethyl, propyl, allyl, butyl, phenyl, benzyl, and p-iodo phenyl.
In another embodiment of the present invention is disclosed the formula lb comprising compound No 22-26

![Formula lb.]

Formula lb.

Where R is selected from a group consisting of ethyl, propyl, allyl, butyl, and phenyl.

In still another embodiment of the present invention, is disclosed the representative compounds of formula 1 comprising:

a) (3-Ethyl-7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-urea. (15)

b) (7-Imino-3-propyl-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-urea (16)

c) (7-Imino-3-butyl-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-urea. (17)

d) (7-Imino-3-allyl-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-urea. (18)

e) (7-Imino-3-phenyl-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-urea. (19)

f) (3-p-iodophenyl-7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-urea (20)

g) (3-Benzyl-7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-urea (21)

h) Furan-2-carboxylic acid (3-ethyl-7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-amide. (22)

i) Furan-2-carboxylic acid (7-imino-3-propyl-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-amide (23)

j) Furan-2-carboxylic acid (3-butyl-7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)
Furan-2-carboxylic acid (7-imino-3-propenyl-2-thioxo-3,7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-amide. (24)

Furan-2-carboxylic acid (7-imino-3-phenyl-2-thioxo-3,7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-amide. (25)

In a further embodiment of the present invention are disclosed the compounds which are useful for the treatment of central nervous disorders including, Parkinson disease, Huntington's disease, attention disorder, cognition, Alzheimer disease, depression and hypertension.

In an embodiment of the present invention are disclosed the compound which showed Adenosine A$_{2A}$ receptor affinity ranges (0.0038-1.2 nM) which is better than the standard antagonist SCH58261 (1.23 nM).

In an embodiment of the present invention is disclosed the compounds which show Adenosine A$_{2A}$ receptor antagonistic ability in the range of 0.048-0.14 nM cAMP concentration) which is better than the standard antagonist SCH58261 (0.25 nM).

Accordingly the present invention provides a process for preparation of novel 3-substituted (7-imino-2-thioxo-3,7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)amide wherein the process steps comprising

a) reacting imino ether derivatives of formula A

\[ R \]

in alcoholic solvent in presence of basic catalyst selected from a group consisting of amine, KOH, NaOH, at a temperature ranging between 20-32°C for a period ranging between 6-12 hrs to obtain precipitated compound.
b) filtering the precipitated compound as obtained in step (a) and followed by washing with ethanol/water to obtain the desired compound of formula 1.

In an embodiment of the present invention, the acid hydrazide is selected for the group consisting of semicarbazide, furoic acid hydrazide, thiophene-2-carboxylic acid hydrazide, benzoic acid hydrazide, iso-nicotinic acid hydrazide, pyrimidine-4-carboxylic acid hydrazide, triazole-4-carboxylic acid hydrazide.

In another embodiment of the present invention, the alcoholic solvent used is selected from a group consisting of ethanol, methanol, propanol, iso-propanol, butanol, and mixture thereof.

DETAILED DESCRIPTION OF THE INVENTION

Novel bicyclic thiazolopyrimide compounds containing urea and furonamide group were synthesized as adenosine $A_2$ receptors ($A_2$AR) antagonists (scheme 1). Their binding affinities with $A_2$AR have been evaluated using radioligand-binding assay on isolated membranes from stably transfected HEK 293 cells. Selectivity of the compounds towards $A_2$AR was assessed by comparing their binding affinities with $A_i$ receptors (AtR). Functional antagonism activity was confirmed by performing cAMP assay in HEK cell. The result revealed that the compounds having good $A_2$A antagonistic property as compared to known $A_2$A antagonist SCH58261 and said compound might be useful in various central nervous system disorder.

![Structure of designed and synthesized compounds](image-url)

Synthesis of compound 1-14 has been carried out according to the procedure as disclosed and claimed in Patent Application No. 890/DEL/2009. Synthesis of novel designed compound 15-26 was carried according to scheme 1 described below.
Reagents and conditions: (A) triethyl amine, RT; (B) triethyl orthoformate, PTSA, reflux; (C) Furoic acid hydrazide, triethyl amine, 25-30°C and (D) semi-carbazide HCl, triethyl amine, RT.

The following examples are given by way of illustration and should not construed to limit the scope of the present invention.

**EXAMPLE 1**

*Synthesis of (3-Ethyl-7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-urea (15)*

A mixture of 4- (Ethoxymethylene)-amino-3-(ethyl)-2-thioxo-l, 3-thiazole-5-carbonitrile 8 (5g, 22.84 mmol), semicarbazide hydrochloride (2.6g, 22.84 mmol) and triethyl amine (11ml) in absolute ethanol (60ml) was stirred at 20°C for 12 hrs. The appeared precipitate was filtered and washed with absolute ethanol (36ml) and water (38ml) to give pure target compound 15 (4g) and purity of compound was confirmed by HPLC.

Yield: 85% (HPLC purity 100%), White solid; mp:212°C. IR (KBr), 3248, 3164(NH₂), 2958, 2781(alkyl), 1674(C=O). cml'H NMR (DMSO-d₆): δ 1.25(t, 3H, J= 6.6Hz, CH₃), 4.26(q, 2H, J= 7.2Hz, CH₂).
6.6Hz, CH₂), 6.59(s, 2H, NH₂), 8.19(s, 1H, N=CH), 9.24(br, 1H, NH) C NMR(DMSO) : δ 12.3, 40.7, 105.5, 115.5, 157.9, 159, 186.5. LC-MS: m/z 270 (M⁺).

EXAMPLE 2

Synthesis of 7-Imino-3-propyl-2-thioxo-3,7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-urea(16).

A mixture of 4- (Ethoxymethylene)-amino-3- (propyl)-2-thioxo-l, 3-thiazole-5-carbonitrile 9(6g, 24.7mmol), semicarbazide hydrochloride (2.8g, 24.7mmol) and triethyl amine (12ml) in absolute ethanol (75ml) were stirred at 25°C for 12 hrs. The appeared precipitate was filtered and washed with absolute ethanol (35ml) and water (34ml) to give pure target compound 16 (5.2g) and purity of compound was confirmed by HPLC.

Yield: 86% (HPLC purity 100%), White solid; mp: 220 ° C. IR (KBr), 3249,3 163(NH₂), 2957,2782(alkyl), 1673(C=0) cm⁻¹. H NMR (DMSO): δ 0.89(t, 3H, J= 7.2, CH₃), 9.70 (s, 1H, NH), 1.67-1.79 (m, 2H,CH₂), 4.28 (t, 2H, J= 7.2 Hz, CH₂), 6.35(s, 2H, NH₂), 8.40 (s, 1H, N=CH), 9.70(s, 1H, NH) C NMR(DMSO) : δ 10.9, 20.2, 46.3, 98, 154, 155.8, 158.5, 159, 190.3.

EXAMPLE 3

Synthesis of (7-Imino-3-butyl-2-thioxo-3,7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-urea(17)

A mixture of 4- (Ethoxymethylene)-amino-3- (butyl)-2-thioxo-l,3-thiazole-5-carbonitrile 10 (4g, 15.6mmol), semicarbazide hydrochloride (1.715.6mmol) and triethyl amine(8ml) in absolute ethanol (45ml) was stirred at 25°C for 14 hrs. The appeared precipitate was filtered and washed with absolute ethanol (50ml) and water (45ml) to give pure target compound 17 (3.5g) and purity of compound was confirmed by HPLC.

Yield: 89%, (HPLC purity 100%), White solid; mp: 222 ° C. IR (KBr), 3246,3 163(NH₂), 2955,2782(alkyl), 1675(C=0). cm⁻¹. H NMR (DMSO): δ 0.90(t, 3H, J= 7.2, CH₃), 1.26-1.38(m, 2H, CH₂), 1.64-1.74(m, 2H, CH₂), 4.31(t, 2H, J= 7.2 Hz, CH₂), 6.34(s, 2H, NH₂), 8.34(s, 1H, N=CH), 9.70(s, 1H, NH) C NMR(DMSO) : δ 14,19.9,28,9,45.1,98.5,156.3, 158.7,159, 159.7, 190.7 LC-MS: m/z 298(M⁺), 299(M⁺).
EXAMPLE 4

Synthesis of 7-Imino-3-allyl-2-thioxo-3,7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-urea(18)

A mixture of 4-(Ethoxymethylene)-amino-3-(allyl)-2-thioxo-1,3-thiazole-5-carbonitrile (12g, 49.8mmol), semicarbazide hydrochloride (5.5g, 49.8mmol) and triethyl amine (25ml) in absolute ethanol (105ml) were stirred at 28°C for 13 hrs. The appeared precipitate was filtered and washed with absolute ethanol (80ml) and water (60ml) to give pure target compound. 18 (10g) and purity of compound was confirmed by HPLC.

Yield: 90%. (HPLC purity 99.5%), White solid; mp: 202 °C. IR (KBr), 3244, 3164(NH₂), 2959, 2782(alkyl) cm⁻¹. ¹H NMR (DMSO): δ 4.82(d, 3H, CH₃), 5.19(d, 1H, J=10.2 Hz, CH), 5.83-5.96(m, 1H, CH), 6.60(s, 2H, NH₂), 7.8(br, 1H, NH), 8.40(s, 1H, N=CH), 9.23(s, 1H, NH) ¹³C NMR (DMSO): δ 47.1, 105.4, 117.9, 130.3, 146.5, 149.4, 154.2, 157, 186.9. LC-MS: m/z 283 (M⁺).

EXAMPLE 5

Synthesis of (7-Imino-3-phenyl-2-thioxo-3,7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-urea(19).

A mixture of 4-(Ethoxymethylene)-amino-3-(phenyl)-2-thioxo-1,3-thiazole-5-carbonitrile (12g, 28.8mmol), semicarbazide hydrochloride (3.2g, 28.8mmol) and triethyl amine (14ml) in absolute ethanol (80ml) was stirred at 22°C for 10 hrs. The appeared precipitate was filtered and washed with absolute ethanol (60ml) and water (40ml) to give pure compound. 19 (6.5g) and purity of compound was confirmed by HPLC.

Yield: 85%. (HPLC purity 99%) White solid; mp: 225 °C. IR (KBr), 3245, 3162(NH₂), 2959, 2786(alkyl), 1671(C=O) cm⁻¹. ¹H NMR (DMSO): δ 6.37(s, 2H, NH₂), 7.38-7.58(m, 5H, CH), 6.60(s, 2H, NH₂), 7.8(br, 1H, NH), 8.40(s, 1H, N=CH), 9.23(s, 1H, NH) ¹³C NMR(DMSO): δ 98.3, 128.7, 129.3, 131.3, 133.8, 135.7, 155.9, 158.5, 159.1, 164, 191.7. LC-MS: m/z 319 (M⁺).

EXAMPLE 6

Synthesis of (3-p-iodophenyl-7-imino-2-thioxo-3,7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-urea(20)
A mixture of 4-(Ethoxymethylene)-amino-3-(p-iodophenyl)-2-thioxo-1,3-thia \( \Sigma \)ole-5-carbonitrile 13 (4g, \( \lambda \)0mmol), semicarbazide hydrochloride (1.2g, \( \lambda \)0mmol) and triethyl amine(5ml) in absolute ethanol(45ml) was stirred at 20\( ^\circ \)C for 12 hrs. The appeared precipitate was filtered and washed with absolute ethanol (50ml) and water (40ml) to give pure target compound. 20 (2.7g) and purity of compound was confirmed by HPLC. 

\[ \text{Yield: 68\%, purity 99\% (HPLC), White solid; mp: 235}^\circ \text{C. IR (KBr), 3249,3 163(NH\(_2\)), 1673(C=0). \ cm}^{-1} \]

\( ^1\)H NMR (DMSO): \( \delta \) 6.37(s, 2H, NH\(_2\)), 7.23(d, 2H, \( J=8.7 \) Hz, Ar), 7.94(d, 2H, \( J=8.7 \)Hz, Ar), 8.47 (s, 1H, NH), 9.75 (s, 1H, NH), \( ^{13}\)C NMR(DMSO) : \( \delta \) 98.3, 128.8, 129, 131, 133.8, 136, 156, 158.5, 159.1, 164, 191. , LC-MS: m/z 443 (M\(^+\)), 444 (M\(^{+1}\)).

**EXAMPLE 7**

**Synthesis of (3-Benzyl-7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-urea(21)**

A mixture of (3- Benzyl -7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-urea 14 (6g, 20.6mmol), semicarbazide hydrochloride (2.3g, 20.6mmol) and triethyl amine (12ml) in absolute ethanol (60ml) was stirred at 26\( ^\circ \)C for 8 hrs. The appeared precipitate was filtered and washed with absolute ethanol (60ml) and water (50ml) to give pure target compound. 21(4.5g) and Purity of compound was confirmed by HPLC.

\[ \text{Yield: 75\%. (HPLC purity 100\%), White solid; mp: 190}^\circ \text{C. IR (KBr), 3249,3 165(NH\(_2\)), 1674(C=0). \ cm}^{-1} \]

\( ^1\)H NMR (DMSO): \( \delta \) 5.46(s, 2H, CH\(_2\)), 6.60 (s, 2H, NH\(_2\)), 7.06-7.31(m, 5H, Ar) 8.18 (s, 1H, N=CH), 9.24 (br, 1H, NH), \( ^{13}\)C NMR(DMS0) : \( \delta \) 52, 98.3, 128.7, 129.3, 131.4, 133.7, 158.5, 158.8, 159.1,159.4, 164, 191.8 LC-MS: m/z 332 (M\(^+\)), 333 (M\(^{+1}\)).

**EXAMPLE 8**

**Synthesis of Furan-2-carboxylic acid (3-ethyl-7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-amide(22).**

\[ \text{ } \]
A mixture of 4-NEthoxymethylene)-amino-3-(ethyl)-2-thioxo-1, 3-thiazole-5-carbonitrile 8 (12g, 52.4 mmol), furoic acid hydrazide (6.6g, 52.4 mmol) and triethyl amine (26ml) in absolute ethanol (112ml) was stirred at 24°C for 19 hrs. The appeared precipitate was filtered and washed with absolute ethanol (108ml) and water (50ml) to give pure compound 22 (12.4g) and Purity of compound was confirmed by HPLC.

Yield: 95%. (HPLC purity 100%), White solid; mp: 226 °C. IR (KBr), 3376 (NH), 2966, 2946(alkyl), 1673(C=O) cm⁻¹. ¹H NMR (CDCl₃): δ 1.27(t, 3H, J=7.2Hz, CH₃), 4.36(q, 2H, J=7.2 Hz, CH₂), 6.50(q, 1H, J=1.7Hz, furan), 6.91(d, 1H, J=2.7 Hz), 7.67(sJH, furan), 8.24(br, 1H, NH), 8.74 (s,lH, N=CH), 9.42 (br, 1H, NH). ¹³C NMR(DMSO) : δ 13.9, 48.2, 100.9, 110, 127.5, 127.7, 128.5, 135.0, 146.0, 154.3, 163.0, 187.4. LC-MS: m/z 321 (M⁺).

EXAMPLE 9

Synthesis of Furan-2-carboxylic acid (7-imino-3-propyl-2-thioxo-3, 7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-amide 23.

A mixture of 4- (Ethoxymethylene)-amino-3-(propyl)-2-thioxo-1,3-thiazole-5-carbonitrile 9 (9g, 37mmol), furoic acid hydrazide (4.7g, 37mmol) and triethyl amine (16ml) in absolute ethanol (75ml) was stirred at 24°C for 6 hrs. The appeared precipitate was filtered and washed with absolute ethanol (84ml) and water (52ml) to give pure compound 23 (8g) and purity of compound was confirmed by HPLC.

Yield: 92%. (HPLC purity 100%), White solid; mp: 206 °C. IR (KBr), 3376 (NH), 2964, 2946(alkyl), 1672(C=0) cm⁻¹. ¹H NMR (CDCl₃): δ 0.92 (t, 3H, J=6.9, CH₃), 1.76 (m, 2H, CH₂), 4.28 (t, 2H, J=6.9Hz, CH₂), 6.53(q, 1H, furan), 6.93(d, 1H, furan), 7.69(s, 1H, furan), 8.29(br, 1H, NH), 8.77(s, 1H, N=CH), 9.48(br, 1H, NH). LC-MS: m/z 335 (M⁺), 356 (M⁺).

EXAMPLE 10

Synthesis of Furan-2-carboxylic acid (3-butyl-7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo[4,5-d] pyrimidin-6-yl)-amide (24)

A mixture of 4- (Ethoxymethylene)-amino-3-(butyl)- 2-thioxo-1,3-thiazole-5-carbonitrile 10 (8g,
31mmol), furoic acid hydrazide (4g, 31mmol) and triethyl amine (16ml) in absolute ethanol (75ml) was stirred at 25°C for 8 hrs. The appeared precipitate was filtered and washed with absolute ethanol (65ml) and water (45ml) to give pure compound 24 (6.6g) and Purity of compound was confirmed by HPLC.

Yield: 86% (HPLC purity 100%), White solid; mp: 210°C. IR (KBr), 3375(NH), 2873, 2961(alkyl), 1674(C=0) cm\(^{-1}\). 1H NMR (CDCl\(_3\)): \(\delta\) 0.89 (t, 3H, J = 7.2 Hz, CH\(_3\)), 1.33(q, 2H, J = 7.2 Hz, CH\(_2\)), 4.30(t, 2H, J = 7.2 Hz, CH\(_2\)), 6.50(q, 1H, furan), 6.91(d, 1H, furan), 7.67(s, 1H, furan), 8.24(br, 1H, NH), 8.72(s, 1H, NH). 13C NMR (DMSOd\(_6\)): 51.3, 19.4, 28.6, 45.4, 100.9, 110.9, 111.6, 143.1, 147.5, 151.5, 151.9, 153.4, 163.8, 188.9, LC-MS: m/z 349 (M\(^+\)), 350 (M\(^+\)).

**EXAMPLE 1**

**Synthesis of Furan-2-carboxylic acid (7-imino-3-propenyl-2-thioxo-3,7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-amide (25).**

A mixture of 4-(Ethoxymethylene)-amino-3-(allyl)-2-thioxo-1,3-thiazole-5-carbonitrile 11 (12g, 49.8mmol), furoic acid hydrazide (6.3g, 49.8mmol) and triethyl amine (24ml) in absolute ethanol (116ml) was stirred at 21°C for 2 hrs. The appeared precipitate was filtered and washed with absolute ethanol (125ml) and water (108ml) to give pure compound 25 (11g) and Purity of compound was confirmed by HPLC.

Yield: 94%. (HPLC purity 100%), White solid; mp: 218°C. IR (KBr), 3377(NH), 2964, 2946(alkyl), 1673(C=0) cm\(^{-1}\). 1H NMR (CDCl\(_3\)): \(\delta\) 4.98 (d, 3H, CH\(_3\)), 5.14(d, 1H, J = 10.2 Hz, CH), 5.89-5.98(m, 1H, CH), 6.53(q, 1H, J = 1.5 Hz, furan), 6.94 (d, 1H, J = 3Hz, furan), 7.69(s, 1H, furan), 8.87 (s, 1H, N=CH), 9.86 (s, 1H, NH). 13C NMR (DMSOd\(_6\)): \(\delta\) 47.3, 100.9, 110.9, 111.6, 118.1, 129.8, 143.1, 147.5, 151.5, 152, 153, 163, 166.9, LC-MS: m/z 333 (M\(^+\)), 334 (M\(^+\)).

**EXAMPLE 12**

**Synthesis of Furan-2-carboxylic acid (7-imino-3-phenyl-2-thioxo-3,7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-amide (26)**

A mixture of 4-(Ethoxymethylene)-amino-3-(phenyl)-2-thioxo-1,3-thiazole-5-carbonitrile 12 (8g, 29
mmol), furoic acid hydrazide (3.6g, 29 mmol) and triethyl amine (14ml) in absolute ethanol (116ml) was stirred at 24°C for 4. The appeared precipitate was filtered and washed with absolute ethanol (88ml) and water (54ml) to give pure compound 26 (7g) and Purity of compound was confirmed by HPLC.

Yield: 88%. White solid; mp: 228 °C. IR (KBr), 3376 (NH), 2964, 2946(alkyl), 1672(C=O) cm⁻¹. ¹H NMR (CDCl₃): δ 6.78 (q, 1H, furan), 7.39 (d, 1H, furan), 7.59-7.65 (m, 6H, Ar including furan), 8.01 (s, 1H, N=CH), 9.71 (s, 1H, NH). ¹³C NMR (DMSOd₆): 5100, 111, 112, 143.2, 147, 128.8, 129.3, 131, 135, 156, 158, 159.1, 164, 192, LC-MS: m/z 369 (M⁺), 370 (M⁺).

Pharmacological activity of compound of the invention was determined by the following in vitro assay to evaluate A₂₅ receptor antagonist activity.

**IN VITRO RADIOLIGAND BINDING ASSAYS**

**Procedure**

**Membrane preparations**

About 1 x 10⁶ cells per ml of HEK 293 cells (stably expressing human A₂₅R and AiR), were centrifuged at 2,500 rpm for 2 minutes in 15 ml centrifuge tubes. Cells were washed twice with ice-cold PBS (pH 7.4). Pellet of washed cells was resuspended in hypotonic lysis buffer (10mM NaCl, 2mM MgCl₂, 1mM DTT, 10mM Hepes, 2mM PMSF, pH 7.4) and sonicated (4 cycles of 10 s duration each). Homogenate were centrifuged at 2,500 rpm for 10 minutes at 4 °C. Resulting supernatants was again centrifuged at 38,000 rpm for 30 minutes at 4 °C. Pellets obtained was resuspended in Tris-HCl (pH 7.4) buffer. Membrane protein concentrations were determined using Lowry reagent method (Lowry et al., 1951) and absorbance was read at 660 nm using UV/Vis. spectrophotometer. Aliquots of membrane proteins from both A₂₅R and AiR were rapidly frozen and stored at -20 °C.

**Radioligand binding assay**

Radioligand [³H] ZM 241385 was a kind gift from Dr. Surendra Gupta (president, American Radiolabeled Chemicals, St. Louis, USA) and [³H] DPCPX was purchased from American Radiolabeled Chemicals, St. Louis, USA.

Saturation binding analysis was carried out to determine two important parameters: $K_D$ (equilibrium dissociation constant) and $B_{\text{max}}$ (receptor density) (Bylund and Yamamura, 1990). $K_D$ is defined as the concentration of ligand that will occupy 50% of the receptors. $K_D$ value can be used to calculate the concentration of radiolabeled ligand required to occupy a desired proportion of receptors. $B_{\text{max}}$ is the maximum density of receptors. This is usually corrected using the amount of protein present in the binding assay and expressed as amount of ligand bound/mg protein.

$[^3]H$ ZM 241385 (standard $A_{2A}$ antagonist) has been used to evaluate $K_D$ and $B_{\text{max}}$ values for human and rat $A_{2A}$. Similarly, $[^3]H$ DPCPX (standard $A_{1}$ antagonist) has been used to determine $K_D$ and $B_{\text{max}}$ values for human and rat $A_{1}$.

About 10 μg of membrane protein was added to each well of multiscreen 96-well plate equipped with GF/B filters. Incubation buffer (50 mM Tris, 1 mM EDTA, pH 7.4) containing adenosine deaminase (IU/ml) was added to each well to remove endogenous adenosine bound to the receptors and volume was adjusted to 100 μl by adding incubation buffer. Plate was incubated at 37 °C for 1 hour. Varying concentrations (0.125, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7 and 8 nM) for $[^3]H$ ZM 241385 and 0.1, 4, 6, 8, 10, 12, 14 and 16 nM for $[^3]H$ DPCPX were added to respective wells in triplicates. Final volume was adjusted to 200 μl by adding incubation buffer and incubated at 26 °C for 30 minutes. Binding reaction was terminated by rapid Alteration of filter plates using vacuum manifold system. Filterate (unbound radioligand) was collected in a 96-well plate laying down the filter plate. Filters were washed three times with ice-cold washing buffer (50 mM Tris-Cl; 2.5 mM MgCl$_2$ pH 7.4). Finally, 100 μl of scintillation fluid was added to all wells of plate containing unbound filtrate as well as to the filter plate (bound radioligand) and incubated overnight at room temperature. Non-specific binding (binding of a ligand at non-specific sites, other than ligand-binding sites of receptor) was determined by adding 50 μM of NECA (for $[^3]H$ ZM 241385) and 50 μM of CPA (for $[^3]H$ DPCPX). β-counts emitted by $[^3]H$ ZM 241385 and $[^3]H$ DPCPX were read using β-counter.

Competitive binding assay

To evaluate the binding affinity of standard ($A_{2A}$ antagonist SCH 58261 and agonist NECA) and synthesized compounds 15-26 displacement/competitive-binding assays were performed. About 10 μg
of membrane protein was added to each well of a 96-well filter plate. Incubation buffer containing
adenosine deaminase (1 U/ml) was added to the membrane protein and incubated at 37 °C for 1 hour, to
remove endogenous adenosine. Varying concentrations (1 pM to 1 µM) of test compounds 15-26 were
added in duplicate and volume was adjusted to 50 µl by adding incubation buffer. Further, constant
concentration of radioligands (1 nM for [3H] ZM 241385 and 0.75 nM of [3H] DPCPX) was added to
respective wells and final volume was adjusted to 200 µl by adding the incubation buffer. Filter plates
were incubated at 26 °C for 30 minutes and reaction was terminated by rapid filtration of unbound
radioligands. Filters containing ligand bound receptors were washed three times with ice-cold washing
buffer to completely remove any unbound radioligand or receptor. Finally, 100 µl of scintillation fluid
was added to each well and incubated overnight at room temperature, β-counts emitted from bound
radioligands ([3H] ZM241385 and [3H] DPCPX) were counted using β-counter. Duplicate values of β-
counts per minute at corresponding concentrations (1pM to 1µM) were added to the data sheet of graph
pad prism 4.0. Concentration values were considered as X-values and counts per minute were
considered as Y-values (in duplicate). X-values were transformed into logX and Kj value was calculated
using nonlinear regression (curve fit program). The calculated Kj values for A2A and A1R are given
bellow (Table 1).

Table 1: Radioligand binding assay result of thiazolopyrimidine compounds (15-26).

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<tr>
<th>Compound no</th>
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<th>ratio</th>
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<td>Ki ± SDa (nM)</td>
<td>Ki ± SDb (nM)</td>
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<td>0.09 ± 0.01</td>
<td>0.00016 ± 0.007</td>
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<td>0.0038 ± 0.001</td>
<td>2.8 ± 0.8</td>
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<tr>
<td>17</td>
<td>0.089 ± 0.01</td>
<td>1.04 ± 0.84</td>
<td>11.685</td>
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<td>18.</td>
<td>0.092 ± 0.01</td>
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<td>19.</td>
<td>0.063 ± 0.008</td>
<td>1.5 ± 1.10</td>
<td>23.81</td>
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</table>

Table 1: Radioligand binding assay result of thiazolopyrimidine compounds (15-26).
The result of $A_2A\beta R$ binding assay are expressed as inhibition constants ($K_i$ in nM). The $A_1R/A_2A\beta R$ describes their selectivity over $A_1R$. In the set of thiazolopyrimidine urea derivatives (15-21), ethyl substitution (15) exhibited significantly higher binding affinity with $A_1i$ receptor ($0.00016 \pm 0.007$ nM) as compared to $A_2A\beta R$ ($0.0-9 \pm 0.01$ nM). Homologation of one carbon in compound 15 gave the propyl derivative of thiazolo pyrimidine urea (16). The binding affinity of 16 with $A_2A\beta R$ was significantly improved with very high selectivity for the receptor (766-fold selectivity over $A_1j$ adenosine receptor), and was better than the known antagonist SCH 58261 ($K_i=1.23\pm 0.016$, $hA_1i/hA_2 = 483$). However 3-carbon chain with π-overlap in allyl derivative (18) displayed good binding affinity ($K_i=0.092 \pm 0.01$) but reduced selectivity ($hA_1i/hA_2 = 5.11$). Further extending the alkyl chain to give butyl derivative of thiazolo-pyrimidine urea (17) resulted in decreased selectivity over $A_1i$ receptor. Incorporation of aromatic ring (phenyl) in thiazolopyrimidine urea (19) showed enhanced binding affinity and selectivity, however, p-iodophenyl substitution (20) on the pharmacophore gave extremely superior binding affinity and selectivity (144 fold). Insertion of one carbon homologation in planer aromatic ring in thiazolopyrimidine urea (21) led decreased selectivity. Hence, it can be concluded that both 19 and 20 possessed promising activity, yet the compound (16) is most active among all thiazolopyrimidine urea derivatives.
The amino (N\(^\text{3}\)) group of urea moiety of thiazolo-pyrimidine pharmacophore was replaced by furan ring to give another set of compounds (22-26). Overall substituent effects to binding affinity (propyl>butyl>allyl>aryl>ethyl) and selectivity (propyl>allyl>butyl>aryl>ethyl) profile of thiazolopyrimidine furanamide (22-26) decreased, however in the set of compound (22-26) propyl derivative (23) showed maximum binding and selectivity to A\(_{2A}\)R. The finding clearly demonstrated that bicyclic thiazolo-pyrimidine urea derivatives (15-21) were more potent and selective than the corresponding bicyclic thiazolo-pyrimidine furanamide derivatives (22-26).

**cAMP FUNCTIONAL ASSAY**

**Procedure**

To determine the modulation in cAMP concentrations, cells were pre-treated with Forskolin. Forskolin is commonly used to activate adenylyl cyclase, so as to raise the levels of cAMP, in the various cell physiology experiments. About 1x10\(^6\) of HEK 293 cells were treated with 25 \(\mu\)M of Forskolin at 37°C for 2 hours in the C0\(_2\) incubator, followed by 100nM concentrations of A\(_{2A}\)R agonist (NECA), antagonists (SCH 58261) and synthesized compound (15-26) for 24 h. Cells were washed with ice-cold PBS (pH 7.4). Further, cells were treated with 0.1M HCl, incubated for 10 minutes and visually inspected to verify cell lysis. Lysed cells were centrifuged at 1000 rpm at room temperature and the supernatant was used directly for cAMP assay using direct cAMP assay kit. All standards and samples were run in duplicate. 50 \(\mu\)l of the neutralizing reagent was added into each well of 96-well microplate coated with goat anti-rabbit IgG antibody, except the total activity (TA) and blank wells. Again, 100 \(\mu\)l of HCl (0.1M) was added into the NSB (Non-specific bound) and the Bo (0 pmol/ml standard) wells. 100 \(\mu\)l of standards 1 to 5 was pipetted into the appropriate wells. 50 \(\mu\)l of 0.1M HCl was added into the NSB wells, followed by 50 \(\mu\)l of blue conjugate (alkaline phosphatase conjugated with cAMP) into each well except the TA and blank wells. 50 \(\mu\)l of yellow coloured primary antibody against cAMP into each well, except the blank, TA and NSB wells. Microplate was incubated at room temperature for 2 hours on a plate shaker. Wells were washed twice with 400 \(\mu\)l of wash solution. 5 \(\mu\)l of blue conjugate was added to the TA wells, followed by the addition of 200 \(\mu\)l of p-nitrophenyl phosphate substrate solution to every well. Plate was again incubated for 1 hour without shaking. Reaction was stopped by adding 50 \(\mu\)l of stop solution to every well. Optical density was read at 405 nm with correction between 570 and 590 nm.
The average net O.D. bound for each standard and sample was calculated using formula:

\[
\text{Average Net OD} = \text{Average bound OD} - \text{Average NSB OD}
\]

The binding of each pair of standard wells as a percentage of the maximum binding well (Bo) was calculated using the formula:

5 \[
\text{Percent Bound} = \frac{\text{Net OD}}{\text{Net Bo OD}} \times 100
\]

Standard curve was prepared using Logit-Log Paper plot by drawing percent bound (B/Bo) versus concentration of cAMP for the standards. The concentration of the cAMP in the samples was determined by interpolation.

Statistical analysis

Binding parameters were estimated by the computerized non-linear fitting program Graph Pad (Prism 4.0). Calculations were made according to Cheng and Prusoff (1973). Data were expressed as geometric means with 95% confidence limits in parentheses. Estimation of cAMP concentrations in functional assay was carried by Student's paired t-test. P<0.05 was considered significant. All analysis was performed by using GraphPad Prism 4.0 (GraphPad Software, San Diego, USA). Results are given, as mean ± S.E.M

Table 2: RESULTS OF cAMP FUNCTIONAL ASSAY

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<tr>
<th>Compound no</th>
<th>cAMP (nM)</th>
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<tr>
<td>15.</td>
<td>0.085</td>
</tr>
<tr>
<td>16.</td>
<td>0.14</td>
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<td>17</td>
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<td>18.</td>
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<tr>
<td>19.</td>
<td>0.078</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>20</td>
<td>0.076</td>
</tr>
<tr>
<td>21</td>
<td>0.067</td>
</tr>
<tr>
<td>22</td>
<td>0.12</td>
</tr>
<tr>
<td>23</td>
<td>0.092</td>
</tr>
<tr>
<td>24</td>
<td>0.06</td>
</tr>
<tr>
<td>25</td>
<td>0.084</td>
</tr>
<tr>
<td>26</td>
<td>0.048</td>
</tr>
<tr>
<td>SCH58261</td>
<td>0.25</td>
</tr>
<tr>
<td>NECA</td>
<td>0.40</td>
</tr>
</tbody>
</table>

All synthesized compound significantly decreased cAMP concentration as compared to NECA (A_{2A} agonist) and result indicate that all compound have very good A_{2A} receptor antagonist capability. cAMP concentration for SCH 58261 is 0.25 nM. cAMP concentration in all the compounds (15-26) was lower than known antagonist SCH58261 (Table 2). The results demonstrated that the compounds 15-26 possessed great potential as A_{2A} receptor antagonists.
We claim:

1. Compounds of formula 1,

\[
\text{Formula 1}
\]

wherein R is selected from the group consisting of hydrogen, alkyl having carbon No. up to 10, allyl, allyl, cycloalkyl, aromatic, substituted aromatics (halogenj OH, COOH, OCH₃, alkyl), pyridyl, piperidine, piprazine, morphine.

Rᵱ is selected from the group consisting of NH₂, NHR, N(R)₂ (where R is aliphatic or olefinic having carbon No. up to 10), heterocycles selected from the group consisting of furan, thiophene, pyrole, pyridyl, piprazine, morphine, and

R₂ is O or S.

2. Compounds as claimed in claim 1, represented by formula 1a

\[
\text{Formula 1a}
\]

wherein R is selected from a group consisting of ethyl, propyl, allyl, butyl, phenyl, benzyl, and p-iodo phenyl.

3. Compounds as claimed in claim 1 represented by Formula 1b
wherein R is selected from a group consisting of ethyl, propyl, allyl, butyl, and phenyl.

4. Compounds as claimed in claim 1, wherein the representative compounds of formula 1 comprises:

   a) (3-Ethyl-7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-urea. (15)
   b) (7-Imino-3-propyl-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-urea (16)
   c) (7-Imino-3-butyl-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-urea. (17)
   d) (7-Imino-3-allyl-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-urea. (18)
   e) (7-Imino-3-phenyl-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-urea. (19)
   f) (3-p-iodophenyl-7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-urea (20)
   g) (3-Benzyl-7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-urea(21)
   h) Furan-2-carboxylic acid (3-ethyl-7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-amide. (22)
   i) Furan-2-carboxylic acid (7-imino-3-propyl-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-amide (23)
   j) Furan-2-carboxylic acid (3-butyl-7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl)-amide. (24)
   k) Furan-2-carboxylic acid (7-imino-3-propenyl-2-thioxo-3, 7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-amide. (25)
Furan-2-carboxylic acid (7-imino-3-phenyl-2-thioxo-3, 7-dihydro-2H-thiazolo[4,5-d]pyrimidin-6-yl)-amide. (26)

5. The compound as claimed in claim 1, wherein the compounds are useful for the treatment of central nervous disorders including, Parkinson disease, Huntington’s disease, attention disorder, cognition, Alzheimer disease, depression and hypertension.

6. The compound as claimed in claim 1, wherein the compound are having Adenosine A2A receptor affinity in the range of 0.0038-1.2 nM.

7. The compound as claimed in claim 1, wherein the compound are having Adenosine A2A receptor antagonistic ability in the range of 0.048-0.14nM cAMP concentration

8. A process for preparation of novel 3-substituted (7-imino-2-thioxo-3, 7-dihydro-2H-thiazolo [4,5-d] pyrimidin-6-yl -amide as claimed in claim 1, where the process steps comprises

a) reacting imino ether derivatives of general formula A

b) filtering the precipitated compound as obtained in step (a), followed by washing with ethanol/water to obtain the compound of Formula 1.

9. The process as claimed in claim 8, wherein the acid hydrazide is selected for the group consisting
### A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D513/04
A61K31/429 A61K31/519 A61P25/00

**ADD.**

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

### B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

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

EPO-Internal, CHEM ABS Data, WPI Data

### C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 99/51608 AI (DU PONT PHARM CO [US]) 14 October 1999 (1999-10-14) page 1, line 7 - line 23 tables 1, 2 claims 1, 4, 5</td>
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Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:*

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**A** document member of the same patent family

**Date of the actual completion of the international search**

8 March 2011

**Date of mailing of the international search report**

15/03/2011

**Name and mailing address of the ISA/ Authorized officer**

European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Koch, Kristian
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