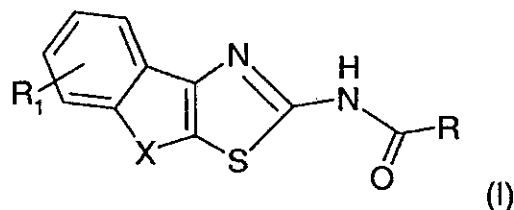


Substituted N-Acyl-2-Aminothiazoles

The invention relates to novel substituted N-acyl-2-aminothiazoles of the formula (I)



or pharmaceutically acceptable salts thereof, wherein X, R and R₁ are described in
5 this application. These compounds are believed to act primarily as Adenosine 2B
Receptor Antagonists and therefore to have potential for the treatment of diabetes,
diabetic retinopathy, asthma and diarrhea.

Adenosine is an autocooid produced in many tissues to mediate various
functions through four receptor subtypes, A₁, A_{2A}, A_{2B} and A₃. All four receptors
10 belong to the class of G-protein coupled receptors (GPCRs), which contain seven
helical hydrophobic domains that span plasma membrane, connected by
hydrophilic extracellular and intracellular loops. A₁ and A₃ receptors couple to Gi
and Go proteins, while A_{2A} and A_{2B} receptors are coupled to Gs proteins.
Because of these differences, adenosine signals an increase in intracellular cAMP
15 levels via its action through A_{2A} and A_{2B} receptors, and a decrease through A₁
and A₃ receptors. In addition, adenosine increases intracellular calcium ion levels
via A_{2B} receptor, because of its coupling to Gq proteins.

The compounds of formula I have potent adenosine human A_{2B} receptor
antagonist activity as measured in CHO-A_{2B}-cAMP assay. These compounds
20 also have residual potent human A₁ and human A_{2A} antagonist activity, as
measured in the radiolabeled ligand binding assays.

The study of role of A_{2B} receptor's functional activity on various cell types
was complicated by the absence of selective A_{2B} agonists and antagonists vs
other three receptors. Typically, the functional activity of A_{2B} receptor is deduced
25 by the absence of effects of the selective agonists and antagonists at other three

adenosine receptors, while eliciting response with NECA, a potent and non-selective adenosine receptor agonist. Usually, the role of A2B receptor on a given cell type, is identified when the following unique order of agonist potency is observed; NECA (non-selective)>PIA (A1-selective agonist)>IB-MECA (A3-selective agonist)>CGS-21680 (A2A-selective agonist).

Adenosine's relative agonist potency against the four receptors was determined to be, A1 ($EC_{50} = 0.31 \mu M$) > A3 ($EC_{50} = 0.29 \mu M$) > A2A ($EC_{50} = 0.7$) > A2B ($EC_{50} = 24 \mu M$), suggesting a unique role for A2B receptor during chronic, high oxidative stress conditions, including but not limited to hyperglycemia, mast-cell activation, and gastrointestinal tract inflammation. In spite of low agonist potency of adenosine to the A2B receptor, numerous compounds with high A2B receptor antagonist potency have been reported.

Using specific agonists and antagonists, Eisai researchers demonstrated the key role of A2B receptor antagonism in inhibiting hepatic glucose production, and a potent A2B receptor antagonist and an inhibitor of glucose production in rat primary hepatocytes was also shown to lower fasting and fed glucose levels in KK-Ay mice, a well recognized model of type 2 diabetes. Thus, compounds of present invention have utility in preventing and/or treating type 2 diabetes.

A2B receptors are also present in the plasma membranes of endothelial cells and have been found to stimulate their growth. Since this will lead to growth of new blood vessels (angiogenesis). An object of this invention is to prevent and/or treat diseases characterized by abnormal blood vessel growth, such as diabetic retinopathy.

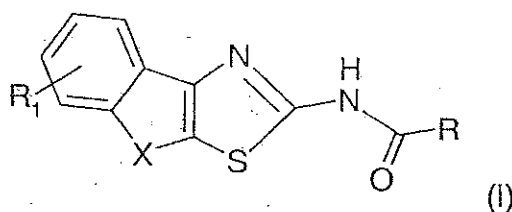
Using immuno-fluorescence techniques with a specific anti-human A2B-antibody indicated the presence of A2B receptors in human lung mast cells obtained from asthmatics by bronchoalveolar lavage cells. Thus, the compound of formula I provide a method of preventing and/or treating asthma, bronchospastic and allergic diseases as well as other obstructive airway-type diseases.

A2B receptors are found in the colon in the basolateral domains of intestinal epithelial cells, and increases chloride ion secretion in reaction to the gastrointestinal tract inflammation in diseases such as, diarrhea. Thus, the compounds of formula I provide a method to treat inflammatory gastrointestinal tract disorders including diarrhea.

The compounds of present invention also have potent antagonist activity against A1 and A2A receptors, in addition to the A2B receptors. Hence, compounds of formula I provide methods to treat diseases where adenosine A1, A2A and A2B receptor antagonism plays a role, such as depression, Parkinsons disease, and hypertension.

Some substituted N-acyl aminothiazoles are known in the art, for example, indenothiazolyl phosphonates have been disclosed in U.S. Patent No. 5,480,874; 2-amino-6-hydroxybenzothiazoles in U.S. Patent No. 4,929,623; 2-benzoylaminonaphtho[1,2-d] thiazoles in Synthetic Communications (1993), 23(17), 2347-53; benzamido- and 2-acetamidobenzothiazole derivatives in Indian Drugs, (1985), 23(3), 146-51 and certain acylaminothiazole derivatives in U.S. Patent 5,189,049. In U.S. Patent No. 4,877,876 there are disclosed 2-substituted-8H-indeno(1,2-d)-thiazole derivatives which are similar to the presently claimed compounds.

In detail, the disclosure refers to compounds of formula (I)



or pharmaceutically acceptable salts thereof, wherein

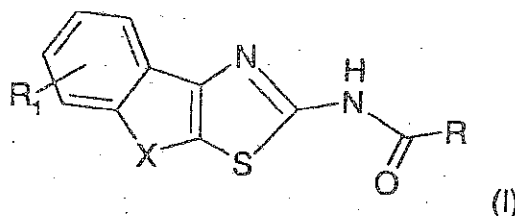
X is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CHCH}_2-$, $-(\text{CH}_2)_3-$ and $-\text{O}(\text{CH}_2)-$;

R is an alkyl group, an alkenyl group, $-\text{NHR}'$ or a 5- or 6- membered saturated or unsaturated carbocyclic or heterocyclic ring which optionally may contain one or more hetero atoms and said rings being optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, lower-alkyl, acetamidomethyl, alkoxy, carbonyl, amidomethyl, a nitrile group, a sulfonamido group, alkylsulfonyl, alkoxy, benzyl, benzoyl, arylsulfonyl and acyl, which benzyl, benzoyl or arylsulfonyl is optionally substituted by halogen, trihalo-lower-alkyl, lower-alkyl, alkoxy, alkylsulfonyl or cyano;

R_1 is selected from the group consisting of hydrogen, halogen, lower-alkyl, alkoxy or a nitrile group;

R' is an alkyl group or a 5- or 6- membered saturated or unsaturated carbocyclic or heterocyclic ring which optionally may contain one or more hetero atoms and said rings being optionally substituted with one or more substituents selected from the group consisting of halogen, lower-alkyl, a nitrile group, alkylsulfonyl, alkoxy and acyl.

In a first aspect, there is provided pharmaceutical compositions comprising a compound of formula (I)



or pharmaceutically acceptable salts thereof, wherein

X is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-(\text{CH}_2)_3-$ and $\text{O}(\text{CH}_2)-$;

R is a 5- or 6- membered saturated or unsaturated carbocyclic or heterocyclic ring which optionally may contain one or more hetero atoms and said rings being optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, lower-alkyl, acetamidomethyl, alkoxycarbonyl, amidomethyl, a nitrile group, a sulfonamido group, alkylsulfonyl, alkoxy, benzyl, benzoyl, arylsulfonyl and acyl, which benzyl, benzoyl or arylsulfonyl is optionally substituted by halogen, trihalo-lower-alkyl, lower-alkyl, alkoxy, alkylsulfonyl or cyano;

R_1 is selected from the group consisting of hydrogen, halogen, lower-alkyl, alkoxy or a nitrile group.

In a second aspect, there is provided compounds selected from the group consisting of:

N-(8H-Indeno[1,2-d]thiazol-2-yl)-benzamide,

4-Fluoro-N-(8H-indeno[1,2-d]thiazol-2-yl)-benzamide,

4-Cyano-N-(8H-indeno[1,2-d]thiazol-2-yl)-benzamide,

N-(8H-indeno[1,2-d]thiazol-2-yl)-4-methyl-benzamide,

Thiophene-2-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide,

N-(8H-indeno[1,2-d]thiazol-2-yl)nicotinamide,

N-(8H-indeno[1,2-d]thiazol-2-yl)isonicotinamide,

2-Methyl-2H-pyrazole-3-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide,

N-(6-chloro-8H-indeno[1,2-d]thiazol-2-yl)-isonicotinamide,

1H-Pyrazole-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide,

N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl)-isonicotinamide,

N-(4H-Chromeno[4,3-d]thiazol-2-yl)-isonicotinamide,

N-Naphtho[1,2-d]thiazol-2-yl-isonicotinamide, and

3-Methyl-3H-imidazole-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide trifluoroacetate.

In a third aspect, there is provided compounds selected from the group consisting of:

4-(8H-Indeno[1,2-d]thiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester,

3-(trifluoromethyl-benzoyl)-piperidine-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide,

1-(3-trifluoromethyl-benzyl)-piperidine-4-carboxylic acid (9H-indeno[1,2-d]thiazol-2-yl)-amide,

1-(3-Trifluoromethyl-benzenesulfonyl)-piperidine-4-carboxylic acid(8H-indeno[1,2-d]thiazol-2-yl)-amide,

N-(8H-Indeno[1,2-d]thiazol-2-yl) 3-fluorobenzamide,

N-(8H-Indeno[1,2-d]thiazol-2-yl) 3-hydroxybenzamide,

N-(8H-Indeno[1,2-d]thiazol-2-yl) 2-methylpent-5-enoylamide,

N-(8H-Indeno[1,2-d]thiazol-2-yl) 2-methylbutanoylamide,

N-(8H-Indeno[1,2-d]thiazol-2-yl) 5-methylsulfonylthiophene-2-carboxyamide,

N-(8H-Indeno[1,2-d]thiazol-2-yl) 2-furoylamide, and

N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) 4-hydroxynicotinamide:

In a fourth aspect, there is provided compounds selected from the group consisting of:

N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) (4-aminosulfonyl)benzamide,

N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) (4-t-butoxycarbonylmethyl)benzamide,

N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) thiophene-3-carboxyamide,

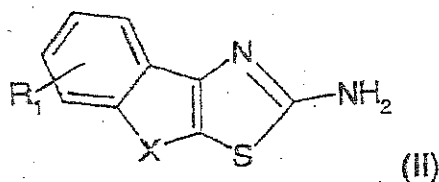
N-(4,5-Dihydro-naphtho[1,2-d]thiazol-2-yl) 4-hydroxynicotinamide,

N-(4,5-Dihydro-naphtho[1,2-d]thiazol-2-yl) thiophene-3-carboxyamide,

N-(4,5-Dihydro-7-methoxynaphtho[1,2-d]thiazol-2-yl) 4-hydroxynicotinamide,

N-(4,5-Dihydro-7-methoxynaphtho[1,2-d]thiazol-2-yl) 5-methylsulfonylthiophene-2-carboxamide,
 N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl) 4-hydroxynicotinamide,
 N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl) thiophene-3-carboxamide,
 N-(8H-Indeno[1,2-d]thiazol-2-yl) 3-chloro-4-hydroxybenzamide, and
 N-(8H-Indeno[1,2-d]thiazol-2-yl) (4-aminosulfonyl)benzamide.

In a fifth aspect, there is provided a process for the manufacture of compounds as defined above, which process comprises reacting a compound of formula (II)



with a compound $R-C(O)Cl$, wherein R, R_1 and X are as defined above.

In a sixth aspect, there is provided compounds as defined above, when manufactured by a process as defined above.

In a seventh aspect, there is provided pharmaceutical compositions comprising a compound of formula (I) as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

In an eighth aspect, there is provided compounds of formula (I) as defined above for use as therapeutic active substances.

In a ninth aspect, there is provided compounds of formula (I) as defined above for use as therapeutic active substances for the treatment and/or prophylaxis of diseases which are mediated by antagonism of the adenosine A2B receptor.

The compounds according to this disclosure show primary activity as Adenosine A2B antagonists and may therefore be useful for the treatment of diseases mediated said receptor. The compounds of the disclosure may be used as active agents in the prevention and therapy of, for example, diabetes, diabetic retinopathy, asthma and diarrhea. Secondary antagonism of Adenosine A1 and A2A receptors leads to the compound's use in depression, Parkinson's disease and hypertension.

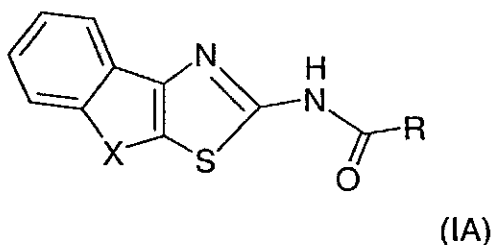
Objects of the embodiments disclosed herein are the compounds of formula I and pharmaceutically acceptable salts and their enantiomeric forms, the preparation of the above mentioned compounds, medicaments containing them and their

manufacture as well as methods for using the above mentioned compounds in the control or prevention of illnesses, especially of illnesses and disorders as mentioned above or in the manufacture of corresponding medicaments.

- 5 Compounds of formula (I) are individually preferred and physiologically acceptable salts thereof are individually preferred, with the compounds of formula (I) being particularly preferred.

The compounds of formula (I) can have one or more asymmetric C atoms and can therefore exist as an enantiomeric mixture, diastereomeric mixture or as optically pure compounds.

- 10 Preferred compounds of formula (I) as described above are those characterized by formula (IA)



or a pharmaceutically acceptable salt thereof, wherein

X is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CHCH}-$, $-(\text{CH}_2)_3-$ and $\text{O}(\text{CH}_2)-$;

- 15 R is an alkyl group, $-\text{NHR}'$ or a 5- or 6- membered saturated or unsaturated carbocyclic or heterocyclic ring which optionally may contain one or more hetero atoms and said rings being optionally substituted with one or more substituents selected from the group consisting of halogen, lower-alkyl, a nitrile group, alkylsulfonyl, alkoxy and acyl, and
- 20 R' is an alkyl group or a 5- or 6- membered saturated or unsaturated carbocyclic or heterocyclic ring which optionally may contain one or more hetero atoms and said rings being optionally substituted with one or more substituents selected from the group consisting of halogen, lower-alkyl, a nitrile group, alkylsulfonyl, alkoxy and acyl.
- 25 Preferred are those compounds of formula (I) as described above, wherein R is an alkyl group, an alkenyl group or a 5- or 6- membered saturated or unsaturated carbocyclic or heterocyclic ring which optionally may contain one or

more hetero atoms and said rings being optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, lower-alkyl, acetamidomethyl, alkoxy, carbonyl, amidomethyl, a nitrile group, a sulfonamido group, alkylsulfonyl, alkoxy, benzyl, benzoyl, arylsulfonyl and acyl, which benzyl, benzoyl or arylsulfonyl is optionally substituted by halogen, trihalo-lower-alkyl, lower-alkyl, alkoxy, alkylsulfonyl or cyano.

Further preferred compounds are those, wherein X is $-\text{CH}_2-$. Other preferred compounds are those, wherein R_1 is hydrogen, halogen or lower-alkoxy. Hydrogen, halogen and lower-alkoxy individually constitute preferred embodiments for R_1 .

Another preferred embodiment of the present invention relates to compounds of formula (I) as described above, wherein R is lower-alkyl, lower-alkenyl, phenyl or a heterocyclic ring selected from the group consisting of thienyl, pyridinyl, pyrazolyl, imidazolyl, furyl or piperidinyl, which phenyl or heterocyclic ring is optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, hydroxy, nitrile, lower-alkyl, sulfonamido, lower-alkyl-sulfonyl, lower-alkoxy-carbonyl, lower-alkoxy- $\text{C}(\text{O})\text{-NH-CH}_2-$, benzyl which is optionally substituted with CF_3 , benzoyl which is optionally substituted with CF_3 , or phenylsulfonyl which is optionally substituted with CF_3 .

Other preferred compounds as defined above are those, wherein R is lower-alkenyl or a heterocyclic ring selected from the group consisting of thienyl, pyridinyl, pyrazolyl, imidazolyl, furyl or piperidinyl, which heterocyclic ring is optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, hydroxy, nitrile, lower-alkyl, sulfonamido, lower-alkyl-sulfonyl, lower-alkoxy-carbonyl, lower-alkoxy- $\text{C}(\text{O})\text{-NH-CH}_2-$, benzyl which is optionally substituted with CF_3 , benzoyl which is optionally substituted with CF_3 , or phenylsulfonyl which is optionally substituted with CF_3 .

In the compounds of formula (I) as defined above, it is preferred that R is not phenyl, 4- NO_2 -phenyl or 4-Cl-phenyl, particularly if X is $-\text{CH}_2-$ and R_1 is hydrogen. Furthermore, in the compounds of formula (I) as defined above, it is preferred that R is not phenyl, 4- NO_2 -phenyl or 4-Cl-phenyl, particularly if X is $-\text{CH}_2\text{CH}_2-$ and R_1 is hydrogen or alkoxy. Furthermore, in the compounds of formula (I) as defined above, it is preferred that R is not alkyl, particularly if X is $-\text{CH}_2\text{CH}_2-$ and R_1 is hydrogen.

Each of the exemplified substituents X, R and R₁ as in the compounds mentioned below and in the examples, individually and in each combinations, individually constitutes a preferred embodiment, preferably in the specific combinations as in the compounds mentioned above and in the examples.

5 Especially preferred compounds include:

- N-(8H-Indeno[1,2-d]thiazol-2-yl)-benzamide,
- 4-Fluoro-N-(8H-indeno[1,2-d]thiazol-2-yl)-benzamide,
- 4-Cyano-N-(8H-indeno[1,2-d]thiazol-2-yl)-benzamide,
- N-(8H-indeno[1,2-d]thiazol-2-yl)-4-methyl-benzamide,
- 10 Thiophene-2-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide,
- N-(8H-indeno[1,2-d]thiazol-2-yl)nicotinamide,
- N-(8H-indeno[1,2-d]thiazol-2-yl)isonicotinamide,
- 2-Methyl-2H-pyrazole-3-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide,
- N-(6-chloro-8H-indeno[1,2-d]thiazol-2-yl)-isonicotinamide,
- 15 1H-Pyrazole-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide,
- N-(4,5-Dihydro-naphtho[1,2-d]thiazol-2-yl)-isonicotinamide,
- N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl)-isonicotinamide,
- N-(4H-Chromeno[4,3-d]thiazol-2-yl)-isonicotinamide,
- N-Naphtho[1,2-d]thiazol-2-yl-isonicotinamide,
- 20 3-Methyl-3H-imidazole-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide
- trifluoroacetate,
- 4-(8H-Indenol[1,2-d]thiazol-2-ylcarbonyl)-piperidine-1-carboxylic acid tert-butyl
- ester,
- 3-(trifluoromethyl-benzoyl)-piperidine-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-
- 25 yl)-amide,
- 1-(3-trifluoromethyl-benzyl)-piperidine-4-carboxylic acid (9H-indeno[1,2-d]thiazol-2-
- yl)-amide,
- 1-(3-Trifluoromethyl-benzenesulfonyl)-piperidine-4-carboxylic acid(8H-indeno[1,2-
- d]thiazol-2-yl)-amide,
- 30 N-(8H-Indeno[1,2-d]thiazol-2-yl) 3-fluorobenzamide,
- N-(8H-Indeno[1,2-d]thiazol-2-yl) 3-hydroxybenzamide,
- N-(8H-Indeno[1,2-d]thiazol-2-yl) 2-methylpent-5-enoylamide,
- N-(8H-Indeno[1,2-d]thiazol-2-yl) 2-methylbutanoylamide,
- N-(8H-Indeno[1,2-d]thiazol-2-yl) 5-methylsulfonylthiophene-2-carboxyamide,
- 35 N-(8H-Indeno[1,2-d]thiazol-2-yl) 2-furoylamide,
- N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) 4-hydroxynicotinamide,
- N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) (4-aminosulfonyl)benzamide,

- N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) (4-t-butoxycarbonylmethyl)benzamide,
 N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) thiophene-3-carboxamide,
 N-(4,5-Dihydro-naphtho[1,2-d]thiazol-2-yl) 4-hydroxynicotinamide,
 N-(4,5-Dihydro-naphtho[1,2-d]thiazol-2-yl) thiophene-3-carboxamide,
 5 N-(4,5-Dihydro-7-methoxynaphtho[1,2-d]thiazol-2-yl) 4-hydroxynicotinamide,
 N-(4,5-Dihydro-7-methoxynaphtho[1,2-d]thiazol-2-yl) 5-methylsulfonylthiophene-2-carboxamide,
 N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl) 4-hydroxynicotinamide,
 N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl) thiophene-3-carboxamide,
 10 N-(8H-Indeno[1,2-d]thiazol-2-yl) 3-chloro-4-hydroxybenzamide, and
 N-(8H-Indeno[1,2-d]thiazol-2-yl) (4-aminosulfonyl)benzamide.

Each of the compounds mentioned above individually constitutes a preferred embodiment.

- Preferred compounds of formula (I) as described above are those selected
 15 from the group consisting of:
 N-(8H-Indeno[1,2-d]thiazol-2-yl)-benzamide,
 4-Fluoro-N-(8H-indeno[1,2-d]thiazol-2-yl)-benzamide,
 4-Cyano-N-(8H-indeno[1,2-d]thiazol-2-yl)-benzamide,
 N-(8H-indeno[1,2-d]thiazol-2-yl)-4-methyl-benzamide,
 20 Thiophene-2-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide,
 N-(8H-indeno[1,2-d]thiazol-2-yl)nicotinamide,
 N-(8H-indeno[1,2-d]thiazol-2-yl)isonicotinamide,
 2-Methyl-2H-pyrazole-3-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide,
 N-(6-chloro-8H-indeno[1,2-d]thiazol-2-yl)-isonicotinamide,
 25 1H-Pyrazole-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide,
 N-(4,5-Dihydro-naphtho[1,2-d]thiazol-2-yl)-isonicotinamide,
 N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl)-isonicotinamide,
 N-(4H-Chromeno[4,3-d]thiazol-2-yl)-isonicotinamide,
 N-Naphtho[1,2-d]thiazol-2-yl-isonicotinamide, and
 30 3-Methyl-3H-imidazole-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide trifluoroacetate.

Other preferred compounds of formula (I) as described above are those selected from the group consisting of:

- 4-(8H-Indeno[1,2-d]thiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl
 35 ester,
 3-(trifluoromethyl-benzoyl)-piperidine-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-

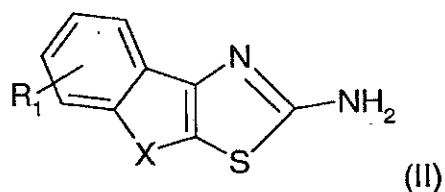
- yl)-amide,
 1-(3-trifluoromethyl-benzyl)-piperidine-4-carboxylic acid (9H-indeno[1,2-d]thiazol-2-yl)-amide,
 1-(3-Trifluoromethyl-benzenesulfonyl)-piperidine-4-carboxylic acid(8H-indeno[1,2-d]thiazol-2-yl)-amide,
 5 N-(8H-Indeno[1,2-d]thiazol-2-yl) 3-fluorobenzamide,
 N-(8H-Indeno[1,2-d]thiazol-2-yl) 3-hydroxybenzamide,
 N-(8H-Indeno[1,2-d]thiazol-2-yl) 2-methylpent-5-enoylamide,
 N-(8H-Indeno[1,2-d]thiazol-2-yl) 2-methylbutanoylamide,
 10 N-(8H-Indeno[1,2-d]thiazol-2-yl) 5-methylsulfonylthiophene-2-carboxyamide,
 N-(8H-Indeno[1,2-d]thiazol-2-yl) 2-furoylamide, and
 N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) 4-hydroxynicotinamide.

Other preferred compounds of formula (I) as described above are those selected from the group consisting of:

- 15 N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) (4-aminosulfonyl)benzamide,
 N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) (4-t-butoxycarbonylmethyl)benzamide,
 N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) thiophene-3-carboxyamide,
 N-(4,5-Dihydro-naphtho[1,2-d]thiazol-2-yl) 4-hydroxynicotinamide,
 N-(4,5-Dihydro-naphtho[1,2-d]thiazol-2-yl) thiophene-3-carboxyamide,
 20 N-(4,5-Dihydro-7-methoxynaphtho[1,2-d]thiazol-2-yl) 4-hydroxynicotinamide,
 N-(4,5-Dihydro-7-methoxynaphtho[1,2-d]thiazol-2-yl) 5-methylsulfonylthiophene-2-carboxyamide,
 N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl) 4-hydroxynicotinamide,
 N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl) thiophene-3-carboxyamide,
 25 N-(8H-Indeno[1,2-d]thiazol-2-yl) 3-chloro-4-hydroxybenzamide, and
 N-(8H-Indeno[1,2-d]thiazol-2-yl) (4-aminosulfonyl)benzamide.

It will be appreciated that the compounds of general formula (I) in this invention may be derivatised at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo.

Another embodiment of the present invention refers to a process for the manufacture of compounds of formula (I) as defined above, which process comprises reacting a compound of formula (II)



- 5 with a compound $R-C(O)Cl$, wherein R , R_1 and X are as defined above.

Appropriate reaction conditions are described in schemes 1 and 2 as well as in the examples.

Furthermore, the invention relates to compounds of formula (I) as defined above, when manufactured by a process according to claim 9.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

5 In this specification the term "lower" is used to mean a group consisting of one to six, preferably of one to four carbon atom(s).

"Alkyl" denotes a straight-chained or branched saturated aliphatic hydrocarbon. Alkyl groups preferably have 1 to 20 carbon atoms, more preferably 1 to 16 carbon atom, more preferably 1 to 10 carbon atoms. Lower-alkyl groups as described below also are preferred alkyl groups.

10 "Lower-alkyl" groups denote C₁-C₆ alkyl groups and include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, 2-butyl, pentyl, hexyl, and the like. Generally, lower-alkyl is preferably C₁-C₄ alkyl, and more preferably C₁-C₃ alkyl.

"Trihalo-lower-alkyl" denotes lower-alkyl groups which are substituted with 3 halogen atoms. CF₃ is a preferred trihalo-lower-alkyl group.

15 "Alkoxy" denotes -O-alkyl. "Lower-alkoxy" denotes -O-lower-alkyl.

"Alkenyl" groups refer to a straight-chain or branched hydrocarbon residue comprising an olefinic bond and up to 7, preferably up to 4 carbon atoms, such as e.g. 2-propenyl

20 The term "carbocyclic" refers to a 5- or 6-membered saturated or unsaturated carbon containing ring, such as, an aryl ring.

25 The term "heterocyclic" refers to a 5- or 6-membered ring which can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen and/or sulfur such as tetrahydropyridine, dihydrofuran, dihydropyran, furyl, pyrrolyl, pyridyl, 1,2-, 1,3- and 1,4-diazinyl, thienyl, oxazolyl, oxadiazolyl, isoxazolyl, thiazolyl, isothiazolyl or imidazolyl. A heterocyclic group may be optionally substituted with an aryl group. As noted above the heterocyclic group may be substituted by a variety of substituents and in the case of the benzyl, benzoyl and arylsulfonyl substituents these substituents may be further substituted by halo, trihalo lower-alkyl, lower-alkyl, alkoxy, alkylsulfonyl or cyano.

30 The term "halogen" means an atom selected from chlorine, fluorine and bromine.

"Effective amount" means an amount that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

"Hetero atom" means an atom selected from N, O and S.

5 "IC₅₀" refers to the concentration of a particular compound required to inhibit 50% of a specific measured activity. IC₅₀ can be measured, *inter alia*, as is described subsequently.

"Aryl" means a monovalent, monocyclic or bicyclic, aromatic carbocyclic hydrocarbon radical, preferably a 5 to 6 membered aromatic ring system. An
10 example of such a radical is phenyl.

"Acyl" denotes -C(O)-C₁-C₆-alkyl, -C(O)H or C(O)-O alkyl.

"Pharmaceutically acceptable ester" refers to a conventionally esterified compound of formula I having a carboxyl group, which esters retain the biological effectiveness and properties of the compounds of formula I and are cleaved *in vivo*
15 (in the organism) to the corresponding active carboxylic acid.

Information concerning esters and the use of esters for the delivery of pharmaceutical compounds is available in Design of Prodrugs. Bundgaard H ed. (Elsevier, 1985). See also, H. Ansel et. al., Pharmaceutical Dosage Forms and Drug Delivery Systems (6th Ed. 1995) at pp. 108-109; Krogsgaard-Larsen, et. al.,
20 Textbook of Drug Design and Development (2d Ed. 1996) at pp. 152-191.

"Pharmaceutically acceptable salt" refers to conventional acid-addition salts or base-addition salts that retain the biological effectiveness and properties of the compounds of the present invention and are formed from suitable non-toxic organic or inorganic acids or organic or inorganic bases. Sample acid-addition
25 salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid and nitric acid, and those derived from organic acids such as p-toluenesulfonic acid, salicylic acid, methanesulfonic acid, oxalic acid, succinic acid, citric acid, malic acid, lactic acid, fumaric acid, and the like. Sample base-addition salts include
30 those derived from ammonium, potassium, sodium and, quaternary ammonium hydroxides, such as for example, tetramethylammonium hydroxide. Chemical modification of a pharmaceutical compound (i.e. drug) into a salt is a technique well known to pharmaceutical chemists to obtain improved physical and chemical

stability, hygroscopicity, flowability and solubility of compounds. *See, e.g., H. Ansel et. al., Pharmaceutical Dosage Forms and Drug Delivery Systems (6th Ed. 1995) at pp. 196 and 1456-1457.*

5 “Pharmaceutically acceptable,” such as pharmaceutically acceptable carrier, excipient, etc., means pharmacologically acceptable and substantially non-toxic to the subject to which the particular compound is administered.

 “Substituted” means that the substitution can occur at one or more positions and, unless otherwise indicated, that the substituents at each substitution site are independently selected from the specified options.

10 The compounds of formula (I) can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to the person skilled in the art. Starting materials are either commercially available or can
15 be prepared by methods analogous to the methods given below or in the examples or by methods known in the art.

The compounds of formula I and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.

The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula (I) and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives. Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavor-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of the compounds of formula (I) can vary within wide limits depending on the disease to be controlled, the age and the individual condition of

the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case. For adult patients a daily dosage of about 1 to 1000 mg, especially about 1 to 100 mg, comes into consideration. Depending on severity of the disease and the precise pharmacokinetic profile the
5 compound could be administered with one or several daily dosage units, e.g. in 1 to 4 dosage units.

As described above, the novel compounds of the present invention have been found to be antagonists of adenosine A2B receptor. The compounds of the present invention can therefore be used in the treatment and/or prophylaxis of diseases which are mediated by antagonism of the adenosine A2B receptor, particularly diabetes, diabetic retinopathy, asthma and diarrhea, especially diabetes.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

The invention likewise embraces compounds as described above for use as therapeutically active substances, especially as therapeutically active substances for the treatment and/or prophylaxis of diseases which are mediated by antagonism of the adenosine A2B receptor, particularly as therapeutically active substances for the treatment and/or prophylaxis of diabetes, diabetic retinopathy, asthma and diarrhea, especially diabetes.

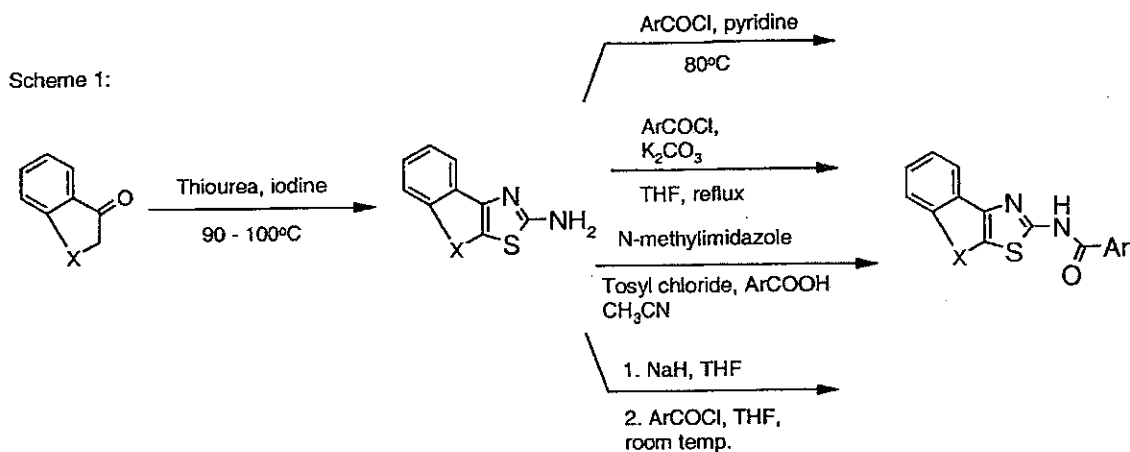
In another preferred embodiment, the invention relates to a method for the therapeutic and/or prophylactic treatment of diseases which are mediated by antagonism of the adenosine A2B receptor, particularly for the therapeutic and/or prophylactic treatment of diabetes, diabetic retinopathy, asthma and diarrhea, especially diabetes, which method comprises administering a compound as defined above to a human being or animal.

The invention also embraces the use of compounds as defined above for the therapeutic and/or prophylactic treatment of diseases which are mediated by antagonism of the adenosine A2B receptor, particularly for the therapeutic and/or prophylactic treatment of diabetes, diabetic retinopathy, asthma and diarrhea, especially diabetes.

The invention also relates to the use of compounds as described above for the preparation of medicaments for the therapeutic and/or prophylactic treatment of diseases which are mediated by antagonism of the adenosine A2B receptor, particularly for the therapeutic and/or prophylactic treatment of diabetes, diabetic retinopathy, asthma and diarrhea, especially diabetes. Such medicaments comprise a compound as described above.

Prevention and/or treatment of diabetes is the preferred indication.

The following reaction scheme and narrative therewith sets forth the general methodology for making the novel compounds of the present invention.

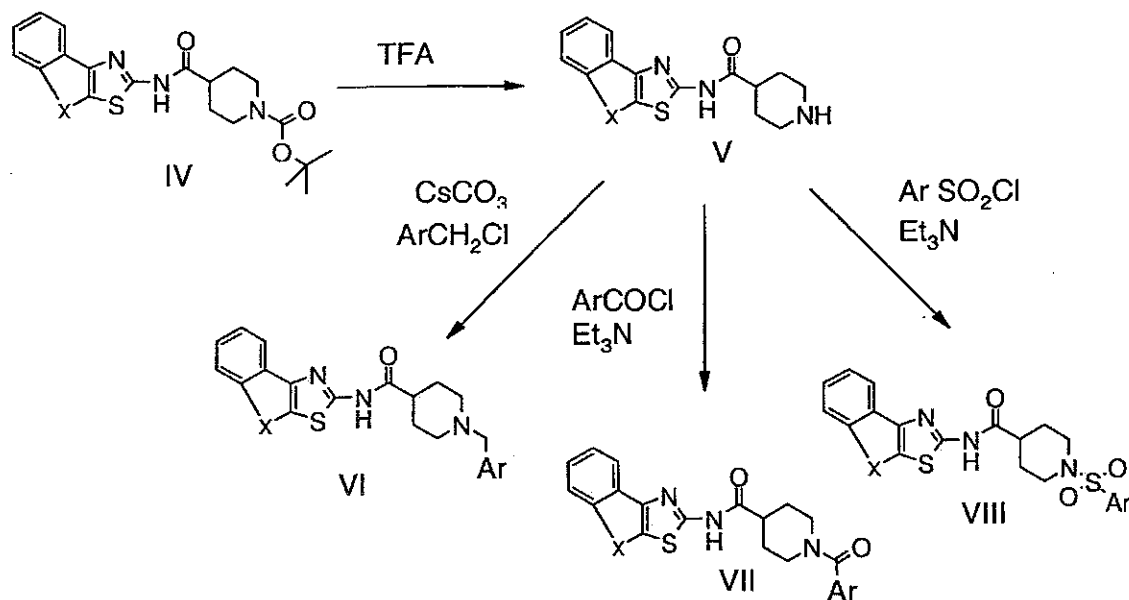


Description of Scheme 1:

- 5 Heating a mixture of the appropriate ketone I with thiourea and iodine to 90 – 100°C in the absence of solvent provided the thiazole intermediates II.
- Acylation of II with an aroyl or heteroaroyl chloride in the presence of a base such as potassium carbonate or pyridine with heating provided the acyl products III.
- Alternatively, deprotonation of II with a strong base such as sodium hydride
- 10 followed by acylation with the aroyl or heteroaroyl chloride also gave rise to the acyl products III.

- Compounds of structure III may also be prepared via coupling of amine II with aryl carboxylic acids using O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) or a combination of p-
- 15 toluenesulfonyl chloride and N-methylimidazole as coupling agents.

Scheme 2:



Description of Scheme 2:

Deprotection of compound IV with trifluoroacetic acid provides the intermediate piperidine compound V. Compound V may then be reacted with a suitable aryl halide, benzoyl halide or arylsulfonyl halide in the presence of a base such as triethyl amine to provide compounds VI, VII and VIII.

The reaction conditions for the above reactions can vary to a certain extent. Methods to perform the above described reactions and processes are known in the art or can be deduced in analogy from the examples. Starting materials are commercially available or can be made by methods analogous to those described in the examples.

The following examples shall illustrate preferred embodiments of the present invention but are not intended to limit the scope of the invention.

Example 1:**N-(8H-Indeno[1,2-d]thiazol-2-yl)-benzamide****Step 1: 8H-Indeno[1,2-d]thiazol-2-ylamine hydroiodide**

A mixture of 1-indanone (6.00g; 45.4 mmol), thiourea (6.92g; 90.8 mmol) and
5 iodine (11.52g; 45.4 mmol) was heated to 95°C with stirring. After 3 hours, the
mixture was allowed to cool to room temperature. The crude solid was triturated
with absolute ethanol and filtered. The light yellow solid was washed twice with
absolute ethanol then allowed to air dry to provide 9.13g of 8H-Indeno[1,2-
d]thiazol-2-ylamine hydroiodide **1a**.

10 Step 2: 8H-Indeno[1,2-d]thiazol-2-ylamine

Indeno[1,2-d]thiazol-2-ylamine hydroiodide **1a** (9.13g) was stirred with 100 mL of
1N sodium hydroxide for 1 hour at room temperature then filtered. The solid was
washed with water (3 X 20 mL) and then allowed to air dry to provide 5.30g of 8H-
Indeno[1,2-d]thiazol-2-ylamine **1b**.

15 Step 3: N-(8H-Indeno[1,2-d]thiazol-2-yl)-benzamide

To a mixture of Indeno[1,2-d]thiazol-2-ylamine hydroiodide **1a** (100 mg; 0.32
mmol) in pyridine (2 mL) was added benzoyl chloride (0.12 mL; 0.96 mmol)
dropwise. The mixture was then agitated at 80°C in a sealed tube overnight. The
mixture was allowed to cool to room temperature and the solvent removed *in*
20 *vacuo*. The residue was taken up into ethyl acetate and the extract allowed to stir
with 2M sodium carbonate solution for 2 hours at room temperature. The organic
layer was then washed with brine solution, dried over sodium sulfate and
concentrated *in vacuo*. The crude product was chromatographed on silica gel
(eluent: 10% ethyl acetate/hexanes to 40% ethyl acetate gradient) to provide 53
25 mg of N-(8H-Indeno[1,2-d]thiazol-2-yl)-benzamide **2**. EI-HRMS m/e calcd for
C₁₇H₁₂N₂OS 292.0670, found 292.0666.

Example 2:**4-Fluoro-N-(8H-indeno[1,2-d]thiazol-2-yl)-benzamide**

Acylation of 8H-Indeno[1,2-d]thiazol-2-ylamine hydroiodide **1a** (Prepared in
30 Example 1, Step 1, 100 mg; 0.32 mmol) with 4-fluorobenzoyl chloride (0.116 mL;
0.96 mmol) in a manner similar to that described in Example 1, Step 3 provided 35

mg of 4-Fluoro-N-(8H-indeno[1,2-d]thiazol-2-yl)-benzamide **3**. EI-HRMS m/e calcd for $C_{17}H_{11}FN_2OS$ 310.0576, found 310.0577.

Example 3

4-Cyano-N-(8H-indeno[1,2-d]thiazol-2-yl)-benzamide

- 5 Acylation of 8H-Indeno[1,2-d]thiazol-2-ylamine hydroiodide **1a** (Prepared in Example 1, Step 1, 100 mg; 0.32 mmol) with 4-cyanobenzoyl chloride (164 mg; 0.96 mmol) in a manner similar to that described in Example 1, Step 3 provided 26 mg of 4-Cyano-N-(8H-indeno[1,2-d]thiazol-2-yl)-benzamide **4**. EI-HRMS m/e calcd for $C_{18}H_{14}N_2OS$ (M^+) 306.0827, found 306.0827.

Example 4

N-(8H-Indeno[1,2-d]thiazol-2-yl)-4-methyl-benzamide

- 15 Acylation of 8H-Indeno[1,2-d]thiazol-2-ylamine hydroiodide **1a** (Prepared in Example 1, Step 1, 100 mg; 0.32 mmol) with 4-methylbenzoyl chloride (0.130 mL; 0.96 mmol) in a manner similar to that described in Example 1, Step 3 provided 25 mg of N-(8H-Indeno[1,2-d]thiazol-2-yl)-4-methyl-benzamide **5**. EI-HRMS m/e calcd for $C_{16}H_{11}N_3OS$ (M^+) 293.0623, found 293.0621.

Example 5

Thiophene-2-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide

- 20 Acylation 8H-Indeno[1,2-d]thiazol-2-ylamine hydroiodide **1a** (Prepared in Example 1, Step 1, 100 mg; 0.32 mmol) with 2-thiophenecarbonyl chloride (0.106 mL; 0.96 mmol) in a manner similar to that described in Example 1, Step 3 provided 17 mg of Thiophene-2-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide **6**. EI-HRMS m/e calcd for $C_{15}H_{10}N_2OS_2$ (M^+) 298.0235, found 298.0233.

Example 6

N-(8H-Indeno[1,2-d]thiazol-2-yl)-nicotinamide

- 25 A suspension of 8H-Indeno[1,2-d]thiazol-2-ylamine hydroiodide **1a** (Prepared in Example 1, Step 1, mg; mmol), nicotinoyl chloride hydrochloride (92 mg; 0.50 mmol) and diisopropylethylamine (0.50 mL; 2.77 mmol) in dichloroethane was heated in a sealed tube to 120°C in a microwave oven for 10 minutes. The mixture was allowed to cool to room temperature and the solvent removed *in*
- 30

vacuo. The residue was taken up into 2 M sodium carbonate solution and extracted with ethyl acetate. The extracts were dried (sodium sulfate), filtered and concentrated *in vacuo*. The crude product was chromatographed on silica gel (eluent = 50% ethyl acetate/ hexanes to 100% ethyl acetate / hexanes gradient) to provide 43 mg of N-(8H-Indeno[1,2-d]thiazol-2-yl)-nicotinamide **7**. EI-HRMS m/e calcd for C₁₆H₁₁N₄OS (M⁺) 293.0623, found 293.0620.

Example 7

N-(8H-Indeno[1,2-d]thiazol-2-yl)-isonicotinamide

To a mixture of 8H-Indeno[1,2-d]thiazol-2-ylamine **1b** (Prepared in Example 1, Step 2, 640 mg; 3.4 mmol) and potassium carbonate (5.40g; 39.1 mmol) in dry tetrahydrofuran (20 mL) under nitrogen was added isonicotinoyl chloride hydrochloride (959 mg; 5.10 mmol). The slurry was then heated to reflux for 18 hr. At this point, potassium carbonate (5.40g; 39.1 mmol) and isonicotinoyl chloride hydrochloride (959 mg; 5.10 mmol) were added and reflux continued for 22 hr., then allowed to cool to room temperature. The solvent was removed *in vacuo* and the residue diluted with water and extracted with methylene chloride. The insoluble material was filtered off and washed methylene chloride and water and finally triturated with diethyl ether to provide 253 mg of N-(8H-Indeno[1,2-d]thiazol-2-yl)-isonicotinamide **8**. EI-HRMS m/e calcd for C₁₆H₁₁N₃OS (M⁺) 293.0623, found 293.0621.

Example 8

2-Methyl-2H-pyrazole-3-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide

To a mixture 8H-Indeno[1,2-d]thiazol-2-ylamine **1b** (Prepared in Example 1, Step 2, 320 mg; 1.70 mmol) and potassium carbonate (3.10g; 22.4 mmol) in dry tetrahydrofuran (10 mL) under nitrogen was added 2-methyl-2H-pyrazole-3-carbonyl chloride (516 mg; 3.57 mmol). The slurry was then heated to reflux for 3 hr. The solvent was removed *in vacuo*, and the residue diluted with water and extracted with ethyl acetate. The organic layer was washed with 50 mL of 1N hydrochloric acid solution followed by brine solution and dried (sodium sulfate) filtered and concentrated *in vacuo*. The crude product was purified by trituration with diethyl ether to provide 155 mg of 2-Methyl-2H-pyrazole-3-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide **9**. EI-HRMS m/e calcd for C₁₅H₁₂N₄OS (M⁺) 296.0732, found 296.0731.

Example 9**N-(6-Chloro-8H-indeno[1,2-d]thiazol-2-yl)-isonicotinamide****Step 1: 6-Chloro-8H-indeno[1,2-d]thiazol-2-ylamine hydroiodide**

A mixture of 5-chloro-1-indanone (1.00g; 6.00 mmol), thiourea (0.917g; 12.0 mmol) and iodine (1.55g; 6.10 mmol) was heated to 100°C in a sealed tube. After 1 hr., the mixture was allowed to cool to room temperature. The solid was triturated with water and filtered. The solid was then triturated with absolute ethanol, filtered and washed several times with absolute ethanol to provide 0.60g of 6-Chloro-8H-indeno[1,2-d]thiazol-2-ylamine hydroiodide **10**.

Step 2: N-(6-Chloro-8H-indeno[1,2-d]thiazol-2-yl)-isonicotinamide

A mixture of 6-Chloro-8H-indeno[1,2-d]thiazol-2-ylamine hydroiodide **10** (80 mg; 0.23 mmol), potassium carbonate (138mg; 1.0 mmol) and isonicotinoyl chloride hydrochloride (89mg; 0.5 mmol) in dry tetrahydrofuran was heated to 80°C in a sealed tube. After 20 hr., the mixture was allowed to cool to room temperature and concentrated *in vacuo*. The residue was diluted with methylene chloride and washed with water. The organic layer was dried (sodium sulfate), filtered and concentrated *in vacuo*. The crude product was purified by reverse phase HPLC (eluent: acetonitrile/water/0.1% trifluoroacetic acid) to provide 20 mg of N-(6-Chloro-8H-indeno[1,2-d]thiazol-2-yl)-isonicotinamide **11** as the trifluoroacetate salt. EI-HRMS m/e calcd for C₁₆H₁₀ClN₃OS (M⁺) 327.0233, found 327.0217.

Example 10**1H-Pyrazole-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide****Step 1: 4-pyrazolecarbonyl chloride**

A mixture of 4-pyrazolecarboxylic acid (600 mg) in thionyl chloride (5 mL) was heated to 90°C under nitrogen. After 18 hr., the mixture was allowed to cool to room temperature and the solvent removed *in vacuo* to provide 579 mg of 4-pyrazolecarbonyl chloride **12**, which was used without further purification for the next step (Step 2). EI-HRMS m/e calcd for C₁₆H₁₁N₃OS (M⁺) 293.0623, found 293.0621.

Step 2: 1H-Pyrazole-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide

Acylation 8H-Indeno[1,2-d]thiazol-2-ylamine **1b** (Prepared in Example 1, Step 2, 377 mg; 2.00 mmol) with 4-pyrazolecarbonyl chloride **12** (208 mg; 1.6 mmol) in a manner similar to that described in Example 7, provided 190 mg of 1H-Pyrazole-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide **13** as a dark powder.

5

Example 11

3-Methyl-3H-imidazole-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide trifluoroacetate

To a mixture of 8H-Indeno[1,2-d]thiazol-2-ylamine **1b** (Prepared in Example 1, Step 2, 94 mg; 0.50 mmol), 1-methyl-1H-imidazole-5-carboxylic acid (65 mg; 0.50 mmol) and BOP reagent (443 mg; 1.0 mmol) in dry methylene chloride at room temperature was added diisopropylethyl amine (0.55 mL; 3.13 mmol) dropwise. After 96 hours, the reaction mixture was diluted with methylene chloride and washed with water followed by brine solution. The organic layer was dried (sodium sulfate) filtered and concentrated in vacuo. Purification using reverse phase HPLC (eluent: acetonitrile/water/0.1% trifluoroacetic acid) provided 70 mg of **14**. EI-HRMS m/e calcd for C₁₅H₁₂N₄OS (M⁺) 296.0732, found 296.0728.

Example 12

N-(4,5-Dihydro-naphtho[1,2-d]thiazol-2-yl)-isonicotinamide

Step 1: 4,5-Dihydro-naphtho[1,2-d]thiazol-2-ylamine hydroiodide

A mixture of 1-tetralone (5.00 mL; 37.6 mmol), thiourea (5.72g; 75.2 mmol) and iodine (9.54g; 37.6 mmol) were heated to 95°C with stirring. After 4hr., the mixture solidified and was allowed to cool to room temperature. The mixture was diluted with 200 mL of water and the solid material was filtered off and triturated with absolute ethanol. The solid was washed several times with absolute ethanol to provide 4.00g of 4,5-Dihydro-naphtho[1,2-d]thiazol-2-ylamine hydroiodide **15** as an off white powder.

Step 2: N-(4,5-Dihydro-naphtho[1,2-d]thiazol-2-yl)-isonicotinamide

Added sodium hydride (26 mg; 1.1 mmol) to a stirred suspension of 4,5-Dihydro-naphtho[1,2-d]thiazol-2-ylamine hydroiodide **15** in dry tetrahydrofuran under nitrogen at room temperature. After 15 minutes, isonicotinoyl chloride hydrochloride (107mg; 0.60 mmol) was added and the mixture allowed to stir for 2 hr. at room temperature and then concentrated *in vacuo*. The residue was diluted

with water the solid material was filtered off. Purification using reverse phase HPLC (eluent: acetonitrile/water/0.1% trifluoroacetic acid) provided 20 mg of N-(4,5-Dihydro-naphtho[1,2-d]thiazol-2-yl)-isonicotinamide **16** as the trifluoroacetate salt. ES-HRMS m/e calcd for C₁₇H₁₃N₃OS (M+H) 308.0852, found 308.0851.

5

Example 13

N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl)-isonicotinamide

Step 1: 5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-ylamine hydroiodide

A mixture of 1-benzosuberone (1.00 mL; 6.7 mmol), thiourea (1.02g; 13.4 mmol) and iodine (1.70g; 6.7 mmol) were heated to 95°C with stirring. After 20 hr., the mixture was allowed to cool to room temperature, diluted with 200 mL of water, the solid material filtered off washed twice with 25 mL of water followed by diethyl ether (3 X 20 mL) to provide 1.50g of 5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-ylamine hydroiodide **17** as an off white powder.

Step 2: N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl)-isonicotinamide

Added sodium hydride (17 mg; 0.7 mmol) to a stirred suspension of 5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-ylamine hydroiodide **17** (80 mg; 0.23 mmol) in dry tetrahydrofuran under nitrogen at room temperature. After 15 minutes, isonicotinoyl chloride hydrochloride (62mg; 0.35 mmol) was added and the mixture allowed to stir for 1 hr. at room temperature and then concentrated *in vacuo*. The residue was triturated with water the solid material was filtered off. Purification using reverse phase HPLC (eluent: acetonitrile/water/0.1% trifluoroacetic acid) provided 20 mg of N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl)-isonicotinamide **18** as the trifluoroacetate salt. EI-HRMS m/e calcd for C₁₈H₁₅N₃OS (M⁺) 321.0936, found 321.0935.

25

Example 14

N-(4H-Chromeno[4,3-d]thiazol-2-yl)-isonicotinamide

Step 1: 4H-Chromeno[4,3-d]thiazol-2-ylamine hydroiodide

A mixture of 4-chromanone (2.00 g; 13.5 mmol), thiourea (2.06g; 27.0 mmol) and iodine (3.43g; 13.5 mmol) were heated to 95°C with stirring. After 4.5 hr., the mixture was allowed to cool to room temperature, triturated with methylene chloride, the solid material filtered off. The solid was further triturated with ethyl

acetate, filtered and washed with ethyl acetate to provide 3.00g of 4H-Chromeno[4,3-d]thiazol-2-ylamine hydroiodide **19** as an off white powder.

Step 2: N-(4H-Chromeno[4,3-d]thiazol-2-yl)-isonicotinamide

- Added sodium hydride (19 mg; 0.8 mmol) to a stirred suspension of 4H-Chromeno[4,3-d]thiazol-2-ylamine hydroiodide **19** (90 mg; 0.27 mmol) in dry tetrahydrofuran under nitrogen at room temperature. After 15 minutes, isonicotinoyl chloride hydrochloride (62mg; 0.35 mmol) was added and the mixture allowed to stir for 3 hr. at room temperature and then concentrated *in vacuo*. The residue was diluted with water and extracted with ethyl acetate. The extracts were dried (sodium sulfate), filtered and concentrated *in vacuo*. Purification using reverse phase HPLC (eluent: acetonitrile/water/0.1% trifluoroacetic acid) provided 12 mg of N-(4H-Chromeno[4,3-d]thiazol-2-yl)-isonicotinamide **20** as the trifluoroacetate salt. ES-HRMS m/e calcd for C₁₆H₁₁N₃OS (M+H) 310.0645, found 310.0646.

Example 15

N-Naphtho[1,2-d]thiazol-2-yl-isonicotinamide

Step 1: Naphtho[1,2-d]thiazol-2-ylamine hydrobromide

- Bromine (0.26 mL; 5.14 mmol) was added dropwise to a stirred mixture of 2-naphthalene thiourea (800 mg; 3.96 mmol) in dry methylene chloride (10 mL) at room temperature. The mixture was then heated to reflux. After 2 hr., the mixture was allowed to cool to room temperature. The solid was filtered off and washed several times with methylene chloride to provide 1.12g of Naphtho[1,2-d]thiazol-2-ylamine hydrobromide **21**.

Step 2: N-Naphtho[1,2-d]thiazol-2-yl-isonicotinamide

- Added sodium hydride (73 mg; 2.89 mmol) to a stirred suspension of **21** (90 mg; 0.27 mmol) in dry tetrahydrofuran under nitrogen at room temperature. After 30 minutes, isonicotinoyl chloride hydrochloride (150 mg; 0.84 mmol) was added and the mixture allowed to stir for 72 hr. at room temperature. The mixture was concentrated *in vacuo*, the residue taken up into ethyl acetate and washed with saturated ammonium chloride solution. The organic layer was dried (sodium sulfate), filtered and concentrated *in vacuo*. Purification using reverse phase HPLC (eluent: acetonitrile/water/0.1% trifluoroacetic acid) provided 26 mg of N-

Naphtho[1,2-d]thiazol-2-yl-isonicotinamide **22**. ES-HRMS m/e calcd for $C_{17}H_{11}N_3OS$ (M+H) 306.0696, found 306.0691.

Example 16

5 4-(8H-Indenol[1,2-d]thiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester

To a magnetically stirred mixture of piperidine-1,4-dicarboxylic acid mono-tert-butyl ester (195 mg, 0.848 mmol) in CH_3CN (10 mL) at room temperature was added 1-methylimidazole (200 mL, 2.52 mmol, Aldrich). The reaction mixture was cooled in an ice bath and then charged with p-toluenesulfonyl chloride (192 mg, 1.01 mmol, Aldrich). After stirring in the ice bath for 30 minutes, 8H-indeno[1,2-d]thiazol-2-ylamine (160 mg, 0.84 mmol) was added. The ice bath was removed, and the reaction mixture was stirred at room temperature for 2 hours. LC/MS analysis indicated complete consumption of starting material. The reaction mixture was filtered and the resulting solids were washed with acetonitrile to give 4-(8H-indenol[1,2-d]thiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester (330 mg, 99 % yield) as an off-white solid. HRMS calcd for $C_{21}H_{25}N_3O_3S$ (M+H)⁺ 400.169, found 400.169.

Example 17

20 3-(trifluoromethyl-benzoyl)-piperidine-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide (44 mg, 55.2% yield)

step1:

Deprotection of 4-(8H-indenol[1,2-d]thiazol-2-ylcarbamoyl)-piperidine-1-carboxylic acid tert-butyl ester (350 mg, 0.876 mmol) with TFA according to known procedures gave piperidine-4-carboxylic acid(8H-indeno[1,2-d]thiazol-2-yl)-amide TFA salt as a white powder (306 mg, 84.5% yield); HRMS for $C_{16}H_{17}N_3OS$ (M+H)⁺ at m/z = 300.12.

step 2

To a mixture of piperidine-4-carboxylic acid(8H-indeno[1,2-d]thiazol-2-yl)-amide (70 mg; 0.169 mmol), and triethylamine (59 mL; 0.42 mmol) in 10 mL of methylene chloride at room temperature was added 3-(trifluoromethyl)benzoyl chloride (25 mL; 0.169 mmol) dropwise. After 24 hours at room temperature, the reaction mixture was diluted with ethyl acetate and then washed with 1N HCl,

saturated. Aq. NaHCO_3 , water, and brine. The organic layer was dried (sodium sulfate), filtered, and concentrated in vacuo. The crude product was purified by chromatography (gradient elution with 75% ethyl acetate/ hexane to 100% ethyl acetate) to furnish 3-(trifluoromethyl-benzoyl)-piperidine-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide (44 mg, 55.2% yield); HRMS calcd for $\text{C}_{24}\text{H}_{20}\text{N}_3\text{O}_3\text{F}_3\text{S}$ ($\text{M}+\text{H}$)⁺ 472.1301, found 472.1301.

Example 18

In an analogous manner, there was obtained:

10 1-(3-Trifluoromethyl-benzenesulfonyl)-piperidine-4-carboxylic acid(8H-indeno[1,2-d]thiazol-2-yl)-amide

From piperidine-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide (from Example 17, step1) (60mg, 0.145 mmol) and 3-(trifluoromethyl)benzenesulfonyl chloride (42.6 mg, 0.174 mmol) and triethylamine as a white solid (58 mg, 78.9% yield): HRMS calcd for $\text{C}_{23}\text{H}_{20}\text{N}_3\text{O}_3\text{F}_3\text{S}_2$ ($\text{M}+\text{H}$)⁺ 508.0971, found 508.0971.

15 Example 19

1-(3-trifluoromethyl-benzyl)-piperidine-4-carboxylic acid (9H-indeno[1,2-d]thiazol-2-yl)-amide

To a magnetically stirred mixture of piperidine-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide (from Example 17, step1) (70 mg, 0.169 mmol) in DMF (15 mL, Aldrich) at room temperature was added cesium carbonate (0.5 g, 0.0153 mmol) followed by 3-(trifluoromethyl)benzyl chloride (26 mL, 0.169 mmol, Aldrich). The reaction mixture was stirred at room temperature for 3 hours. The crude reaction mixture was filtered and concentrated. Purification using reverse phase HPLC (eluent: acetonitrile/water/0.1% trifluoroacetic acid) provided 1-(3-trifluoromethyl-benzyl)-piperidine-4-carboxylic acid (9H-indeno[1,2-d]thiazol-2-yl)-amide TFA salt (33 mg, 34.1% yield) as a white solid. HRMS calcd for $\text{C}_{24}\text{H}_{22}\text{N}_3\text{OF}_3\text{S}$ ($\text{M}+\text{H}$)⁺ 458.1509, found 458.1506.

Example 20

30 The Product 1-19 amides were prepared following scheme 1 above and the below procedure in a parallel format.

A mixture N-methylpyrrolidin-2-one (NMP) solution of the carboxylic acid (0.3M, 1 ml, 0.3 mmol), O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, HATU (0.3M, 1 ml, 0.3 mmol) and neat diisopropylethylamine (0.05 ml, 0.3 mmol) in a 12 ml tube was shaken for 20 min at RT. Then the aminothiazole in NMP (0.2M, 1 ml, 0.2 mmol) was added. The tube was sealed with a cap and shaken at 90C for 12 hours. After cooling to room temp., the reaction mixture was diluted with ethyl acetate (2 ml) and sodium hydroxide solution (0.5M, 2 ml). The tubes were vortexed for extraction and centrifuged for layer separation. Organic layers were transferred to 20 ml scintillation vials. The aqueous layers were extracted again with ethyl acetate as above. The scintillation vials containing the combined ethyl acetate extracts were then loaded on a Genevac evaporator to remove all the organic solvents. The crude products were checked by HPLC for purity and then purified by HPLC to give pure amides.

Product 1: N-(8H-Indeno[1,2-d]thiazol-2-yl) 3-fluorobenzamide. 37 mg (60% yield). 100% pure (LR-LCMS, calc. 311.06, found 311.03).

Product 2: N-(8H-Indeno[1,2-d]thiazol-2-yl) 3-hydroxybenzamide. 2 mg (3% yield). 100% pure (LR-LCMS, calc. 309.07, found 309.05).

Product 3: N-(8H-Indeno[1,2-d]thiazol-2-yl) 2-methylpent-5-enoylamide. 31 mg (55% yield). 100% pure (LR-LCMS, calc. 285.1, found 285.08).

Product 4: N-(8H-Indeno[1,2-d]thiazol-2-yl) 2-methylbutanoylamide. 28 mg (51% yield). 100% pure (LR-LCMS, calc. 273.1, found 273.09).

Product 5: N-(8H-Indeno[1,2-d]thiazol-2-yl) 5-methylsulfonylthiophene-2-carboxamide. 63 mg (84% yield). 100% pure (LR-LCMS, calc. 377.01, found 377.03).

Product 6: N-(8H-Indeno[1,2-d]thiazol-2-yl) 2-furoylamide. 53 mg (95% yield). 100% pure (LR-LCMS, calc. 283.05, found 283.04).

Product 7: N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) 4-hydroxynicotinamide. 2 mg (3% yield). 100% pure (LR-LCMS, calc. 328.05, found 328.06).

Product 8: N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) (4-aminosulfonyl)benzamide. 7 mg (9% yield). 100% pure (LR-LCMS, calc. 390.03, found 390.03).

Product 9: N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) (4-t-butoxycarbonylmethyl)benzamide. 14mg (16% yield). 100% pure (LR-LCMS, calc. 440.14, found 440.19).

Product 10: N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) thiophene-3-carboxamide.
5 10 mg (16% yield). 100% pure (LR-LCMS, calc. 317.08, found 317.07).

Product 11: N-(4,5-Dihydro-naphtho[1,2-d]thiazol-2-yl) 4-hydroxynicotinamide. 4 mg (6% yield). 100% pure (LR-LCMS, calc. 234.08, found 324.08).

Product 12: N-(4,5-Dihydro-naphtho[1,2-d]thiazol-2-yl) thiophene-3-carboxamide.
10 mg (16% yield). 100% pure (LR-LCMS, calc. 213.04, found 313.03).

10 Product 13: N-(4,5-Dihydro-7-methoxynaphtho[1,2-d]thiazol-2-yl) 4-hydroxynicotinamide. 2 mg (3% yield). 100% pure (LR-LCMS, calc. 354.09, found 354.09).

Product 14: N-(4,5-Dihydro-7-methoxynaphtho[1,2-d]thiazol-2-yl) 5-methylsulfonylthiophene-2-carboxamide. 15mg (18% yield). 100% pure (LR-
15 LCMS, calc. 421.03, found 421.02).

Product 16: N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl) 4-hydroxynicotinamide. 10 mg (15% yield). 100% pure (LR-LCMS, calc. 338.09, found 338.19).

Product 17: N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl) thiophene-3-carboxamide. 22 mg (34% yield). 100% pure (LR-LCMS, calc. 327.06, found
20 327.12).

Product 18: N-(8H-Indeno[1,2-d]thiazol-2-yl) 3-chloro-4-hydroxybenzamide. 16 mg (23% yield). 100% pure (LR-LCMS, calc. 343.03, found 343.07).

Product 19: N-(8H-Indeno[1,2-d]thiazol-2-yl) (4-aminosulfonyl)benzamide. 10 mg
25 (13% yield). 100% pure (LR-LCMS, calc. 372.04, found 373.06).

Example 21**Inhibitory Activity on NECA-Induced Cyclic AMP Production in CHO.K1 Cells
Expressing Human Adenosine A2B Receptor.**

A Chinese hamster ovary (CHO.K1) cell stably transfected with human adenosine A2B receptor cDNA 4b was used in this assay. Cells were cultured under 5%CO₂/95% O₂ atmosphere at 37 °C in DMEM and D-MEM/F-12 (1:1 mixture) medium (Invitrogen, Grand Island, NY) with 10% fetal calf serum (Invitrogen, Grand Island, NY), 100 U/mL penicillin (Invitrogen, Grand Island, NY), 100 U/mL streptomycin (Invitrogen, Grand Island, NY), 1 mg/mL G418 (Invitrogen, Grand Island NY) and 0.2mg/mL Hygromycin B (Invitrogen, Carlsbad, CA). Experimental cultures were grown overnight as a monolayer in 384-well tissue culture plates (0.06ml/well - 7500 cells/well). Each well was washed once with 0.1 mL of Krebs buffer. To each well was added 50 uL of Krebs buffer containing 100 uM phosphodiesterase inhibitor Ro20-1724 (Roche), 100 nM NECA (Sigma-Aldrich, St. Louis, MO), 0.02% BSA Fraction V (Roche Biochemicals) , the test compound (appropriate concentration). The final concentration of DMSO was 1.1%. After incubation for 30-45 min, the wells were emptied and blotted on paper towel to remove residual solution. The HitHunter™ cAMP Assay Kit from DiscoverX for adherent cells (Fremont, CA) was used for lysing the cells and measuring cAMP concentrations. The compounds of Examples 1-20 exhibit IC₅₀ values of <5μM. The following table shows IC₅₀ values measured for some of the examples:

Example	A2B cAMP IC ₅₀ [μM]
2	0.41
5	0.14
12	0.55

Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

<u>Ingredients</u>	<u>Per tablet</u>	
Kernel:		
Compound of formula (I)	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxyde (yellow)	0.8 mg	1.6 mg
Titan dioxide	0.8 mg	1.6 mg

- 5 The active ingredient is sieved and mixed with microcrystalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidone in water. The granulate is mixed with sodium starch glycolate and magnesium stearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aqueous solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

<u>Ingredients</u>	<u>Per capsule</u>
Compound of formula (I)	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

- 5 The components are sieved and mixed and filled into capsules of size 2.

Example C

Injection solutions can have the following composition:

Compound of formula (I)	3.0 mg
Polyethylene Glycol 400	150.0 mg
Acetic Acid	q.s. ad pH 5.0
Water for injection solutions	ad 1.0 ml

- 10 The active ingredient is dissolved in a mixture of Polyethylene Glycol 400 and water for injection (part). The pH is adjusted to 5.0 by Acetic Acid. The volume is adjusted to 1.0 ml by addition of the residual amount of water. The solution is filtered, filled into vials using an appropriate overage and sterilized.

Example D

Soft gelatin capsules containing the following ingredients can be manufactured in a conventional manner:

Capsule contents

Compound of formula (I)	5.0 mg
Yellow wax	8.0 mg
Hydrogenated Soya bean oil	8.0 mg
Partially hydrogenated plant oils	34.0 mg
Soya bean oil	110.0 mg
Weight of capsule contents	165.0 mg

Gelatin capsule

Gelatin	75.0 mg
Glycerol 85 %	32.0 mg
Karion 83	8.0 mg (dry matter)
Titan dioxide	0.4 mg
Iron oxide yellow	1.1 mg

- 5 The active ingredient is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

Example E

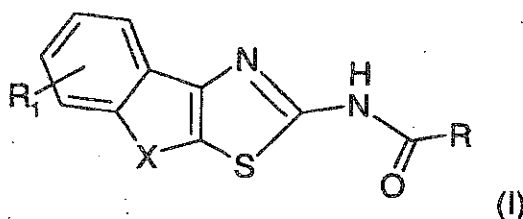
Sachets containing the following ingredients can be manufactured in a conventional manner:

Compound of formula (I)	50.0 mg
Lactose, fine powder	1015.0 mg
Microcrystalline cellulose (AVICEL PH 102)	1400.0 mg
Sodium carboxymethyl cellulose	14.0 mg
Polyvinylpyrrolidon K 30	10.0 mg
Magnesiumstearate	10.0 mg
Flavoring additives	1.0 mg

- 5 The active ingredient is mixed with lactose, microcrystalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidon in water. The granulate is mixed with magnesiumstearate and the flavouring additives and filled into sachets.

Claims:

1. Pharmaceutical compositions comprising a compound of formula (I)



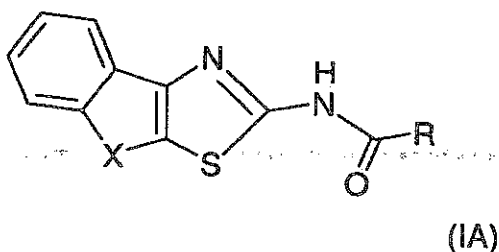
or pharmaceutically acceptable salts thereof, wherein

- 5 X is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-(\text{CH}_2)_3-$ and $\text{O}(\text{CH}_2)-$;

- R is a 5- or 6- membered saturated or unsaturated carbocyclic or heterocyclic ring which optionally may contain one or more hetero atoms and said rings being optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, lower-alkyl, acetamidomethyl, alkoxy, carbonyl
10 amidomethyl, a nitrile group, a sulfonamido group, alkylsulfonyl, alkoxy, benzyl, benzoyl, arylsulfonyl and acyl, which benzyl, benzoyl or arylsulfonyl is optionally substituted by halogen, trihalo-lower-alkyl, lower-alkyl, alkoxy, alkylsulfonyl or cyano;

- R₁ is selected from the group consisting of hydrogen, halogen, lower-alkyl, alkoxy
15 or a nitrile group.

2. Pharmaceutical compositions according to claim 1, wherein the compound of formula (I) is characterized by formula (IA)



or a pharmaceutically acceptable salt thereof, wherein

- 20 X is $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-(\text{CH}_2)_3-$ and $\text{O}(\text{CH}_2)-$;

R is a 5- or 6- membered saturated or unsaturated carbocyclic or heterocyclic ring which optionally may contain one or more hetero atoms and said rings being

optionally substituted with one or more substituents selected from the group consisting of halogen, lower-alkyl, a nitrile group, alkylsulfonyl, alkoxy and acyl.

3. Pharmaceutical compositions according to claim 1, wherein R is a 5- or 6-membered saturated or unsaturated carbocyclic or heterocyclic ring which
5 optionally may contain one or more hetero atoms and said rings being optionally substituted with one or more substituents selected from the group consisting of halogen, hydroxy, lower-alkyl, acetamidomethyl, alkoxycarbonyl amidomethyl, a nitrile group, a sulfonamido group, alkylsulfonyl, alkoxy, benzyl, benzoyl, arylsulfonyl and acyl, which benzyl, benzoyl or arylsulfonyl is optionally substituted
10 by halogen, trihalo-lower-alkyl, lower-alkyl, alkoxy, alkylsulfonyl or cyano.
4. Pharmaceutical compositions according to any of claims 1 - 3, wherein X is $-\text{CH}_2-$.
5. Pharmaceutical compositions according to any of claims 1 - 4, wherein R_1 is hydrogen, halogen or lower-alkoxy.
- 15 6. Pharmaceutical compositions according to any of claims 1 - 5, wherein R is phenyl or a heterocyclic ring selected from the group consisting of thienyl, pyridinyl, pyrazolyl, imidazolyl, furyl or piperidinyl, which phenyl or heterocyclic ring is optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, hydroxy, nitrile, lower-alkyl, sulfonamido, lower-alkyl-sulfonyl, lower-
20 alkoxy-carbonyl, lower-alkoxy- $\text{C}(\text{O})-\text{NH}-\text{CH}_2-$, benzyl which is optionally substituted with CF_3 , benzoyl which is optionally substituted with CF_3 , or phenylsulfonyl which is optionally substituted with CF_3 .
7. Pharmaceutical compositions according to any of claims 1 - 6, wherein R is a heterocyclic ring selected from the group consisting of thienyl, pyridinyl, pyrazolyl,
25 imidazolyl, furyl or piperidinyl, which heterocyclic ring is optionally substituted with 1 to 3 substituents selected from the group consisting of halogen, hydroxy, nitrile, lower-alkyl, sulfonamido, lower-alkyl-sulfonyl, lower-alkoxy-carbonyl, lower-alkoxy- $\text{C}(\text{O})-\text{NH}-\text{CH}_2-$, benzyl which is optionally substituted with CF_3 , benzoyl which is optionally substituted with CF_3 , or phenylsulfonyl which is optionally substituted
30 with CF_3 .
8. Compounds selected from the group consisting of:
N-(8H-Indeno[1,2-d]thiazol-2-yl)-benzamide,
4-Fluoro-N-(8H-indeno[1,2-d]thiazol-2-yl)-benzamide,
4-Cyano-N-(8H-indeno[1,2-d]thiazol-2-yl)-benzamide,

N-(8H-indeno[1,2-d]thiazol-2-yl)-4-methyl-benzamide,
Thiophene-2-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide,
N-(8H-indeno[1,2-d]thiazol-2-yl)nicotinamide,
N-(8H-indeno[1,2-d]thiazol-2-yl)isonicotinamide,
2-Methyl-2H-pyrazole-3-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide,
N-(6-chloro-8H-indeno[1,2-d]thiazol-2-yl)-isonicotinamide,
1H-Pyrazole-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide,
N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl)-isonicotinamide,
N-(4H-Chromeno[4,3-d]thiazol-2-yl)-isonicotinamide,
N-Naphtho[1,2-d]thiazol-2-yl-isonicotinamide, and
3-Methyl-3H-imidazole-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-yl)-amide
trifluoroacetate.

9. Compounds selected from the group consisting of:

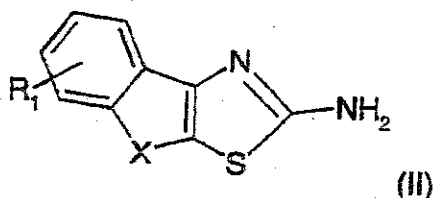
4-(8H-Indeno[1,2-d]thiazol-2-ylcarbonyl)-piperidine-1-carboxylic acid tert-butyl
ester,
3-(trifluoromethyl-benzoyl)-piperidine-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-
yl)-amide,
1-(3-trifluoromethyl-benzyl)-piperidine-4-carboxylic acid (8H-indeno[1,2-d]thiazol-2-
yl)-amide,
1-(3-Trifluoromethyl-benzenesulfonyl)-piperidine-4-carboxylic acid(8H-indeno[1,2-
d]thiazol-2-yl)-amide,
N-(8H-Indeno[1,2-d]thiazol-2-yl) 3-fluorobenzamide,
N-(8H-indeno[1,2-d]thiazol-2-yl) 3-hydroxybenzamide,
N-(8H-Indeno[1,2-d]thiazol-2-yl) 2-methylpent-5-enoylamide,
N-(8H-Indeno[1,2-d]thiazol-2-yl) 2-methylbutanoylamide,
N-(8H-Indeno[1,2-d]thiazol-2-yl) 5-methylsulfonylthiophene-2-carboxyamide,
N-(8H-Indeno[1,2-d]thiazol-2-yl) 2-furoylamide, and
N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) 4-hydroxynicotinamide.

10. Compounds selected from the group consisting of:

N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) (4-aminosulfonyl)benzamide,
N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) (4-t-butoxycarbonylmethyl)benzamide,
N-(6-Fluoro-8H-Indeno[1,2-d]thiazol-2-yl) thiophene-3-carboxyamide,
N-(4,5-Dihydro-naphtho[1,2-d]thiazol-2-yl) 4-hydroxynicotinamide,
N-(4,5-Dihydro-naphtho[1,2-d]thiazol-2-yl) thiophene-3-carboxyamide,
N-(4,5-Dihydro-7-methoxynaphtho[1,2-d]thiazol-2-yl) 4-hydroxynicotinamide,

- N-(4,5-Dihydro-7-methoxynaphtho[1,2-d]thiazol-2-yl) 5-methylsulfonylthiophene-2-carboxamide,
N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl) 4-hydroxynicotinamide,
N-(5,6-Dihydro-4H-3-thia-1-aza-benzo[e]azulen-2-yl) thiophene-3-carboxamide,
5 N-(8H-Indeno[1,2-d]thiazol-2-yl) 3-chloro-4-hydroxybenzamide, and
N-(8H-Indeno[1,2-d]thiazol-2-yl) (4-aminosulfonyl)benzamide.

11. A process for the manufacture of compounds according to any of claims 8 - 10, which process comprises reacting a compound of formula (II)



- 10 with a compound $R-C(O)Cl$, wherein R , R_1 and X are as defined in any of claims 8 to 10.
12. Compounds according to any of claims 8 - 10, when manufactured by a process according to claim 11.
13. Pharmaceutical compositions comprising a compound of formula (I) as
15 defined in any of claims 1 - 10 and a pharmaceutically acceptable carrier and/or adjuvant.
14. Compounds of formula (I) as defined in any of claims 1 - 10 for use as therapeutic active substances.
15. Compounds of formula (I) as defined in any of claims 1 - 10 for use as
20 therapeutic active substances for the treatment and/or prophylaxis of diseases which are mediated by antagonism of the adenosine A2B receptor.

16. The use of compounds of formula (I) as defined in any of claims 1 - 10 for the preparation of medicaments for the therapeutic and/or prophylactic treatment of diseases which are mediated by antagonism of the adenosine A2B receptor.
- 5 17. The use of compounds of formula (I) as defined in any of claims 1 - 10 for the preparation of medicaments for the therapeutic and/or prophylactic treatment of diabetes, diabetic retinopathy, asthma and diarrhea.