Title: 1,2,4-Triazin-3-yl-hydrazine or 5H-1,2,4-Triazino[5,6-b]indol-3-yl-hydrazine compounds as inhibitors of bace useful in the treatment of Alzheimer's disease.

Abstract: A compound of formula (I) wherein R1 is aryl and R2 is hydrogen; or R1 and R2 taken together form a group of formula (i) wherein R6 is alkyl or -alkyl-aryl; and R2 is hydrogen, halogen, alkyl, alkoxy or aryl; R1 is aryl, heteroaryl or -aryl-aryl; R4 is hydrogen, hydroxy or alkyl; and R3 is hydrogen or alkyl; or a pharmacologically acceptable salt thereof, is new, for use in therapy, e.g. of Alzheimer's disease.
Field of the Invention

This invention relates to triazine compounds and their therapeutic use.

Background to the Invention

Alzheimer's disease (AD) is the most common form of dementia among older people, and affects parts of the brain that control thought, memory and language. Susceptibility to Alzheimer's disease increases with age, but Alzheimer's disease is not a normal part of the ageing process.

Alzheimer's disease is associated with regions of accumulated proteins in the brain. These dense regions, termed "amyloid plaques" and "neurofibrillary tangles", contain β-amyloid precursor protein (β-APP). β-APP is degraded by β-amyloid converting enzyme (BACE, also known as β-secretase) to produce β-amyloid peptide Aβ 40/42, which accumulates in the plaques. Research has shown that the activity of BACE is an early step in the pathogenesis pathway common to all familial and sporadic forms of Alzheimer's disease; thus inhibitors of BACE may have utility in the treatment of this disease.

The following compounds are known:

N-(5-ethyl-5H-[1,2,4]triazino[5,6-b]indol-3-yl)-N'-[1-(1H-indol-3-yl)methylidene]-hydrazine;

N'-[1-(1H-indol-3-yl)methylidene]-N-[5-(2-methoxy-phenyl)-1,2,4-triazin-3-yl]-hydrazine;

N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-(2-propoxy-phenyl)methylidene]-hydrazine;

{4-[(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazonomethyl]-phenyl}-dimethyl-amine;

N-(5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-(4-bromo-phenyl)methylidene]-hydrazine;

N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-(4-fluoro-phenyl)methylidene]-hydrazine;

4-[(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazonomethyl]-phenol;

and

N-[1-(5-methyl-furan-2-yl)-ethylidene]-N'(5-methyl-5H-[1,2,4]triazino[5,6-b]indol-3-yl)-hydrazine.
Summary of the Invention

A first aspect of the invention is a compound of formula (I)

\[
\begin{array}{c}
\text{N} \\
\text{R}^1 \quad \text{N} \\
\text{R}^2 \\
\text{N} \\
\text{R}^3 \\
\end{array}
\]

wherein

R\(^1\) is aryl and R\(^2\) is hydrogen;
or R\(^1\) and R\(^2\) taken together form a group of formula (i)

\[
\begin{array}{c}
\text{R}^7 \\
\text{N} \\
\text{R}^6 \\
\end{array}
\]

wherein

R\(^8\) is alkyl or -alkyl-aryl; and
R\(^7\) is hydrogen, halogen, alkyl, alkoxy or aryl;
R\(^3\) is aryl, heteroaryl or -aryl-aryl;
R\(^4\) is hydrogen, hydroxy or alkyl; and
R\(^5\) is hydrogen or alkyl;
or a pharmaceutically acceptable salt thereof.

These compounds are new, for use in therapy. With the exception of the compounds identified in the Background section of the present specification, they are new per se.

Compounds of the invention may act as inhibitors of BACE and as a consequence may have utility in the treatment or prevention of diseases or conditions in which BACE is implicated. In particular, they may have utility in the treatment or prevention of a disease or condition associated with the deposition
and/or elevated levels of amyloid beta peptide (Aβ), for example Alzheimer's disease.

Another aspect of the invention is a pharmaceutical composition comprising a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

Description of Preferred Embodiments

For the present invention, certain compounds and combinations of substituents are preferred; in particular see the sub-claims.

When $R^1$ is aryl and $R^2$ is hydrogen, it is preferred that $R^1$ is optionally substituted phenyl, e.g. phenyl substituted with alkoxy.

Preferred compounds of the invention also include those wherein $R^1$ and $R^2$ taken together form a group of formula (i), i.e. compounds having the generic structure shown below:

In this case, $R^6$ is preferably methyl, ethyl, propyl or tolyl. $R^7$ is preferably hydrogen, methyl or methoxy.

$R^3$ is preferably indol-3-yl or biphenyl. Another preference is that $R^3$ is benzopyran-6-yl, phenyl or thiophenyl, any of which is optionally substituted with one or more substituents selected from alkyl, alkoxy, dialkylamino, halogen and hydroxy. $R^4$ is preferably hydrogen, hydroxy or methyl. $R^5$ is preferably hydrogen.

The term "alkyl" as used herein refers to a straight or branched chain alkyl moiety having from one to six carbon atoms. The term includes, for example, methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, penty1, hexyl and the like. "C_{1-8} alkyl" has the same meaning.
The term "alkoxy" as used herein refers to a straight or branched chain alkoxy group containing one to six carbon atoms. The term includes, for example, methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, hexoxy and the like. "C_{1-8} alkoxy" has the same meaning.

The term "halogen" as used herein refers to F, Cl, Br or I.

The term "aryl" as used herein refers to optionally substituted aromatic ring systems comprising six to ten ring atoms, and optionally substituted polycyclic ring systems having two or more cyclic rings at least one of which is aromatic. This term includes, for example, phenyl and naphthyl. The group may be optionally substituted with the substituents being the same or different in each occurrence and selected from alkyl, alkoxy, alkylamino, dialkylamino, halogen, hydroxy and the like.

The term "heteroaryl" as used herein refers to optionally substituted aromatic ring systems and optionally substituted heteropolycyclic ring systems having two or more rings, at least one of which is aromatic. The group comprises five to ten ring atoms, at least one of which is selected from O, N, P and S. The term includes, for example, furanyl, thiophenyl, pyridyl, indolyl, benzopyranyl, quinolyl and the like. The group may be optionally substituted, the substituents being the same or different in each occurrence and selected from alkyl, alkoxy, alkylamino, dialkylamino, halogen, hydroxy and the like.

Preferred compounds of the invention include:

N-((5-ethyl-5H-[1,2,4]triazino[5,6-b]indol-3-yl)-N'-[1-(1H-indol-3-yl)]-methylidene]-hydrazine;

N'-[1-(1H-indol-3-yl)]-methylidene]-N-[(5-methoxy-phenyl)-1,2,4-triazin-3-yl]-hydrazine;

N-((5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)]-N'-[1-(2-propoxy-phenyl)]-methylidene]-hydrazine;

{4-[(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)]-hydrazonomethyl]-phenyl]-dimethyl-amine;

N-((5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)]-N'-[1-(4-bromo-phenyl)]-methylidene]-hydrazine;
N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-(4-fluoro-phenyl)\text{-methylidene} hydrazine;
4-[(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)\text{-hydrazonomethyl}] phenol;
N-[1-(5-methyl-furan-2-yl)\text{-ethylidene}]-N'-(5-methyl-5H-1,2,4\text{triazino[5,6-b]}\text{indol-3-yl}) hydrazine;
N'-(1-(2,2-dimethyl-1-benzopyran-6-yl)\text{-methylidene}]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl) hydrazine;
N'-(1-(2,5-dichloro-phenyl)-methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl) hydrazine;
N'-(1-(2,6-dichloro-phenyl)-methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl) hydrazine;
N'-(1-(2-chloro-4,5-dimethoxy-phenyl)-methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl) hydrazine;
N'-(1-(3,5-dibromo-phenyl)-methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl) hydrazine;
N'-(1-(5-bromo-thiophen-2-yl)-methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl) hydrazine;
N'-(1-(4-methoxy-phenyl)-methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl) hydrazine;
N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-(1-thiophen-2-yl-methylidene) hydrazine;
N'-[1-(3-chloro-phenyl)-methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl) hydrazine;
N'-(1-(2-ethoxy-phenyl)-methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl) hydrazine;
2-[(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazonomethyl] phenol;
N'-[1-(2-hexyloxy-phenyl)-methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl) hydrazine;
N'-[1-biphenyl-2-yl-methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl) hydrazine;
N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-(1-phenyl-methylidene) hydrazine;
N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-(1-(2-methoxy-phenyl)-methylidene)-hydrazine;
N'-[1-(2-ethoxy-phenyl)-methylidene]-N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine;
N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-(2-propoxy-phenyl)-methylidene]-hydrazine;
2-[(5-propyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazonomethyl]-phenol
N'-[1-(2-methoxy-phenyl)-methylidene]-N-(5-propyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine;
N'-[1-(2-ethoxy-phenyl)-methylidene]-N-(5-propyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine;
N'-[1-(2-propoxy-phenyl)-methylidene]-N-(5-propyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine;
N-(5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-(2-methoxy-phenyl)-methylidene]-hydrazine;
N-(5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-(2-ethoxy-phenyl)-methylidene]-hydrazine;
N-(5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-(2-propoxy-phenyl)-methylidene]-hydrazine;
N-(5,8-dimethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-(2-propoxy-phenyl)-methylidene]-hydrazine;
N-(8-methoxy-5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-(2-propoxy-phenyl)-methylidene]-hydrazine;
N-(5-methyl-8-phenyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-(2-propoxy-phenyl)-methylidene]-hydrazine; and
2-propoxy-benzoic acid N'-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazide.
Alternative names for the first seven compounds listed above are, respectively:
N-(9-ethyl-9H-1,3,4,9-tetraazafluoren-2-yl)-N'(1H-indol-3-ylmethylene)-hydrazine;
N-(1H-indol-3-ylmethylene)-N'-(5-(2-methoxyphenyl)-1,2,4-triazin-3-yl)-hydrazine;
N-(9-methyl-9H-1,3,4,9-tetraazafluoren-2-yl)-N'-(2-propoxybenzylidene)-hydrazine;
5 {4-[(9-ethyl-9H-1,3,4,9-tetraazafluoren-2-yl)hydrazonomethyl]phenyl}dimethylamine;
N-(9-benzyl-9H-1,3,4,9-tetraazafluoren-2-yl)-N'-(4-bromobenzylidene)-hydrazine;
N-(9-ethyl-9H-1,3,4,9-tetraazafluoren-2-yl)-N'-(4-fluorobenzylidene)-hydrazine; and

Compounds of the invention may be chiral. They may be in the form of a single enantiomer or diastereomer, or a racemic mixture.

The compounds of the invention may be prepared in racemic form, or prepared in individual enantiomeric form by specific synthesis or resolution as will be appreciated in the art. The compounds may, for example, be resolved into their enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid followed by fractional crystallisation and regeneration of the free base. Alternatively, the enantiomers of the novel compounds may be separated by HPLC using a chiral column.

It will be appreciated that compounds of the invention may exist in various tautomeric forms. Compounds having $R^4$ is hydroxy (i.e. hydrazides) are examples of such compounds.

A compound of the invention may be in a protected form, for example protected amino or protected hydroxy form. The terms "protected amino" and "protected hydroxy" refer to amino and hydroxy group protected in a manner familiar to those skilled in the art. For example, an amino group can be protected by a benzylxycarbonyl, tert-butoxycarbonyl, acetyl or like group. A hydroxy group may be protected by an alkyl or like group.

Some compounds of the formula may exist in the form of solvates, for example hydrates, which also fall within the scope of the present invention.
Compounds of the invention may be in the form of pharmaceutically acceptable salts, for example, addition salts of inorganic or organic acids. Such inorganic acid addition salts include, for example, salts of hydrobromic acid, hydrochloric acid, nitric acid, phosphoric acid and sulphuric acid. Organic acid addition salts include, for example, salts of acetic acid, benzenesulphonic acid, benzoic acid, camphorsulphonic acid, citric acid, 2-(4-chlorophenoxy)-2-methylpropionic acid, 1,2-ethanedisulphonic acid, ethanesulphonic acid, ethylenediaminetetraacetic acid (EDTA), fumaric acid, glucoheptonic acid, gluconic acid, glutamic acid, N-glycolylarsanilic acid, 4-hexyloresorcinol, hippuric acid, 2-(4-hydroxybenzoyl)benzoic acid, 1-hydroxy-2-naphthoic acid, 3-hydroxy-2-naphthoic acid, 2-hydroxyethanesulphonic acid, lactobionic acid, n-dodecyl sulphuric acid, maleic acid, malic acid, mandelic acid, methanesulphonic acid, methyl sulphuric acid, mucic acid, 2-naphthalenesulphonic acid, pamoic acid, pantothenic acid, phosphanilic acid ([(4-aminophenyl)phosphonic acid], picric acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric acid, terephthalic acid, p-toluenesulphonic acid, 10-undecenoic acid and the like.

Salts may also be formed with inorganic bases. Such inorganic base salts include, for example, salts of aluminium, bismuth, calcium, lithium, magnesium, potassium, sodium, zinc and the like. Organic base salts include, for example, salts of N,N'-dibenzylethlenediamine, choline (as a counterion), diethanolamine, ethanolamine, ethylenediamine, N,N'-bis(dehydroabietyl)-ethylenediamine, N-methylglucamine, procaine, tris(hydroxymethyl)aminomethane ("TRIS") and the like.

It will be appreciated that such salts, provided that they are pharmaceutically acceptable, may be used in therapy. Such salts may be prepared by reacting the compound with a suitable acid or base in a conventional manner.

A compound of the invention may be prepared by any suitable method known in the art and/or by the following processes (in which CDI and MCPAA are abbreviations for, respectively carbonyldiimidazole and m-chloroperbenzoic acid):
Scheme 2

In Scheme 2, the product of the step having R^4 is hydroxy is represented as a hydrazide, a compound capable of tautomeration.

It will be understood that the processes detailed above are solely for the purpose of illustrating the invention and should be not construed as limiting. A process utilising similar or analogous reagents and/or conditions known to one skilled in the art may also be used to obtain a compound of the invention.

Any mixtures of final products or intermediates obtained can be separated on the basis of the physico-chemical differences of the constituents, in a known manner, into the pure final products or intermediates, for example by chromatography, distillation, fractional crystallisation, or by the formation of a salt if appropriate or possible under the circumstances.
The activity and selectivity of the compounds may be determined by any suitable assay known in the art.

The compounds of the invention may be used in the treatment of numerous ailments, conditions and diseases including, but not limited thereto, Alzheimer's disease.

In therapeutic use, the active compound may be administered orally, intravenously, rectally, parenterally, by inhalation (pulmonary delivery), topically, ocularly, nasally, or to the buccal cavity. Oral administration is preferred. Thus, the therapeutic compositions of the present invention may take the form of any of the known pharmaceutical compositions for such methods of administration. The compositions may be formulated in a manner known to those skilled in the art so as to give a controlled release, for example rapid release or sustained release, of the compounds of the present invention. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art. The compositions of the invention may contain 0.1-99% by weight of active compound. The compositions of the invention are generally prepared in unit dosage form. Preferably, a unit dose comprises the active ingredient in an amount of 1-500 mg. The excipients used in the preparation of these compositions are the excipients known in the art.

Appropriate dosage levels may be determined by any suitable method known to one skilled in the art. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the disease undergoing treatment.

Compositions for oral administration are preferred compositions of the invention and there are known pharmaceutical forms for such administration, for example tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions, and such
compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, for example starch gelatin, acacia, microcrystalline cellulose or polyvinyl pyrrolidone; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glycercyl monostearate or glycercyl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long-chain aliphatic alcohols, for example heptadecaethylenoxyctanol, or condensation products of ethylene oxide with partial esters derived from fatty acids, for example polyoxyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl or n-propyl p-
hydroxybenzoate, one or more colouring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable sweetening, flavoring and colouring agents may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin, or mixtures of these. Suitable emulsifying agents may be naturally occurring gums, for example gum acacia or gum tragacanth, naturally occurring phosphatides, for example soya bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be in a sterile injectable solution or suspension in a non-toxic
parenterally acceptable diluent or solvent, for example as a solution in 1,3-
butanediol. Among the acceptable vehicles and solvents that may be employed
are water, Ringer’s solution and isotonic sodium chloride solution. In addition,
sterile, fixed oils are conventionally employed as a solvent or suspending
medium. For this purpose, any bland fixed oil may be employed including
synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid, find
use in the preparation of injectables.

The compounds of the invention may also be administered in the form of
suppositories for rectal administration of the drug. These compositions can be
prepared by mixing the drug with a suitable non-irritating excipient which is solid
at ordinary temperatures but liquid at the rectal temperature and will therefore
melt in the rectum to release the drug. Such materials are cocoa butter and
polyethylene glycols.

Compositions for topical administration are also suitable for use in the
invention. The pharmaceutically active compound may be dispersed in a
pharmaceutically acceptable cream, ointment or gel. A suitable cream may be
prepared by incorporating the active compound in a topical vehicle such as light
liquid paraffin, dispersed in a aqueous medium using surfactants. An ointment
may be prepared by mixing the active compound with a topical vehicle such as
a mineral oil or wax. A gel may be prepared by mixing the active compound with
a topical vehicle comprising a gelling agent. Topically administrable
compositions may also comprise a matrix in which the pharmaceutically active
compounds of the present invention are dispersed so that the compounds are
held in contact with the skin in order to administer the compounds transdermally.

The following Examples illustrate the invention:

In the Examples, analytical hplc was carried out using a Waters 2525 LC
pump and Waters Xterra C18 column (5μm, 50mm x 4.6mm). Mobile phases A
(0.1% formic acid in 10mM aqueous ammonium acetate) and B (0.1% formic acid
in acetonitrile) were used. Elution with 5% B was held for 1 minute, raised to
95% B over 4.5 minutes and held for 1 minute at a flow rate of 2ml/minute.
Photodiode array detection was by a Waters 996, range 210-350nm UV. The
mass spectrometer was a Micromass ZQ operating in electrospray ionisation mode.

**Intermediate 1: 5-methyl-4,5-dihydro-1,2,4-triazino[5,6-b]indole-3-thione**


1-Methyl isatin (1.0 g, 6.2 mmol), thiosemicarbazide (0.565 g, 6.2 mmol) and potassium carbonate (1.28 g, 9.26 mmol) were suspended in water (40 ml) then brought to reflux. Reflux was maintained for 16 hours. The mixture was then cooled to room temperature, filtered and acidified with glacial acetic acid. The resulting yellow precipitate was filtered and dried under vacuum to give the product, 1.175 g (87.6%), hplc/ms (positive ion) Rt 2.49 min, m/z 217 (M+H+).

**Intermediate 2: (5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine**


A solution of 5-methyl-4,5-dihydro-1,2,4-triazino[5,6-b]indole-3-thione (Intermediate 1, 0.4 g, 1.85 mmol) in hydrazine hydrate (4 ml) was refluxed for 4 hours. On cooling, the yellow precipitate was filtered, washed with water (10 ml), then methanol (2 ml) and dried under vacuum to give the product, 0.298 g (75.1%), NMR (d6-DMSO) d (300MHz): 3.7 (s, 3H); 4.4 (bs, 2H); 7.35 (t, 1H); 7.55 (m, 2H); 8.1 (d, 1H); 8.7 (bs, 1H).

**Intermediate 3: 4,5-dihydro-1,2,4-triazino[5,6-b]indole-3-thione**

Isatin (20g, 0.135 mol), thiosemicarbazide (12.39g, 0.135 mol) and potassium carbonate (28.18g, 0.203 mol) were stirred in water (500ml) and heated to reflux under an argon atmosphere. Heating was maintained for 17 hour then the reaction mixture cooled. The orange precipitate was collected by filtration, washed with water (100ml) and dried under vacuum to give the product, 18.7g (69%), m/z (positive ion) 203 (M+H+).

**Intermediate 4: (5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine**

3-Ethenesulphonyl-5-ethyl-5H-1,2,4-triazino[5,6-b]indole (150mg, 0.52 mmol) in industrial methylated spirit (0.5ml) was added dropwise to a stirred solution of hydrazine hydrate (76μl, 1.54 mmol) in industrial methylated spirit (1.5ml). The reaction mixture was heated at 85°C for 3 hours, cooled, filtered and the solid washed with industrial methylated spirit (1ml). The solid was dried
under vacuum to give the title compound, 75mg (61%), m/z (positive ion) 229 (M+H+).

The 3-ethanesulphonyl-5-ethyl-5H-1,2,4-triazino[5,6-b]indole used as starting material was prepared as follows:

A mixture of 4,5-dihydro-1,2,4-triazino[5,6-b]indole-3-thione (Intermediate 3, 3.5g, 17.4 mmol) and potassium carbonate (12g, 86.8 mmol) was stirred in dimethyl formamide (50ml) for 15 min. Ethyl iodide (4.18ml, 52 mmol) was added and the mixture stirred at room temperature overnight. The reaction mixture was poured into water (200ml) and extracted with ethyl acetate (2x 100ml). The combined organic fractions were washed with water (2x 100ml), dried over magnesium sulphate, filtered and evaporated. Crystallisation of the residue from ethyl acetate/hexane gave 2.8g (62%) of 5-ethyl-3-ethylsulfonyl-5H-1,2,4-triazino[5,6-b]indole. The product (0.4g, 1.55 mmol) was dissolved in dry dichloromethane (5ml) and treated with 70% meta chloro perbenzoic acid (0.55g, 3.18 mmol). The mixture was stirred at room temperature overnight then filtered. The filtrate was washed with aqueous sodium bicarbonate (2x 20ml), aqueous sodium sulphite (2x 20ml), dried over magnesium sulphate, filtered and evaporated. The residue was crystallised from ethyl acetate/hexane to give 3-ethanesulphonyl-5-ethyl-5H-1,2,4-triazino[5,6-b]indole (227mg, 51%), m/z (positive ion) 291 (M+H+).

**Intermediate 5: (5-propyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine**

In a manner analogous to that of Intermediate 4, using propyl bromide in place of ethyl iodide, was prepared the title compound, m/z (positive ion) 243 (M+H+).

**Intermediate 6: (5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine**

In a manner analogous to that of Intermediate 4, using benzyl bromide in place of ethyl iodide, was prepared the title compound, m/z (positive ion) 291 (M+H+).

**Intermediate 7: (5,8-dimethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine**

3-Methanesulphonyl-5,8-dimethyl-5H-1,2,4-triazino[5,6-b]indole (73mg, 0.26 mmol) in industrial methylated spirit (0.5ml) was added to hydrazine hydrate (40μl, 0.79 mmol) in industrial methylated spirit (1ml). The reaction mixture was
heated at 85°C for 3 hours, cooled, filtered and the solid washed with industrial methylated spirit (1ml). The solid was dried under vacuum to give the title compound, 27mg (46%), hplc/ms RT 1.68 min, m/z (positive ion) 229 (M+H+).

The 3-methanesulphonyl-5,8-dimethyl-5H-1,2,4-triazino[5,6-b]indole used as starting material was prepared as follows:

5-methyl isatin (0.5g, 3.1 mmol), thiosemicarbazide (0.28g, 3.1 mmol) and potassium carbonate (0.64g, 4.63 mmol) were stirred in water (5ml) and heated to reflux under an argon atmosphere. Heating was maintained for 17 hour then the reaction mixture cooled. The orange precipitate was collected by filtration, washed with hexane (5ml) and dried under vacuum to give 8-methyl-4,5-dihydro-1,2,4-triazino[5,6-b]indole-3-thione, 278mg (42%), hplc/ms RT 1.13 min, m/z (positive ion) 217 (M+H+).

The product (278mg, 1.28 mmol) was stirred with potassium carbonate (890mg, 6.4 mmol) in dimethylformamide (10ml) for 15 min, then treated with methyl iodide (0.24ml, 3.88 mmol). The reaction mixture was stirred at room temperature overnight then poured into water (40ml). The precipitate was isolated by filtration, washed with water (5ml) and dried under vacuum to give 5,8-dimethyl-3-methylsulphonyl-5H-1,2,4-triazino[5,6-b]indole, 130mg (42%), hplc/ms RT 2.44 min, m/z (positive ion) 245 (M+H+).

5,8-dimethyl-3-methylsulphonyl-5H-1,2,4-triazino[5,6-b]indole (130mg, 0.53 mmol) was dissolved in dichloromethane (5ml) and treated with 70% meta chloro perbenzoic acid (270mg, 1.09 mmol). The mixture was stirred at room temperature overnight, filtered and the filtrate washed with 5% aqueous sodium bicarbonate (5ml) and 5% aqueous sodium sulphite (5ml). The organic phase was dried and evaporated to give 3-methanesulphonyl-5,8-dimethyl-5H-1,2,4-triazino[5,6-b]indole, 73mg (50%), hplc/ms RT 1.88 min, m/z (positive ion) 277 (M+H+).

**Intermediate 8:** (8-methoxy-5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

In a manner analogous to that of Intermediate 7, starting from 5-methoxy isatin, was prepared the title compound, hplc/ms RT 1.55 min, m/z (positive ion) 244 (M+).
Intermediate 9: (5-methyl-8-phenyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

In a manner analogous to that of Intermediate 7, starting from 5-phenyl isatin, was prepared the title compound, m/z (positive ion) 291 (M+H+).

The 5-phenyl isatin used as starting material was prepared as follows:

A mixture of 5-bromo isatin (2g, 8.85 mmol), phenyl boronic acid (1.13g, 9.29 mmol), tetrakis triphenylphosphine palladium (307mg, 0.27 mmol) and sodium carbonate (3.02g, 28 mmol) in diglyme (85ml) under argon atmosphere was heated at reflux overnight. 2M hydrochloric acid (80ml) was added and the resulting precipitate removed by filtration. The filtrate was allowed to stand at room temperature overnight and then filtered. The solid was washed with water and dried under vacuum to give 212mg (11%) of 5-phenyl isatin as a red solid, hplc/ms RT 2.16 min, m/z (positive ion) 223 (M+).

Example 1: N-(5-ethyl-5H-[1,2,4]triazino[5,6-b]indol-3-yl)-N'-[1-(1H-indol-3-yl)-methylidene]-hydrazine

This compound is commercially available.

Example 2: N'-[1-(1H-indol-3-yl)-methylidene]-N-[5-(2-methoxy-phenyl)-1,2,4-triazin-3-yl]-hydrazine

This compound is commercially available.

Example 3: N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'[1-(2-propoxy-phenyl)-methylidene]-hydrazine

This compound is commercially available.

Example 4: {4-[(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)]-hydrazonomethyl-phenyl} dimethyl-amine

This compound is commercially available.

Example 5: N-(5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'[1-(4-bromo-phenyl)-methylidene]-hydrazine

This compound is commercially available.

Example 6: N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'[1-(4-fluoro-phenyl)-methylidene]-hydrazine

This compound is commercially available.
Example 7: 4-[[5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl]-hydrazonomethyl]-phenol

This compound is commercially available.

Example 8: N-[1-(5-methyl-furan-2-yl)-ethylidene]-N’-(5-methyl-5H-[1,2,4]triazino[5,6-b]indol-3-yl)-hydrazine

This compound is commercially available.

Example 9: N’-[1-(2,2-dimethyl-1-benzopyran-6-yl)-methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

A mixture of (5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine (Intermediate 2, 10mg, 0.047 mmol) and 2,2-dimethyl-1-benzopyran-6-carbaldehyde (9mg, 0.047 mmol) in dimethylformamide (1ml) was heated in a sealed tube under microwave conditions at 180°C for 10 min. After cooling, water (1ml) was added with stirring and the suspension filtered. The solid was washed with water (1ml) and dried under vacuum at 40°C to give 11.6mg (60%) of the title compound, hplc/ms RT 3.88 min, m/z 387 (M+H+).

Example 10: N’-[1-(2,5-dichloro-phenyl)-methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

In a manner analogous to that of Example 9, using 2,5-dichlorobenzaldehyde in place of 2,2-dimethyl-1-benzopyran-6-carbaldehyde, was prepared 11.9mg (68%) of the title compound, hplc/ms RT 4.16 min, m/z 371 (M+H+).

Example 11: N’-[1-(2,6-dichloro-phenyl)-methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

In a manner analogous to that of Example 9, using 2,6-dichlorobenzaldehyde in place of 2,2-dimethyl-1-benzopyran-6-carbaldehyde, was prepared 9.7mg (56%) of the title compound, hplc/ms RT 3.94 min, m/z 371 (M+H+).

Example 12: N’-[1-(2-chloro-4,5-dimethoxy-phenyl)-methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

In a manner analogous to that of Example 9, using 2-chloro 4,5-dimethoxy-benzaldehyde in place of 2,2-dimethyl-1-benzopyran-6-carbaldehyde,
was prepared 9.9mg (53%) of the title compound, hplc/ms RT 3.66 min, m/z 397 (M+H+).

Example 13: N'-[1-(3,5-dibromo-phenyl)-ethyldiene]-5-ethyl-H-1,2,4-triazino[5,6-b]indol-3-yl-hydrazine

In a manner analogous to that of Example 9, using 3,5-dibromo-enzaldehyde in place of 2,2-dimethyl-1-benzopyran-6-carbaldehyde, was prepared 10mg (47%) of the title compound, hplc/ms RT 4.32 min, m/z 459 (M+H+).

Example 14: N'-[1-(5-bromo-thiophen-2-yl)-ethyldiene]-(5-ethyl-H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

In a manner analogous to that of Example 9, using 5-bromo-thiophene 2-carbaldehyde in place of 2,2-dimethyl-1-benzopyran-6-carbaldehyde, was prepared 12.4mg (68%) of the title compound, hplc/ms RT 3.76 min, m/z 387 (M+H+).

Example 15: N'-[1-(4-methoxy-phenyl)-methylidene]-(5-ethyl-H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

In a manner analogous to that of Example 9, using 4-methoxy-benzaldehyde in place of 2,2-dimethyl-1-benzopyran-6-carbaldehyde, was prepared 12mg (77%) of the title compound, hplc/ms RT 3.36 min, m/z 333 (M+H+).

Example 16: N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-thiophen-2-yl-methylidene]-hydrazine

In a manner analogous to that of Example 9, using thiophene-2-carbaldehyde in place of 2,2-dimethyl-1-benzopyran-6-carbaldehyde, was prepared 10.4mg (72%) of the title compound, hplc/ms RT 3.12 min, m/z 309 (M+H+).

Example 17: N'-[1-(3-chloro-phenyl)-methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

In a manner analogous to that of Example 9, using 3-chloro-benzaldehyde in place of 2,2-dimethyl-1-benzopyran-6-carbaldehyde, was prepared 10.3mg (65%) of the title compound, hplc/ms RT 3.76 min, m/z 337 (M+H+).
Example 18: N'-[1-(2-ethoxy-phenyl)-methylene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

In a manner analogous to that of Example 9, using 2-ethoxy-benzaldehyde in place of 2,2-dimethyl-1-benzopyran-6-carbaldehyde, was prepared 12.4mg (68%) of the title compound, hplc/ms RT 3.5 min, m/z 347 (M+H+).

Example 19: 2-[(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazonomethyl]-phenol

In a manner analogous to that of Example 9, using 2-hydroxy-benzaldehyde in place of 2,2-dimethyl-1-benzopyran-6-carbaldehyde, was prepared 10.5mg (70%) of the title compound, hplc/ms RT 3.8 min, m/z 319 (M+H+).

Example 20: N'-[1-(2-hexyloxy-phenyl)-methylene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

In a manner analogous to that of Example 9, using 2-hexyloxy-benzaldehyde in place of 2,2-dimethyl-1-benzopyran-6-carbaldehyde, was prepared 11.3mg (60%) of the title compound, hplc/ms RT 4.5 min, m/z 403 (M+H+).

Example 21: N'-[1-biphenyl-2-yl-methylene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

In a manner analogous to that of Example 9, using biphenyl-2-carbaldehyde in place of 2,2-dimethyl-1-benzopyran-6-carbaldehyde, was prepared 2mg (10%) of the title compound, hplc/ms RT 3.96 min, m/z 379 (M+H+).

Example 22: N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-phenyl-methylidene]-hydrazine

A mixture of (5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine (Intermediate 4, 100mg, 0.44 mmol) and benzaldehyde (45μl, 0.44 mmol) in dimethylformamide (3ml) was heated in a sealed vessel at 120°C for 2 hours then cooled to room temperature overnight. The precipitate was filtered and the
solid washed with hexane (2ml) and dried under vacuum to give 100mg (72%) of the title compound, m/z (positive ion) 317 (M+H+).

**Example 23:** N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-(2-methoxy-phenyl)-methylidene]-hydrazine

In a manner analogous to that of Example 22, using 2-methoxy-benzaldehyde in place of benzaldehyde, was prepared 42mg (28%) of the title compound, m/z (positive ion) 347 (M+H+).

**Example 24:** N'-[1-(2-ethoxy-phenyl)-methylidene]-N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

In a manner analogous to that of Example 22, using 2-ethoxy-benzaldehyde in place of benzaldehyde, was prepared 82mg (52%) of the title compound, m/z (positive ion) 361 (M+H+).

**Example 25:** N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-(2-propoxy-phenyl)-methylidene]-hydrazine

In a manner analogous to that of Example 22, using 2-propoxy-benzaldehyde in place of benzaldehyde, was prepared 48mg (29%) of the title compound, m/z (positive ion) 375 (M+H+).

**Example 26:** 2-[[5-propyl-5H-1,2,4-triazino[5,6-b]indol-3-yl]-hydrazonomethyl]-phenol

A mixture of (5-propyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine (Intermediate 5, 50mg, 0.21 mmol) and 2-hydroxy-benzaldehyde (22μl, 0.21 mmol) in dimethylformamide (1.5ml) was heated in a sealed vessel at 120°C for 2 hours then cooled to room temperature overnight. The precipitate was filtered and the solid washed with hexane (2ml) and dried under vacuum to give 45mg (62%) of the title compound, m/z (positive ion) 347 (M+H+).

**Example 27:** N'-[1-(2-methoxy-phenyl)-methylidene]-N-(5-propyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

In a manner analogous to that of Example 26, using 2-methoxy-benzaldehyde in place of 2-hydroxy-benzaldehyde, was prepared 40mg (53%) of the title compound, m/z (positive ion) 361 (M+H+).
Example 28: N’-[1-(2-ethoxy-phenyl)-methylidene]-N-(5-propyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

In a manner analogous to that of Example 26, using 2-ethoxy-benzaldehyde in place of 2-hydroxy-benzaldehyde, was prepared 43mg (55%) of the title compound, m/z (positive ion) 375 (M+H+).

Example 29: N’-[1-(2-propoxy-phenyl)-methylidene]-N-(5-propyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine

In a manner analogous to that of Example 26, using 2-propoxy-benzaldehyde in place of 2-hydroxy-benzaldehyde, was prepared 49mg (60%) of the title compound, m/z (positive ion) 389 (M+H+).

Example 30: N-(5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N’-[1-(2-methoxy-phenyl)-methylidene]-hydrazine

A mixture of (5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine (Intermediate 6, 50mg, 0.17 mmol) and 2-methoxy-benzaldehyde (23μl, 0.17 mmol) in dimethylformamide (1.5ml) was heated in a sealed vessel at 120°C for 2 hours then cooled to room temperature overnight. The precipitate was filtered and the solid washed with hexane (2ml) and dried under vacuum to give 50mg (72%) of the title compound, m/z (positive ion) 409 (M+H+).

Example 31: N-(5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N’-[1-(2-ethoxy-phenyl)-methylidene]-hydrazine

In a manner analogous to that of Example 30, using 2-ethoxy-benzaldehyde in place of 2-methoxy-benzaldehyde, was prepared 32mg (45%) of the title compound, m/z (positive ion) 423 (M+H+).

Example 32: N-(5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N’-[1-(2-propoxy-phenyl)-methylidene]-hydrazine

In a manner analogous to that of Example 30, using 2-propoxy-benzaldehyde in place of 2-methoxy-benzaldehyde, was prepared 37mg (50%) of the title compound, m/z (positive ion) 437 (M+H+).

Example 33: N-(5,8-dimethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N’-[1-(2-propoxy-phenyl)-methylidene]-hydrazine
A mixture of (5,8-dimethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine (Intermediate 7, 27mg, 0.12 mmol) and 2-propoxy-benzaldehyde (19mg, 0.12 mmol) in dimethylformamide (3ml) was heated in a sealed vessel at 120°C for 2 hours then cooled to room temperature overnight. The solution was treated with 3-(4-(hydrazinosulphonyl) phenyl)propionyl AM resin (35mg, 0.05 mmol), heated at 50°C for 2 hours, filtered and evaporated to dryness. The residue was purified by preparative hplc to give 10mg (22%) of the title compound, m/z (positive ion) 375 (M+H+).

Example 34: N-(8-methoxy-5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N’-[1-(2-propoxy-phenyl)-methylidene]-hydrazine

A mixture of (8-methoxy-5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine (Intermediate 8, 14mg, 0.057 mmol) and 2-propoxy-benzaldehyde (9.5mg, 0.06 mmol) in dimethylformamide (3ml) was heated in a sealed vessel at 120°C for 2 hours then cooled to room temperature overnight. The solution was treated with 3-(4-(hydrazinosulphonyl) phenyl)propionyl AM resin (35mg, 0.05 mmol), heated at 50°C for 2 hours, filtered and evaporated to dryness. The residue was purified by preparative hplc to give 8mg (36%) of the title compound, m/z (positive ion) 391 (M+H+).

Example 35: N-(5-methyl-8-phenyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N’-[1-(2-propoxy-phenyl)-methylidene]-hydrazine

A mixture of (5-methyl-8-phenyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine (Intermediate 9, 44mg, 0.15 mmol) and 2-propoxy-benzaldehyde (24mg, 0.15 mmol) in dimethylformamide (2.3ml) was heated in a sealed vessel at 120°C for 2 hours then cooled to room temperature overnight. The precipitate was filtered and the solid washed with hexane (2ml) and dried under vacuum to give 27mg (41%) of the title compound, m/z (positive ion) 437 (M+H+).

Example 36: 2-propoxy-benzoic acid N’-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazide

A solution of 2-propoxy-benzoic acid (252mg, 1.4 mmol) in dimethylformamide (5ml) was treated with carbonyl diimidazole (249mg, 1.54 mmol) and warmed to 80°C for 10 minutes. The solution was cooled to 40°C and treated with (5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazine (Intermediate
2, 300mg, 1.4 mmol). The mixture was heated at 80°C for 10 minutes then poured into water (120ml) and filtered. The solid was washed successively with 50% water/isopropanol (5ml), isopropanol (5ml), 50% isopropanol/hexane (5ml) and hexane (5ml). Crystallisation of the solid from ethyl acetate gave 100mg (19%) of the title compound, m/z (positive ion) 377 (M+H+).

**Example 37: Activity Assay**

The compounds of Examples 3, 8, 21, 27, 31, 35 and 36 were tested for their inhibitory activity towards BACE.

All enzyme assays were performed at 20°C on an AlphaFusion (Packard Instruments) using 384 well plates (Greiner Bio-One Ltd). The assay volume was 30 µl. Inhibitors were dissolved in dimethyl sulphoxide (DMSO) and added into a well with 50 mM sodium acetate buffer pH 4.5 and 10 µM EDANS-EVNLDAEFK-DABCYL peptide substrate. The DMSO concentration was set at 10% in the assay.

The reaction was started with the addition of 1 µg/ml recombinant human soluble BACE-1. After 3 hours the fluorescence increase was measured in the plate reader at 365ex/485em. The EDANS-DABCYL peptide substrate becomes slightly fluorescent upon enzymatic cleavage due to disruption of the resonance energy transfer between the EDANS donor and DABCYL quenching acceptor in the intact substrate.
The activities (IC$_{50}$ values in μM) of certain compounds of the Examples are tabulated below. The results demonstrate the desirability of compounds of the invention.

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC$_{50}$ (μM)</th>
</tr>
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<tbody>
<tr>
<td>3</td>
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</tr>
<tr>
<td>8</td>
<td>44.7</td>
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<td>36</td>
<td>16.6</td>
</tr>
</tbody>
</table>
CLAIMS

1. A compound for use in therapy, wherein the compound is of formula (I)

\[
\begin{align*}
&\text{R}^2 &\text{N} &\text{N} \\
&\text{R}^1 &\text{N} &\text{N} &\text{N} &\text{R}^3 \\
&\text{R}^4 &\text{R}^5 \\
\end{align*}
\]

(1)

wherein

- \(\text{R}^1\) is aryl and \(\text{R}^2\) is hydrogen;
- or \(\text{R}^1\) and \(\text{R}^2\) taken together form a group of formula (i)

\[
\begin{align*}
&\text{R}^7 \\
&\text{R}^8 \\
\end{align*}
\]

(i)

wherein

- \(\text{R}^8\) is alkyl or -alkyl-aryl; and
- \(\text{R}^7\) is hydrogen, halogen, alkyl, alkoxy or aryl;
- \(\text{R}^3\) is aryl, heteroaryl or -aryl-aryl;
- \(\text{R}^4\) is hydrogen, hydroxy or alkyl; and
- \(\text{R}^5\) is hydrogen or alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound as defined in claim 1, independent of use, with the proviso that the compound is not a compound selected from:

- \(\text{N}-(5\text{-ethyl}-5\text{H}-[1,2,4]\text{triazino}[5,6-b]\text{indol-3-yl})-\text{N'}-[1-(1\text{H}\text{-indol-3-yl})\text{-methylidene}]\text{-hydrazine}\

- \(\text{N'}-[1-(1\text{H}\text{-indol-3-yl})\text{-methylidene}]\text{-N-[5-(2\text{-methoxy-phenyl})-1,2,4}\text{-triazin-3-yl}]\text{-hydrazine}\

N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'[1-(2-propoxy-phenyl)-methylidene]-hydrazine;

{4-[(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazonomethyl]-phenyl}dimethyl-amine;

N-(5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'[1-(4-bromo-phenyl)-methylidene]-hydrazine;

N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'[1-(4-fluoro-phenyl)-methylidene]-hydrazine;

4-[(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazonomethyl]-phenol;

and

N-[1-(5-methyl-furan-2-yl)-ethylidene]-N'-(5-methyl-5H-[1,2,4]triazino[5,6-b]indol-3-yl)-hydrazine.

3. A compound according to claim 1 or claim 2, wherein R¹ and R² taken together form a group of formula (i).

4. A compound according to claim 3, wherein R⁸ is methyl, ethyl, propyl or tolyl.

5. A compound according to claim 3 or claim 4, wherein R⁷ is hydrogen, methyl or methoxy.

6. A compound according to claim 1 or claim 2, wherein R¹ is optionally substituted phenyl.

7. A compound according to claim 6, wherein R¹ is phenyl substituted with alkoxy.

8. A compound according to any preceding claim, wherein R³ is indol-3-yl or biphenyl.

9. A compound according to any of claims 1 to 7, wherein R³ is benzopyran-6-yl, phenyl or thiophenyl, any of which is optionally substituted with one or more substituents selected from alkyl, alkoxy, dialkylamino, halogen and hydroxy.

10. A compound according to any preceding claim, wherein R⁴ is hydrogen, hydroxy or methyl.

11. A compound according to any preceding claim, wherein R⁵ is hydrogen.

12. A compound according to claim 1, selected from
N-(5-ethyl-5H-[1,2,4]triazino[5,6-b]indol-3-yl)-N'-[1-(1H-indol-3-yl)-methylidene]hydrazine;
N'-[1-(1H-indol-3-yl)methylidene]-N-[5-(2-methoxyphenyl)-1,2,4-triazin-3-yl]hydrazine;
N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-(2-propoxyphenyl)-methylidene]hydrazine;
{4-[(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazonomethyl]phenyl}dimethylamine;
N-(5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-(4-bromophenyl)-methylidene]hydrazine;
N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-(4-fluorophenyl)-methylidene]hydrazine;
4-[(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazonomethyl]phenol; and
N-[1-(5-methyl-furan-2-yl)-ethylidene]-N'-(5-methyl-5H-[1,2,4]triazino[5,6-b]indol-3-yl)-hydrazine.

13. A compound according to claim 1 or claim 2, selected from:
N'-[1-(2,2-dimethyl-1-benzopyran-6-yl)methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazine;
N'-[1-(2,5-dichlorophenyl)methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazine;
N'-[1-(2,6-dichlorophenyl)methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazine;
N'-[1-(2-chloro-4,5-dimethoxyphenyl)methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazine;
N'-[1-(3,5-dibromophenyl)methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazine;
N'-[1-(5-bromothiophen-2-yl)methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazine;
N'-[1-(4-methoxyphenyl)methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazine;
N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'[1-thiophen-2-yl-methylidene]hydrazine;
N'-[1-(3-chlorophenyl)methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazine;
N'-[1-(2-ethoxyphenyl)methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazine;
2-[(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazonomethyl]phenol;
N'-[1-(2-hexyloxyphenyl)methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazine;
N'-[1-(biphenyl-2-yl)methylidene]-N-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazine;
N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-[1-phenylmethylidene]hydrazine;
N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'[1-(2-methoxyphenyl)methylidene]hydrazine;
N'-[1-(2-ethoxyphenyl)methylidene]-N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazine;
N-(5-ethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'[1-(2-propoxyphenyl)methylidene]hydrazine;
2-[(5-propyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazonomethyl]phenol
N'[1-(2-methoxyphenyl)methylidene]-N-(5-propyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazine;
N'-[1-(2-ethoxyphenyl)methylidene]-N-(5-propyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazine;
N'[1-(2-propoxyphenyl)methylidene]-N-(5-propyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)hydrazine;
N-(5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'[1-(2-methoxyphenyl)methylidene]hydrazine;
N-(5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'[1-(2-ethoxyphenyl)methylidene]hydrazine;
N-(5-benzyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'[1-(2-propoxyphenyl)methylidene]hydrazine;
N-(5,8-dimethyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'[1-(2-propoxyphenyl)methylidene]hydrazine;
N-(8-methoxy-5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-(1-(2-propoxyphenyl)methylidene)hydrazine;
N-(5-methyl-8-phenyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-N'-(1-(2-propoxyphenyl)methylidene)hydrazine; and
5 2-propoxybenzoic acid N'-(5-methyl-5H-1,2,4-triazino[5,6-b]indol-3-yl)-hydrazide.
14. A pharmaceutical composition comprising a compound according to any preceding claim, together with a pharmaceutically acceptable carrier or diluent.
15. Use of a compound of any of claims 1 to 13, for the manufacture of a medicament for the therapy of Alzheimer’s disease.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbol(s))

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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)

CHEM ABS Data, EPO-Internal, WPI Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>A</td>
<td>WO 02/08849 A (ROMERO ARTHUR GLENN ; AQUINO JOSE (US); BROWN DAVID L (US); TUCKER) 12 December 2002 (2002-12-12) claims 1,3,5,39</td>
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<td>WO 02/089809 A (THE PROCTER &amp; GAMBLE COMPANY, USA) 14 November 2002 (2002-11-14) claims 1,3; examples 14,15</td>
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Further documents are listed in the continuation of box C.

Special categories of cited documents:

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Date of the actual completion of the international search: 21 April 2004

Date of mailing of the international search report: 11/05/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5816 Patentlaan 2 NL - 2330 HV NL
Tel. (+31-70) 940-2040, Tx. 31 651 epo nl Fac. (+31-70) 940-3016

Authorized officer

Schuemacher, A
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<td>SHABAN, M. A. E. ET AL: &quot;Sterically controlled regiospecific heterocyclization of 3-hydrazone-5-methyl-1,2,4-triazino '5,6-b!' indole to 10-methyl-1,2,4-triazolo '4',3':2,3:1,2,4-triazino '5,6-b'!indoles&quot; FARMACO (1999), 54(11-12), 800-809, XP009029546 compounds 12c-12h</td>
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<td>HOLLA, B. SHIVARAMA ET AL: &quot;Synthesis and antibacterial activity of nitrofururaldehyde as-triazino'5,6-b'indol-3-ylhydrazones&quot; JOURNAL OF THE INDIAN CHEMICAL SOCIETY (1988), 65(7), 524-5, XP009029587 compounds 2e-2j Table 1</td>
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<td>ESHBA, NABIL H. ET AL: &quot;Synthesis of some substituted 1,2,4-triazino'5,6-b'indole derivatives as potential antiviral and anticancer agents&quot; PHARMACEUTIA (1987), 42(10), 664-6, XP009029588 examples 4-27</td>
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<td>R. Fusco, R. Trave: &quot;3-Hydrazone-1,2,4-triazine come reattivi delloione ferroso&quot; INSTITUTO LOMBARDO (REND. SC.), vol. 91, 1957, pages 202-217, XP009029541 p.207, compound XIV</td>
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<td>MONGE, A. ET AL: &quot;New platelet aggregation inhibitors with antihypertensive action. New derivatives of 1,2,4-triazino(5,6-b)indole and related compounds&quot; ACTA FARMACEUTICA BONAERENSE (1987), 6(3), 157-62, XP001181022 p.158, compounds IVb)</td>
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<td>LABOUTA, IBRAHIM M. ET AL: &quot;Potential antineoplastics: synthesis and anticancer evaluation of some substituted 1,2,4-triazines&quot; FARMACI, SCIENTIFIC EDITION (1988), 16(2), 29-34, XP001063947 scheme 1, compounds VI(f)-(h)</td>
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