Title: 4-SUBSTITUTED FUSED HETEROPYRIMIDINES AND FUSED HETERO-4-PYRIMIDONES, PHARMACEUTICAL COMPOSITIONS CONTAINING THE SAME, AND THEIR USE IN THE TREATMENT OR PREVENTION OF PDE7b-MEDIATED DISEASES AND CONDITIONS

Abstract: The invention relates to 4-substituted fused heteropyrimidines and fused hetero-4-pyrimidones, pharmaceutical compositions containing the same and their use to treat or prevent diseases and conditions mediated by the phosphodiesterase enzyme 7b (PDE7b). Diseases and conditions mediated by PDE7b include osteoporosis, osteopenia and asthma. The invention also relates to processes for preparing 4-substituted fused heteropyrimidines and fused hetero-4-pyrimidones and processes for preparing compositions containing the same.
Cross-Reference to Related Applications

This application claims benefit of U.S. Application Serial No. 60/344,155 filed December 28, 2001, which is hereby incorporated herein by reference in its entirety.

Field of the Invention

The invention relates to 4-substituted fused heteropyrimidines and fused hetero-4-pyrimidones, pharmaceutical compositions containing the same and their use to treat or prevent diseases and conditions mediated by the phosphodiesterase enzyme \( PDE7B \). Diseases and conditions mediated by \( PDE7B \) include osteoporosis, osteopenia and asthma. The invention also relates to processes for preparing 4-substituted fused heteropyrimidines and fused hetero-4-pyrimidones and processes for preparing compositions containing the same.

Background

Cyclic nucleotide phosphodiesterases (PDEs) show specificity for purine cyclic nucleotide substrates and catalyze cyclic AMP (cAMP) and cyclic GMP (cGMP) hydrolysis (Thompson, W. J. (1991) *Pharma. Ther.* 51:13-33). Cyclic nucleotide phosphodiesterases regulate the steady-state levels of cAMP and cGMP and modulate both the amplitude and duration of cyclic nucleotide signal. These cyclic nucleotides are important second messengers in many physiological processes, including regulation of vascular resistance, cardiac output, visceral motility, immune response, inflammation, neuroplasticity, vision, and reproduction (Hetman, J.M. (2000) *Proc. Nat. Acad. Sci.* 97: 472-476). At least ten different but homologous PDE gene families are currently known to exist in mammalian tissues (Sasaki, T. *et al.* (2000) *Biochem. Biophys. Res. Comm.* 271(3):575-583). Most families contain distinct genes, many of which are expressed in different tissues as functionally unique

All cyclic nucleotide phosphodiesterases contain a core of about 270 conserved amino acids in the COOH-terminal half of the protein thought to be the catalytic domain of the enzyme. A conserved motif of the sequence HDXXHX has been identified in the catalytic domain of cyclic nucleotide phosphodiesterases. The cyclic nucleotide phosphodiesterases within each family display about 65% amino acid homology and the similarity drops to less than 40% when compared between different families with most of the similarity occurring in the catalytic domains.

Most cyclic nucleotide phosphodiesterase genes have more than one alternatively spliced mRNA transcribed from them and in many cases the alternative splicing appears to be highly tissue specific, providing a mechanism for selective expression of different cyclic nucleotide phosphodiesterases (*Beavo supra*). Cell-type-specific expression suggests that the different isozymes are likely to have different cell-type-specific properties.

Type 1 cyclic nucleotide phosphodiesterases are Ca$^{2+}$/calmodulin dependent, are reported to contain three different genes, each of which appears to have at least two different splice variants, and have been found in the lung, heart and brain. Some of the calmodulin-dependent phosphodiesterases are regulated *in vitro* by phosphorylation/dephosphorylation events. The effect of phosphorylation is to decrease the affinity of the enzyme for calmodulin, which decreases phosphodiesterase activity, thereby increasing the steady state level of cAMP. Type 2 cyclic nucleotide phosphodiesterases are cGMP stimulated, are localized in the brain and are thought to mediate the effects of cAMP on catecholamine secretion. Type 3 cyclic nucleotide phosphodiesterases are cGMP-inhibited, have a high specificity for cAMP as a substrate, and are one of the major phosphodiesterase isozymes present in vascular smooth muscle and play a role in cardiac function. One isozyme of type 3 is regulated by one or more insulin-dependent kinases.

Type 4 cyclic nucleotide phosphodiesterases are the predominant isoenzyme in most inflammatory cells, with some of the members being activated by cAMP-
dependent phosphorylation. Type 5 cyclic nucleotide phosphodiesterases have traditionally been thought of as regulators of cGMP function but may also affect cAMP function. High levels of type 5 cyclic nucleotide phosphodiesterases are found in most smooth muscle preparations, platelets and kidney. Type 6 cyclic nucleotide phosphodiesterase family members play a role in vision and are regulated by light and cGMP.

PDE7\(_{A2}\), a Type 7 cyclic nucleotide phosphodiesterase family member, is found in high concentrations in skeletal muscle. Work using mouse tissue has shown that PDE7\(_{A2}\) is found in high concentrations in skeletal muscle, followed by spleen. Lower levels were found in brain, heart, kidney, lung, and uterus (Han, P. et al. (1997) *J. Biol. Chem.* 272:16152-16157). A member of the type 7 cyclic nucleotide phosphodiesterases identified as PDE7\(_B\) has been cloned (Hetman, supra). In the mouse, PDE7\(_B\) has been found in high concentrations in pancreas followed by brain, heart, skeletal muscle, eye, thyroid, ovary, testis, submaxillary gland, epididymus, and liver. PDE7\(_B\) has been identified as a cAMP-specific PDE (Hetman, supra). A human PDE7\(_B\) cDNA was cloned by Sasaki et al. and a dot blot analysis was made to determine the expression pattern of PDE7\(_B\) in human tissues. Human PDE7\(_B\) transcripts were particularly abundant in the putamen and caudate nucleus. Sasaki et al. reported the effects of various PDE inhibitors on recombinant human PDE7\(_B\). The human PDE7\(_B\) gene is thought to be localized at chromosome 6q23-24. The EPM2A gene, which is related to progressive myoclonus epilepsy, is located at 6q24, making it possible that PDE7\(_B\) and its gene is linked to epilepsy (Sasaki et al., supra). Gardner et al. ((2000) *Biochem. Biophys. Res. Comm.* 272:186-192) also identified and characterized human PDE7\(_B\). Gardner et al. reported that mRNA for human PDE7\(_B\) was most highly expressed in caudate nucleus, putamen, and occipital lobe of the brain, heart, liver, ovary, pituitary gland, kidney, small intestine, and thymus. A phylogenetic alignment of the 230 amino acid catalytic domain of PDE7\(_B\) (amino acids 172-420) with representatives of other PDEs showed that PDE7\(_B\) has the highest homology to and clusters with PDE7\(_A\) (70% identity). Gardner et al. also studied the effects of a variety of standard PDE inhibitors on PDE7\(_B\). A listing of cyclic nucleotide phosphodiesterase families 1-7, their localization and physiological role is given in Beavo supra. A Type 8 family is reported in U.S. 5,798,246.
Many functions of the immune and inflammatory responses are inhibited by agents that increase intracellular levels of cAMP (Verghese (1995) *Mol. Pharmacol.* 47:1164-1171) while the metabolism of cGMP is involved in smooth muscle, lung and brain cell function (Thompson W. (1991) *Pharma. Ther.* 51:13-33). A variety of diseases have been attributed to increased cyclic nucleotide phosphodiesterase activity which results in decreased levels of cyclic nucleotides. For example, one form of diabetes insipidus in the mouse has been associated with increased phosphodiesterase Family 4 activity and an increase in low-\(K_m\) cAMP phosphodiesterase activity has been reported in leukocytes of atopic patients. Defects in cyclic nucleotide phosphodiesterases have also been associated with retinal disease. Retinal degeneration in the rd mouse, human autosomal recessive retinitis pigmentosa, and rod/cone dysplasia 1 in Irish setter dogs have been attributed to mutations in the Family 6 phosphodiesterase, gene B. Family 3 phosphodiesterase has been associated with cardiac disease.

Many inhibitors of different cyclic nucleotide phosphodiesterases have been identified and some have undergone clinical evaluation. For example, Family 3 phosphodiesterase inhibitors are being developed as antithrombotic agents, as antihypertensive agents and as cardiotonic agents useful in the treatment of congestive heart failure. Rolipram, a Family 4 phosphodiesterase inhibitor, has been used in the treatment of depression and other inhibitors of Family 4 phosphodiesterase are undergoing evaluation as anti-inflammatory agents. Rolipram has also been shown to inhibit lipopolysaccharide (LPS) induced TNF-alpha which has been shown to enhance HIV-1 replication *in vitro*. Therefore, rolipram may inhibit HIV-1 replication (Angel et al. (1995) *AIDS* 9:1137-44). Additionally, based on its ability to suppress the production of TNF alpha and beta and interferon gamma, rolipram has been shown to be effective in the treatment of encephalomyelitis, the experimental animal model for multiple sclerosis (Sommer et al. (1995) *Nat. Med.* 1:244-248) and may be effective in the treatment of tardive dyskinesia (Sasaki et al. (1995) *Eur. J. Pharmacol.* 282:72-76). Examples of Family 7 phosphodiesterase inhibitors that are imidazole derivatives are taught in WO 01/29049 (Eggenweiler et al.), WO 01/36425 (Eggenweiler et al.), WO 01/34601 (Eggenweiler et al.) and WO 01/32618...
(Eggenweiler et al.). Other examples of Family 7 phosphodiesterase inhibitors are disclosed in Martinez et al. (February 2000) J. Med. Chem. 43:683-699.

There are also nonspecific phosphodiesterase inhibitors such as theophylline, used in the treatment of bronchial asthma and other respiratory diseases, and pentoxifylline, used in the treatment of intermittent claudication and diabetes-induced peripheral vascular disease. Theophylline is thought to act on airway smooth muscle function as well as in an anti-inflammatory or immunomodulatory capacity in the treatment of respiratory diseases (Banner et al. (1995) Eur. Respir. J 8:996-1000) where it is thought to act by inhibiting both cyclic nucleotide phosphodiesterase cAMP and cGMP hydrolysis (Banner et al. (1995) Monaldi Arch. Chest Dis. 50:286-292). Pentoxifylline, also known to block TNF-alpha production, may inhibit HIV-1 replication (Angel et al. supra). Thiopyrimidine derivatives substituted at position 2 of the pyrimidine ring have been taught as inhibitors of cGMP or thromboxane A2 (TXA2), which is known to induce platelet aggregation and to contract smooth muscle (U.S. 5,869,486). A list of cyclic nucleotide phosphodiesterase inhibitors is given in Beavo supra.

Cyclic nucleotide phosphodiesterases have also been reported to affect cellular proliferation of a variety of cell types and have been implicated in the treatment of various cancers. Bang et al. ((1994) Proc. Natl. Acad. Sci. USA 91:5330-5334) reported that the prostate carcinoma cell lines DU 145 and LNCaP were growth-inhibited by delivery of cAMP derivatives and phosphodiesterase inhibitors and observed a permanent conversion in phenotype from epithelial to neuronal morphology; Matousovic et al. ((1995) J. Clin. Invest. 96:401-410) suggest that cyclic nucleotide phosphodiesterase isozyme inhibitors have the potential to regulate mesangial cell proliferation; Joulain et al. ((1995) J. Mediat. Cell Signal 11:63-79) report that cyclic nucleotide phosphodiesterase has been shown to be an important target involved in the control of lymphocyte proliferation; and Deonaran et al. ((1994) Brit. J. Cancer 70:786-94) suggest a tumor targeting approach to cancer treatment that involves intracellular delivery of phosphodiesterases to particular cellular compartments, resulting in cell death.
Accordingly, compounds that interact with cyclic nucleotide phosphodiesterases may provide treatments for various diseases and conditions caused by errors in regulation of cyclic nucleotide phosphodiesterase mediated processes. The present invention advances the state of the art by providing such compounds.

**Summary of the Invention**

The invention provides a method of treating or preventing osteoporosis and/or osteopenia comprising administering to a mammal in need thereof an effective amount of an inhibitor of phosphodiesterase type 7B.

The invention further provides compounds that inhibit the activity of PDE7B, particularly 4-substituted fused heteropyrimidines and fused hetero-4-pyrimidones. The invention further provides pharmaceutical compositions containing such compounds and processes for preparing such compounds and compositions. Finally, the invention provides for methods of treating a mammal for diseases or conditions caused by PDE7B-mediated processes by administering to the mammal an effective amount of a compound that inhibits the activity of PDE7B, particularly 4-substituted fused heteropyrimidines and fused hetero-4-pyrimidones.

The invention relates to a compound according to formula I:

![Chemical Structure](image)

(I)

wherein

(a) X is selected from halogen and NR\(^1\)R\(^2\),

(b) Y is selected from NR\(^3\), S and O, with the proviso that Y is not S when X is Cl,

(c) R\(^1\) and R\(^2\) are independently selected from

(1) hydrogen,

(2) alkyl of 1-8 carbon atoms,

(3) alkenyl of 2-8 carbon atoms,
(4) alkynyl of 2-8 carbon atoms,
(5) cycloalkyl of 3-7 carbon atoms,
(6) polycycloalkyl of 5-9 carbon atoms,
(7) heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms
      selected from NH, S and O,
(8) aryl of 6-12 carbon atoms, which may be substituted with
      (i) alkyl of 1-6 carbon atoms,
      (ii) alkenyl of 2-6 carbon atoms,
      (iii) alkynyl of 2-6 carbon atoms,
      (iv) alkoxy of 1-6 carbon atoms,
      (v) halogen,
      (vi) haloalkyl of 1-6 carbon atoms and a number of halogen
           atoms up to the perhalo level,
      (vii) haloalkoxy of 1-6 carbon atoms and a number of
           halogen atoms up to the perhalo level,
      (viii) aryl of 6-12 carbon atoms, or
      (ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms
           selected from N, S and O,
(9) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected
     from N, S and O, which may be substituted with
     (i) alkyl of 1-6 carbon atoms,
     (ii) alkenyl of 2-6 carbon atoms,
     (iii) alkynyl of 2-6 carbon atoms,
     (iv) alkoxy of 1-6 carbon atoms,
     (v) halogen,
     (vi) haloalkyl of 1-6 carbon atoms and a number of halogen
          atoms up to the perhalo level,
     (vii) haloalkoxy of 1-6 carbon atoms and a number of
          halogen atoms up to the perhalo level,
     (viii) aryl of 6-12 carbon atoms, or
     (ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms
          selected from N, S and O, and
(10) \( R^4 R^5 \),
(11) or \( R^1 \) and \( R^2 \) combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered monocyclic saturated ring, which optionally contains 1-2 additional heteroatoms selected from the group consisting of NH, NR^6, S and O, or combine to form, together with the nitrogen atom to which they are attached, a 6-10 membered fused polycyclic saturated ring, which optionally contains 1-2 additional heteroatoms selected from the group consisting of NH, NR^6, S and O, or combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered unsaturated ring, which optionally contains 1-2 additional heteroatoms selected from the group consisting of N, S and O, wherein said monocyclic saturated ring, polycyclic saturated ring or unsaturated ring may be substituted with 1-2 substituents selected from the group consisting of OH, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-7 carbon atoms, heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O, halogen, haloalkyl of 1-2 carbon atoms and a number of halogen atoms up to the perhalo level, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, and \( R^7R^8 \),

with the proviso that \( R^1 \) and \( R^2 \) do not combine to form, together with the nitrogen atom to which they are attached, a 6-membered monocyclic saturated ring that contains O,

(d) \( R^3 \) is selected from

(1) hydrogen,

(2) alkyl of 1-8 carbon atoms,

(3) alkenyl of 2-8 carbon atoms,

(4) alkynyl of 2-8 carbon atoms,

(5) cycloalkyl of 3-7 carbon atoms, and
(6) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with
   (i) alkyl of 1-6 carbon atoms,
   (ii) alkenyl of 2-6 carbon atoms,
   (iii) alkynyl of 2-6 carbon atoms,
   (iv) alkoxy of 1-6 carbon atoms,
   (v) halogen,
   (vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
   (vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
   (viii) aryl of 6-12 carbon atoms, or
   (ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

with the proviso that $R^2$ is not hydrogen

   (i) when $X$ is Cl;
   (ii) when $R^1$ is hydrogen and $R^2$ is unsubstituted aryl of 6 carbon atoms,
   (iii) when $R^1$ is hydrogen and $R^2$ is alkyl of 4 carbon atoms,
   (iv) when $R^1$ and $R^2$ are both alkyl of 1 carbon atom,
   (v) when $R^1$ is hydrogen and $R^2$ is aryl of 6 carbon atoms substituted with Cl, or
   (vi) when $R^1$ is hydrogen and $R^2$ is alkyl of 1 carbon atom,

with the further proviso that $R^3$ is not methyl or hydrogen when $R^1$ is

hydrogen and $R^2$ is aryl of 6 carbon atoms substituted with Br,

(e) $R^4$ is selected from

   (1) alkyl of 1-8 carbon atoms,
   (2) alkenyl of 2-8 carbon atoms,
   (3) alkynyl of 2-8 carbon atoms,
   (4) C(=O),
   (5) S(=O)$_2$, and
   (6) C(=O)O-,

(f) $R^5$ is selected from
(1) hydrogen,
(2) OH,
(3) alkyl of 1-8 carbon atoms,
(4) alkenyl of 2-8 carbon atoms,
(5) alkynyl of 2-8 carbon atoms,
(6) alkoxy of 1-8 carbon atoms,
(7) thioxy of 1-8 carbon atoms,
(8) aryl of 6-12 carbon atoms, which may be substituted with
   (i) alkyl of 1-6 carbon atoms,
   (ii) alkenyl of 2-6 carbon atoms,
   (iii) alkynyl of 2-6 carbon atoms,
   (iv) alkoxy of 1-6 carbon atoms,
   (v) halogen,
   (vi) haloalkyl of 1-6 carbon atoms and a number of halogen
        atoms up to the perhalo level,
   (vii) haloalkoxy of 1-6 carbon atoms and a number of halogen
        atoms up to the perhalo level,
   (viii) aryl of 6-12 carbon atoms, or
   (ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,
(9) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with
   (i) alkyl of 1-6 carbon atoms,
   (ii) alkenyl of 2-6 carbon atoms,
   (iii) alkynyl of 2-6 carbon atoms,
   (iv) alkoxy of 1-6 carbon atoms,
   (v) halogen,
   (vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
   (vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
   (viii) aryl of 6-12 carbon atoms, or
(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(10) cycloalkyl of 3-7 carbon atoms,

(11) heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O, and

(12) \( NR^9R^{10} \),

with the proviso that \( R^5 \) is not alkoxy of 4 carbon atoms when \( R^1 \) is hydrogen, \( R^3 \) is \( R^4R^5 \), \( R^3 \) is hydrogen, and \( R^4 \) is alkyl of 3 carbon atoms,

with the further proviso that \( R^5 \) is not unsubstituted aryl of 6 carbon atoms when \( R^1 \) is hydrogen, \( R^2 \) is \( R^4R^5 \), \( R^3 \) is hydrogen, and \( R^4 \) is alkyl of 1 carbon atom,

(g) \( R^6 \) and \( R^7 \) are independently selected from

(1) alkyl of 1-8 carbon atoms,

(2) alkenyl of 2-8 carbon atoms, and

(3) alkyny of 2-8 carbon atoms,

(h) \( R^8 \) is selected from

(1) OH,

(2) aryl of 6-12 carbon atoms, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkyny of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

(3) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkyny of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;
R⁹ and R¹⁰ are independently selected from

1. hydrogen,
2. alkyl of 1-8 carbon atoms,
3. alkenyl of 2-8 carbon atoms,
4. alkynyl of 2-8 carbon atoms,
5. or R⁹ and R¹⁰ combine together with the nitrogen atom to
   which they are attached to form
   i. a 5-7 membered, unsaturated ring which may contain 1-
      2 additional heteroatoms selected from N, S and O, or to
      form
   ii. a 5-7 membered, saturated ring which may contain 1-2
      additional heteroatoms selected from NH, NR¹¹, S and
      O;
with the proviso that R⁹ and R¹⁰ are not both alkyl of 1 carbon atom
when R¹ is hydrogen, R² is R⁴R⁵, R³ is hydrogen, R⁴ is alkyl of 2
carbon atoms, and R⁵ is NR⁹R¹⁰, and

R¹¹ is selected from

1. alkyl of 1-8 carbon atoms,
2. alkenyl of 2-8 carbon atoms,
3. alkynyl of 2-8 carbon atoms,

and pharmaceutically acceptable salts thereof.

The invention also provides methods for treating or preventing a PDE7B-
mediated disease or condition in a mammal. The PDE7B-mediated diseases and
conditions include the following: allergic and inflammatory disorders such as
psoriasis, atopic dermatitis, rheumatoid arthritis, osteoarthritis, chronic bronchitis,
allergic rhinitis, system lupus erythematosus, inflammatory bowel disease,
pancreatitis, and multiple sclerosis, central nervous system disorders such as
depression, respiratory disorders such as bronchial asthma, immune disorders,
epilepsy, diabetes, diabetes-induced vascular disease, intermittent claudication,
proliferative disorders such as cancer and more particularly prostate cancer, bone-
related disorders such as osteoporosis and osteopenia, transplant rejection in graft v.
host disease, in pannus formation in rheumatoid arthritis, and restenosis.
The invention therefore includes a method of treating or preventing a PDE7B-mediated disease or condition comprising administering to a mammal in need thereof an effective amount of a compound of formula II:

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[Chemical structure]

wherein

(a) X is selected from halogen and NR^1R^2,
(b) Y is selected from NR^3, S and O,
(c) R^1 and R^2 are independently selected from
   (1) hydrogen,
   (2) alkyl of 1-8 carbon atoms,
   (3) alkenyl of 2-8 carbon atoms,
   (4) alkynyl of 2-8 carbon atoms,
   (5) cycloalkyl of 3-7 carbon atoms,
   (6) polycycloalkyl of 5-9 carbon atoms,
   (7) heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O,
   (8) aryl of 6-12 carbon atoms, which may be substituted with
      (i) alkyl of 1-6 carbon atoms,
      (ii) alkenyl of 2-6 carbon atoms,
      (iii) alkynyl of 2-6 carbon atoms,
      (iv) alkoxy of 1-6 carbon atoms,
      (v) halogen,
      (vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
      (vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
      (viii) aryl of 6-12 carbon atoms, or
(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(9) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with

5 (i) alkyl of 1-6 carbon atoms,
(ii) alkenyl of 2-6 carbon atoms,
(iii) alkynyl of 2-6 carbon atoms,
(iv) alkoxy of 1-6 carbon atoms,
(v) halogen,

10 (vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(viii) aryl of 6-12 carbon atoms, or

15 (ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

(10) $R^4-R^5$,

(11) or $R^1$ and $R^2$ combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered monocyclic saturated ring, which optionally contains 1-2 additional heteroatoms selected from the group consisting of NH, NR^6, S and O, or combine to form, together with the nitrogen atom to which they are attached, a 6-10 membered fused polycyclic saturated ring, which optionally contains 1-2 additional heteroatoms selected from the group consisting of NH, NR^6, S and O, or combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered unsaturated ring, which optionally contains 1-2 additional heteroatoms selected from the group consisting of N, S and O, wherein said monocyclic saturated ring, polycyclic saturated ring or unsaturated ring may be substituted with 1-2 substituents selected from the group consisting of OH, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon
atoms, cycloalkyl of 3-7 carbon atoms, heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O, halogen, haloalkyl of 1-2 carbon atoms and a number of halogen atoms up to the perhalo level, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, and $R^7R^8$, $R^3$ is selected from the group consisting of

1. hydrogen,
2. alkyl of 1-8 carbon atoms,
3. alkenyl of 2-8 carbon atoms,
4. alkynyl of 2-8 carbon atoms,
5. cycloalkyl of 3-7 carbon atoms,
6. aryl of 6-12 carbon atoms, which may be substituted with
   (i) alkyl of 1-6 carbon atoms,
   (ii) alkenyl of 2-6 carbon atoms,
   (iii) alkynyl of 2-6 carbon atoms,
   (iv) halogen,
   (v) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
   (vi) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
   (vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
   (viii) aryl of 6-12 carbon atoms, or
   (ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,
   (x) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with
      (i) alkyl of 1-6 carbon atoms,
      (ii) alkenyl of 2-6 carbon atoms,
      (iii) alkynyl of 2-6 carbon atoms,
      (iv) alkoxy of 1-6 carbon atoms,
      (v) halogen,
(vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,

(vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,

(viii) aryl of 6-12 carbon atoms, or

(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(e) $R^4$ is selected from

(1) alkyl of 1-8 carbon atoms,
(2) alkenyl of 2-8 carbon atoms,
(3) alkylnyl of 2-8 carbon atoms,
(4) C(=O),
(5) S(=O)$_2$, and
(6) C(=O)O$\cdot$,

(f) $R^5$ is selected from

(1) hydrogen,
(2) OH,
(3) alkyl of 1-8 carbon atoms,
(4) alkenyl of 2-8 carbon atoms,
(5) alkylnyl of 2-8 carbon atoms,
(6) alkoxy of 1-8 carbon atoms,
(7) thioxy of 1-8 carbon atoms,
(8) aryl of 6-12 carbon atoms, which may be substituted with

(i) alkyl of 1-6 carbon atoms,
(ii) alkenyl of 2-6 carbon atoms,
(iii) alkylnyl of 2-6 carbon atoms,
(iv) alkoxy of 1-6 carbon atoms,
(v) halogen,
(vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(viii) aryl of 6-12 carbon atoms, and
(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(9) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with

5  
(i) alkyl of 1-6 carbon atoms,
(ii) alkenyl of 2-6 carbon atoms,
(iii) alkynyl of 2-6 carbon atoms,
(iv) alkoxy of 1-6 carbon atoms,
(v) halogen,

10  
(vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(viii) aryl of 6-12 carbon atoms, and

15  
(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(10) cycloalkyl of 3-7 carbon atoms,

(11) heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O, and

20  
(12) NR^9R^{10},

(g) R^6 and R^7 are independently selected from

(1) alkyl of 1-8 carbon atoms,
(2) alkenyl of 2-8 carbon atoms, and
(3) alkynyl of 2-8 carbon atoms;

25  
(h) R^8 is selected from

(1) OH,
(2) aryl of 6-12 carbon atoms, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon
atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

(3) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

10  (i) \( R^9 \) and \( R^{10} \) are independently selected from

(1) hydrogen,
(2) alkyl of 1-8 carbon atoms,
(3) alkenyl of 2-8 carbon atoms, and
(4) alkynyl of 2-8 carbon atoms,

15  (5) or \( R^9 \) and \( R^{10} \) combine together with the nitrogen atom to which they are attached to form

(i) a 5-7 membered, unsaturated ring which may contain 1-2 additional heteroatoms selected from N, S and O, or to form

(ii) a 5-7 membered, saturated ring which may contain 1-2 additional heteroatoms selected from NH, NR^{11}, S and O; and

20  (j) \( R^{11} \) is selected from

(1) alkyl of 1-8 carbon atoms,
(2) alkenyl of 2-8 carbon atoms, and
(3) alkynyl of 2-8 carbon atoms;

and pharmaceutically acceptable salts thereof.

The invention also includes a method of treating or preventing a PDE7_{8-}

30 mediated disease or condition comprising administering to a mammal in need thereof an effective amount of a compound of formula III:
wherein

(a) Y is selected from the group consisting of NR², S, and O, and

(b) R¹ and R² are independently selected from the group consisting of

(1) hydrogen,

(2) alkyl of 1-8 carbon atoms,

(3) alkenyl of 2-8 carbon atoms,

(4) alkynyl of 2-8 carbon atoms,

(5) cycloalkyl of 3-7 carbon atoms,

(6) polycycloalkyl of 5-9 carbon atoms,

(7) heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O,

(8) aryl of 6-12 carbon atoms, which may be substituted with

(i) alkyl of 1-6 carbon atoms,

(ii) alkenyl of 2-6 carbon atoms,

(iii) alkynyl of 2-6 carbon atoms,

(iv) alkoxy of 1-6 carbon atoms,

(v) halogen,

(vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,

(vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,

(viii) aryl of 6-12 carbon atoms, or

(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

(9) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with

(i) alkyl of 1-6 carbon atoms,
(ii) alkenyl of 2-6 carbon atoms,
(iii) alkynyl of 2-6 carbon atoms,
(iv) alkoxy of 1-6 carbon atoms,
(v) halogen,
(vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(viii) aryl of 6-12 carbon atoms, or
(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

and pharmaceutically acceptable salts thereof.

The present invention therefore provides compounds, pharmaceutical compositions containing such compounds, processes for preparing such compounds and compositions, and methods for the treatment or prevention of PDE7b-mediated diseases and conditions. These and other aspects of the invention will be more apparent from the following description and claims.

**Detailed Description of the Invention**

The invention provides compounds, namely 4-substituted fused heteropyrimidines and fused hetero-4-pyrimidones, pharmaceutical compositions containing such compounds, and their use for the treatment or prevention of PDE7b-mediated diseases or conditions. The invention further provides methods of treating or preventing PDE7b-mediated diseases or conditions in mammals, such as humans, by administration of a compound according to formulas I-III, each of which has been broadly described above in the summary.

Preferred embodiments include the following.

A preferred compound according to the invention is a compound according to formula I, wherein

(a) $X$ is $NR^1R^2$,
(b) Y is selected from the group consisting of S and O, and is preferably S, and

(c) \( R^1 \) and \( R^2 \) are independently selected from the group consisting of

\begin{enumerate}
  \item hydrogen,
  \item alkyl of 1-8 carbon atoms,
  \item alkenyl of 2-8 carbon atoms,
  \item alkynyl of 2-8 carbon atoms,
  \item cycloalkyl of 3-7 carbon atoms,
  \item polycycloalkyl of 5-9 carbon atoms,
  \item heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O,
  \item aryl of 6-12 carbon atoms, which may be substituted with
    \begin{enumerate}
      \item alkyl of 1-6 carbon atoms,
      \item alkenyl of 2-6 carbon atoms,
      \item alkynyl of 2-6 carbon atoms,
      \item alkoxy of 1-6 carbon atoms,
      \item halogen,
      \item haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
      \item haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
      \item aryl of 6-12 carbon atoms, or
      \item heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,
    \end{enumerate}
  \item heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with
    \begin{enumerate}
      \item alkyl of 1-6 carbon atoms,
      \item alkenyl of 2-6 carbon atoms,
      \item alkynyl of 2-6 carbon atoms,
      \item alkoxy of 1-6 carbon atoms,
      \item halogen,
      \item haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
    \end{enumerate}
\end{enumerate}
(vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,

(viii) aryl of 6-12 carbon atoms, or

(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

(10) \( R^4 - R^5 \),

(11) or \( R^1 \) and \( R^2 \) combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered monocyclic saturated ring, or combine to form, together with the nitrogen atom to which they are attached, a 6-10 membered fused polycyclic saturated ring, or combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered unsaturated ring, wherein said monocyclic saturated ring, polycyclic saturated ring or unsaturated ring may be substituted with 1-2 substituents selected from the group consisting of OH, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-7 carbon atoms, heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O, halogen, haloalkyl of 1-2 carbon atoms and a number of halogen atoms up to the perhalo level, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, and \( R^7 - R^8 \); and preferably one of \( R^1 - R^2 \) is hydrogen;

and pharmaceutically acceptable salts thereof.

A preferred method of treatment or prevention of PDE7B-mediated diseases or conditions comprises administering to a mammal in need thereof an effective amount of a compound of formula II, wherein Y is S or NH.

As used herein, the term “aryl” includes aromatic ring structures that are substituents on another atom. These aryls may also be substituted with substituents, such as nitrile, nitro, halogen, haloalkyl, etc. Non-limiting examples of aryls include phenyl, napthyl, etc. Likewise, the term “heteroaryl” as used herein includes aromatic
ring structures containing between one and three heteroatoms, such as O, N and S, that are substituents on another atom. These heteroaryl$s$ may also be substituted with substituents, such as nitrile, nitro, halogen, haloalkyl, etc. Non-limiting examples of heteroaryls include pyridyl, furyl, quinolyl, etc.

As used herein the term “alkyl” includes straight-chain or branched alkyl$s$ of between 1 and 8 carbon atoms. The term “alkenyl” includes straight-chain or branched alkenyl$s$ of between 2 and 8 carbon atoms. As used herein the term “alkynyl” includes straight-chain or branched alkynyl$s$ of between 2 and 8 carbon atoms.

Compounds of the invention may be useful in the treatment or prevention of PDE7$_B$-mediated diseases or conditions. An agent that binds to PDE7$_B$ may be employed for a wide variety of indications, including the following: allergic and inflammatory disorders such as psoriasis, atopic dermatitis, rheumatoid arthritis, osteoarthritis, chronic bronchitis, allergic rhinitis, system lupus erythematosus, inflammatory bowel disease, pancreatitis, and multiple sclerosis, central nervous system disorders such as depression, respiratory disorders such as bronchial asthma, immune disorders, epilepsy, diabetes, diabetes-induced vascular disease, intermittent claudication, proliferative disorders such as cancer and more particularly prostate cancer, osteoporosis, osteopenia, transplant rejection in graft vs host disease, in pannus formation in rheumatoid arthritis, and restenosis.

Compounds of the invention are preferably used in the treatment or prevention of osteopenia, osteoporosis, and respiratory disorders such as asthma.

PDE7$_B$ has been shown to be a cAMP specific PDE. Thus, it is possible that any disease or condition involving a pathway in which cAMP is a signaling molecule may be treated or prevented by administration of a PDE7$_B$ inhibitor, such as those of formulas I-V. For example, cAMP regulation has been suggested as a means to control inflammation (Moore, A.R. et al. (1995) Clin. Exp. Immunol. 101: 387-389). cAMP is rapidly broken down by PDE$s$. Because hydrolysis of cAMP is not dependent upon a single PDE but on a range of isoenzymes that differ in their tissue distribution, therapeutic use of specific PDE inhibitors is believed possible for
specific ailments without unacceptable systemic side effects (Moore, A.R. et al. supra). Another example involves T cell-dependent disorders. Selectively reducing PDE7 expression with a PDE7 antisense oligonucleotide inhibited T cell proliferation (Li, Linsong et al. (1999) Science 283: 848-849). Increased PDE7 in T cells correlated with decreased cAMP leading to increased proliferation.

PDE4 has also been shown to be a cAMP-specific PDE. It is believed that disorders associated with PDE4 activity may also be treated or prevented by compounds that modulate PDE7 activity because of the similar cAMP-specificity of the two enzymes. For example, osteoporosis has been associated with PDE4 activity (Kasugai, S. et al. (1999) Drug News Perspect. 12(9); 529-534). Two known medicaments for treating osteoporosis were studied, and their effects were determined to be mainly mediated by an increase in cAMP level. Since PDE4 specifically degrades cAMP, PDE4 inhibitors were added to the tissue system and resulted in increased bone-like tissue formation. When the inhibitors were administered to mice and rats, increased bone mass was seen. In other work on osteoporosis using murine models, administration of two PDE inhibitors was shown to significantly increase both cortical and cancellous bone mass (Kinoshita, T. et al. (2000) Bone 27(6): 811817). The administration of either pentoxifylline, an inhibitor of cAMP PDEs, or rolipram, an inhibitor specific to PDE4, in normal mice significantly increased both cortical and cancellous bone mass. Denbufylline, another selective inhibitor of PDE4, was shown to inhibit the decrease in the bone mineral density of femurs from Walker 256/S-bearing rats without influence on healthy rats (Miyamoto, K. et al. (1997) Biochem. Pharmacol. 54: 613617). Furthermore, cAMP has been shown to inhibit bone-degrading cell production and to stimulate bone-increasing cell production (Kasugai, S. et al., M681 and K. Miyamoto, M682 (1996) Abstracts of American Soc. for Bone and Mineral Res. 18th Ann. Meeting). These studies strongly suggest a role for inhibitors of cAMP-selective PDEs in treatment and prevention of osteoporosis.

The present invention also includes pharmaceutically acceptable salts of the compounds of the invention. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulphonic acid, sulphonic acid, acetic acid,
trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li⁺, Na⁺ or K⁺), alkaline earth cations (e.g., Mg²⁺, Ca²⁺ or Ba²⁺), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations such as those arising from protonation or peralkylation of triethylamine, N,N-diethylamine, N,N-dicyclohexylamine, pyridine, N,N-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

A number of the compounds of the invention possess asymmetric carbons and can therefore exist in racemic and optically active forms. Methods of separation of enantiomeric and diastereomeric mixtures are well known to the skilled in the art. The present invention encompasses any racemic or optically active forms of compounds described in the compounds of the invention which possess PDE7B binding activity or the use of any racemic or optically active forms of compounds described in the compounds of the invention for the treatment or prevention of PDE7B-mediated diseases or conditions.

The therapeutic agents of the invention may be employed alone or concurrently with other therapies. For example, they may be used for the treatment of osteoporosis or osteopenia in combination with a calcium source, vitamin D or analogues of vitamin D, and/or antiresorptive therapies such as estrogen replacement therapy, treatment with a fluoride source, treatment with calcitonin or a calcitonin analogue, or treatment with a bisphosphonate such as alendronate. The agent may be used with therapies such as estrogen replacement therapy. The agent may be used concurrently with therapies such as estrogen replacement therapy and/or a gonadotropin-releasing hormone agonist. Finally, the agent may be used concurrently with therapies such as an androgen.

Therapeutic agents of the invention may be employed for the treatment of asthma and other respiratory disorders in combination with other known asthma
therapies, such as in combination with steroids, non-steroidal anti-inflammatory agents, and/or non-narcotic analgesics.

The method of the invention is intended to be employed for treatment of PDE7B-mediated diseases or conditions in both humans and other mammals.

The compounds may be administered orally, dermally, parenterally, by injection, by inhalation or spray, or sublingually, rectally or vaginally in dosage unit formulations. The term 'administered by injection' includes intravenous, intraarticular, intramuscular, subcutaneous and parenteral injections, as well as use of infusion techniques. Dermal administration may include topical application or transdermal administration. One or more compounds may be present in association with one or more non-toxic pharmaceutically acceptable carriers and, if desired, other active ingredients.

Compositions intended for oral use may be prepared according to any suitable method known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of diluents, sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide 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; and binding 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 adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. These compounds may also be prepared in solid, rapidly released form.

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 containing the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions may also be used. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropyl-methylcellulose, sodium alginate, polyvinylpyrrolidone, 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 heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as saccharin.

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 dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring and coloring agents, may also be present.

The compounds may also be in the form of non-aqueous liquid formulations, e.g., oily suspensions which may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or peanut 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 palatable oral
preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oil 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 soy 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 coloring agents.

The compounds may also be administered in the form of suppositories for rectal or vaginal 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 or vaginal temperature and will therefore melt in the rectum or vagina to release the drug. Such materials include cocoa butter and polyethylene glycols.

Compounds of the invention may also be administered transdermally using methods known to those skilled in the art (see, for example: Chien; “Transdermal Controlled Systemic Medications”; Marcel Dekker, Inc.; 1987. Lipp et al. WO 94/04157 3Mar94). For example, a solution or suspension of a compound of formulas I-V in a suitable volatile solvent optionally containing penetration enhancing agents can be combined with additional additives known to those skilled in the art, such as matrix materials and bacteriocides. After sterilization, the resulting mixture can be formulated following known procedures into dosage forms. In addition, on treatment with emulsifying agents and water, a solution or suspension of a compound of formulas I-V may be formulated into a lotion or salve.
Suitable solvents for processing transdermal delivery systems are known to those skilled in the art, and include lower alcohols such as ethanol or isopropyl alcohol, lower ketones such as acetone, lower carboxylic acid esters such as ethyl acetate, polar ethers such as tetrahydrofuran, lower hydrocarbons such as hexane, cyclohexane or benzene, or halogenated hydrocarbons such as dichloromethane, chloroform, trichlorotrifluoroethane, or trichlorofluoroethane. Suitable solvents may also include mixtures one or more materials selected from lower alcohols, lower ketones, lower carboxylic acid esters, polar ethers, lower hydrocarbons, halogenated hydrocarbons.

Suitable penetration enhancing materials for transdermal delivery systems are known to those skilled in the art, and include, for example, monohydroxy or polyhydroxy alcohols such as ethanol, propylene glycol or benzyl alcohol, saturated or unsaturated \( C_8-C_{18} \) fatty alcohols such as lauryl alcohol or cetyl alcohol, saturated or unsaturated \( C_8-C_{18} \) fatty acids such as stearic acid, saturated or unsaturated fatty esters with up to 24 carbons such as methyl, ethyl, propyl, isopropyl, \( n \)-butyl, sec-butyl isobutyl tert-butyl or monoglycerin esters of acetic acid, capronic acid, lauric acid, myristic acid, stearic acid, or palmitic acid, or diesters of saturated or unsaturated dicarboxylic acids with a total of up to 24 carbons such as diisopropyl adipate, diisobutyl adipate, diisopropyl sebacate, diisopropyl maleate, or diisopropyl fumarate. Additional penetration enhancing materials include phosphatidyl derivatives such as lecithin or cephalin, terpenes, amides, ketones, ureas and their derivatives, and ethers such as dimethyl isosorbide and diethylene glycol monoethyl ether. Suitable penetration enhancing formulations may also include mixtures one or more materials selected from monohydroxy or polyhydroxy alcohols, saturated or unsaturated \( C_8-C_{18} \) fatty alcohols, saturated or unsaturated \( C_8-C_{18} \) fatty acids, saturated or unsaturated fatty esters with up to 24 carbons, diesters of saturated or unsaturated dicarboxylic acids with a total of up to 24 carbons, phosphatidyl derivatives, terpenes, amides, ketones, ureas and their derivatives, and ethers.

Suitable binding materials for transdermal delivery systems are known to those skilled in the art and include polyacrylates, silicones, polyurethanes, block polymers, styrene-butadiene copolymers, and natural and synthetic rubbers. Cellulose ethers, derivatized polyethylenes, and silicates may also be used as matrix.
components. Additional additives, such as viscous resins or oils may be added to increase the viscosity of the matrix.

For all regimens of use disclosed herein for compounds of formulas I-III, the daily oral dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily rectal dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/Kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/Kg. The daily inhalation dosage regimen will preferably be from 0.01 to 10 mg/Kg of total body weight.

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics. It will also be understood, however, that the specific dose level for any given patient will depend upon a variety of factors, including, but not limited to the activity of the specific compound employed, the age of the patient, the body weight of the patient, the general health of the patient, the gender of the patient, the diet of the patient, time of administration, route of administration, rate of excretion, drug combinations, and the severity of the condition undergoing therapy. It will be further appreciated by one skilled in the art that the optimal course of treatment, i.e., the mode of treatment and the daily number of doses of a compound of formulas I-III or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional treatment tests.

The entire disclosures of all applications, patents and publications cited above and below are hereby incorporated by reference.
The compounds of formulas I-III may be prepared by use of known chemical reactions and procedures, from known compounds (or from starting materials which, in turn, are producible from known compounds) through the preparative methods shown below as well as by other reactions and procedures known to the skilled in the art. Nevertheless, the following general preparative methods are presented to aid practitioners in synthesizing the compounds of the invention, with more detailed particular examples being presented in the experimental section. The examples are for illustrative purposes only and are not intended, nor should they be construed, to limit the invention in any way.

The compounds of formulas I-III, where Y is S, may generally be prepared by carrying out the following sequence shown in Reaction Scheme 1 below.
In the first step of this sequence, cyclohexanone 1, is condensed with a cyanoacetic ester and sulfur in the presence of a base, to give compound 2. The reaction is typically carried out in a protic solvent such as ethanol. Suitable bases for the reaction include alkyl amines such as diethylamine. Conversion to compound 3 is accomplished by reaction of compound 2 with an amide such as formamide (when $R^1$ is H), as a neat mixture of the two reactants up to reflux temperature. The resulting compound 3 may then be aromatized to the benzothiophene pyrimidone, compound 4, under a variety of conditions, such as heating with DDQ. Compound 4 may then be converted to the 4-halopyrimidine, compound 5, by reaction with a reagent such as POCl₃, POBr₃, COCl₂, oxalyl chloride or the like. Compound 5 represents the class of formulas I-II compounds in which X is halogen. Conversion of compound 5 to compound 6 may be carried out by reaction with an amine of formula $R^1R^2\text{NH}$, in a solvent such as THF or i-butanol, facilitated by a catalyst such as dilute aqueous HCl.

Compounds of formulas I-III in which Y is O or $NR^3$ may be similarly prepared from the corresponding heterocyclic amino esters, as shown in Reaction Scheme 2.
Compounds of Formula 8 where Y is NR³ or O may also be commercially available. Compounds of Formula 7 may also be commercially available or prepared by standards methods known to those skilled in the art, analogous to that shown in Reaction Scheme 1.

**ABBREVIATIONS AND ACRONYMS**

When the following abbreviations are used herein, they have the following meaning:

- Ac₂O: acetic anhydride
- Celite®: diatomaceous earth filter agent, © Celite Corp.
- conc: concentrated
- DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
- DME: dimethoxyethane
- DMF: N,N-dimethylformamide
- DMSO: dimethylsulfoxide
- EtOAc: ethyl acetate
- EtOH: ethanol (100%)
- Et₂O: diethyl ether
Example 1

**Preparation of 1-(2-amino-4,5,6,7-tetrahydro-1-benzothien-3-yl)-1-propanone**

To a mixture of 40.0 g of cyclohexanone (42.2 mL, 0.408 mol), 46.1 g ethyl cyanoacetate (43.4 mL, 0.408 mol), and sulfur (14.4 g, 0.45 mol) in 100 mL absolute ethanol was added diethylamine (42.2 mL, 0.408 mol). The reaction mixture became warm, the solids dissolved very quickly and a dark red solution formed. After about 20 min, a solid began to form. The mixture was stirred for an additional 2 h, after which the solids were removed by filtration, washed twice with ethanol and dried under vacuum. The filtrate was cooled for several days in a refrigerator and additional solids were formed and separated, washed with ethanol and dried.

Example 2

**Preparation of 5,6,7,8-Tetrahydro[1]benzothieno[2,3-d]pyrimidin-4(3H)-one**
To 68 mL formamide was added 25.0g of the compound prepared in Example 1, and the mixture was heated under argon for 20 h at 180 °C, then at 190 °C for 2.5 h. The mixture was cooled to rt, poured into water and then filtered to remove the solid product. The solids were washed successively with water and EtOAc to yield product which was used in the subsequent reactions without further purification.

**Example 3**

**Preparation of [1]benzothieno[2,3-d]pyrimidin-4(3H)-one**

![Chemical Structure](attachment:image)

The pyrimidone of Example 2 (37.0 g, 0.179 mmol) was added to a suspension of DDQ (101.8 g, 0.448 mmol) in 560 mL dioxane and the mixture was heated to 80-90°C for 2.5 h. The reaction mixture was cooled to 30°C and solids were removed by filtration and rinsed with dioxane (3x 60 mL). The filtrate was set aside (see below). The solids were dried under vacuum at 50°C for 3 h and then suspended in 120 mL 10% MeOH/CH₂Cl₂. The mixture was stirred vigorously for 45 min, the solid collected by filtration, washed with 10% MeOH/CH₂Cl₂ and dried under vacuum at 50°C for 3 h to give solid product.

The initial filtrate (see above) was poured into 1600mL 3N HCl with ice. The suspension was vigorously stirred for 10 min. The solids were collected by filtration, and the filtrate was neutralized with Na₂CO₃ and then NaHCO₃. The mixture was filtered to remove inorganic salts and extracted with 3 L of methylene chloride. The extract was washed with satd NaCl solution and dried over Na₂SO₄ and concentrated to dryness. The residue was triturated with methylene chloride for 0.5 h and the remaining solid was collected by filtration, washed twice with a small amount of methylene chloride and dried under vacuum to give additional product.
**Example 4**

**Preparation of 4-chloro[1]benzothieno[2,3-d]pyrimidine**

To 3.69 g [1]benzothieno[2,3-d]pyrimidin-4(3H)-one (Example 3, 18.2 mmol), 2.5 mL (30.9 mmol) pyridine was added, in one portion, 25 mL POCl₃ (268 mmol). The mixture was heated to 105-110°C for 4 h under argon, cooled and the excess POCl₃ was removed by concentration in vacuo. To the residue was added 40 mL ice/water under stirring. The stirring was continued for 20 min, the separated solids were removed by filtration and washed several times with distilled water. The solid was dried under vacuum at 50°C for 20 h.

HPLC was conducted using a Hewlett-Packard 1100 HPLC equipped with a quaternary pump, a variable wavelength detector and a YMC Pro C18, 4.6 mm x 150mm column. Following injection, the mixture was subjected to gradient elution from 90% A (10% B) for two minutes, 5% A (95% B) over 18 minutes, then held for five minutes. Buffer A was 0.1% TFA in water; buffer B was 0.1% TFA in acetonitrile. The flow rate was 1.25 mL/min and the UV detection was set at 254 nm. The retention time for the compound produced by Example 4 was 18.91 min.

**Example 5**

**Parallel Synthesis Procedure**

To a vial containing 50 mg of the compound of Example 4 were added 1.5 mL THF, 0.1 mL 1% HCl (aq), and roughly 4 eq of an amine R¹R²NH. The process was repeated for a number of amines, the vials were sealed and placed in a J-Kem orbital shaker and shaken at 25°C overnight, then heated in a reaction block at 80°C for 24 h. After 24 h the reactions were checked for starting material via TLC (30% EtOAc/70% hexanes). The reactions were concentrated to a residue in a speed van, taken up in
methanol and purified by HPLC, and characterized by $^1$H NMR(acetone-$d_6$) and analytical HPLC.

By using a combination of the above exemplified procedures and the appropriate starting materials, compounds of formulas I-III were prepared and are listed in Tables 1 and 2. Table 1 includes data on $R_f$ ratio determined through thin layer chromatography in the referenced solvent. Table 1 also includes data on HPLC retention time using the indicated solvent and standard HPLC equipment and columns commonly used for such measurements, such as those used in Example 4.

Table 1

**Benzothienopyrimidines**

<table>
<thead>
<tr>
<th>$R^1$</th>
<th>$R^2$</th>
<th>Data $R_f$ or [HPLC RT min] (solvent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>$i$-PrCH(Me)-</td>
<td>0.52 (1:3 EtOAc:Hex)</td>
</tr>
<tr>
<td>H</td>
<td>2-$n$-Pr-Ph-</td>
<td>-</td>
</tr>
<tr>
<td>H</td>
<td>2-sec-Bu-Ph-</td>
<td>-</td>
</tr>
<tr>
<td>$n$-Pr</td>
<td>$n$-Pr</td>
<td>brown oil</td>
</tr>
<tr>
<td>Structure</td>
<td>Chemistry</td>
<td>Log P Value</td>
</tr>
<tr>
<td>------------</td>
<td>-----------</td>
<td>-------------</td>
</tr>
<tr>
<td>H</td>
<td>cyc-Bu</td>
<td>0.42</td>
</tr>
<tr>
<td>(CH₂)₃</td>
<td></td>
<td>0.68</td>
</tr>
<tr>
<td>H</td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>H</td>
<td></td>
<td>0.55</td>
</tr>
<tr>
<td>Me</td>
<td>n-Pr</td>
<td>0.41</td>
</tr>
<tr>
<td>-CH₂CH₃CH₂CH₃</td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Et</td>
<td>Et</td>
<td>0.48</td>
</tr>
<tr>
<td>-CH₂C(Me)₃(CH₂)₆</td>
<td></td>
<td>0.686</td>
</tr>
<tr>
<td>2-Me-Ph-</td>
<td>H</td>
<td>-</td>
</tr>
<tr>
<td>---------</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>-(CH₂)₄-</td>
<td>0.542</td>
<td>(3:7 EtOAc: Hex)</td>
</tr>
<tr>
<td>-(CH₂)₂CH(Me)-</td>
<td>0.656</td>
<td>(3:7 EtOAc: Hex)</td>
</tr>
<tr>
<td>-(CH₂)₄CH(Me)-</td>
<td>0.656</td>
<td>(3:7 EtOAc: Hex)</td>
</tr>
<tr>
<td>-(CH₂)₂CH(Me)CH₂-</td>
<td>0.649</td>
<td>(3:7 EtOAc: Hex)</td>
</tr>
<tr>
<td>-(CH₂)₄CH(Et)-</td>
<td>0.699</td>
<td>(3:7 EtOAc: Hex)</td>
</tr>
<tr>
<td>Et</td>
<td>n-Pr</td>
<td>0.687</td>
</tr>
<tr>
<td>sec-Bu</td>
<td>H</td>
<td>0.41</td>
</tr>
<tr>
<td>iso-Bu</td>
<td>H</td>
<td>0.482</td>
</tr>
<tr>
<td>3-t-Bu-pyrazol-5-yl</td>
<td>H</td>
<td>[2.69] (10% MeCN/H₂O)</td>
</tr>
<tr>
<td>---------------------</td>
<td>---</td>
<td>-----------------------</td>
</tr>
<tr>
<td>3-(4-oxazolyl)-phenyl</td>
<td>H</td>
<td>-</td>
</tr>
<tr>
<td>(2-furyl)methyl-</td>
<td>H</td>
<td>-</td>
</tr>
<tr>
<td>4-(4-oxazolyl)-phenyl</td>
<td>H</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 2
Misc. Compounds

<table>
<thead>
<tr>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure 1" /></td>
</tr>
<tr>
<td><img src="image2" alt="Structure 2" /></td>
</tr>
<tr>
<td><img src="image3" alt="Structure 3" /></td>
</tr>
<tr>
<td><img src="image4" alt="Structure 4" /></td>
</tr>
</tbody>
</table>

Screening Assay

To determine whether a compound is able to modulate PDE7_B activity, the following procedure is used.

Materials:

SPA 96 well Isolates (Wallac 1450-515)

Phosphodiesterase scintillation proximity (SPA) beads (Amersham RPNQ 0150)
\(^3\)H cAMP tracer (Amersham TRK 559 - 250 \(\mu\)Ci)

PDE7b enzyme (See procedure)

Assay buffer (50 mM Tris/HCl pH 7.5, 8.3 mM MgCl\(_2\), 1.7 mM EGTA)

Method:

SPA beads are prepared according to manufacturer’s directions. \(H_2O\) (28 ml) is added to 500 mg vial. Radiolabeled camp tracer is prepared (\(^3\)H cAMP tracer stock vial is 1 \(\mu\)Ci/\(\mu\)l) 1:400 in Assay buffer. A dilution of PDE7b enzyme (1:800 dilution) is prepared and is placed on ice in cold Assay buffer. Assay buffer is added to all wells of a microtiter plate. Wells of only background buffer and of enzyme are prepared for controls. Compounds to be assayed are added to wells, followed by enzyme addition. The enzyme reaction is started by addition of \(^3\)H cAMP tracer to each well. Wells are incubated at room temperature for 45 minutes. The reaction is stopped with the addition of SPA beads to each well. Scintillation measurements are taken after plates are sealed and at least one hour has passed.

**Tissue Assay**

The inhibition of PDE7b in tissue culture cells is measured using a kit supplied by Amersham Corp., cAMP EIA, #RPN225.

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing examples are included by way of illustration only. Accordingly, the scope of the invention is limited only by the scope of the appended claims.
Claims

What is claimed is:

1. A compound according to formula I:

![Chemical Structure](image)

wherein

(a) X is selected from halogen and NR\(^1\)R\(^2\),

(b) Y is selected from NR\(^3\), S and O, with the proviso that Y is not S when X is Cl,

(c) R\(^1\) and R\(^2\) are independently selected from

1. hydrogen,

2. alkyl of 1-8 carbon atoms,

3. alkenyl of 2-8 carbon atoms,

4. alkynyl of 2-8 carbon atoms,

5. cycloalkyl of 3-7 carbon atoms,

6. polycycloalkyl of 5-9 carbon atoms,

7. heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O,

8. aryl of 6-12 carbon atoms, which may be substituted with

   (i) alkyl of 1-6 carbon atoms,

   (ii) alkenyl of 2-6 carbon atoms,

   (iii) alkynyl of 2-6 carbon atoms,

   (iv) alkoxy of 1-6 carbon atoms,

   (v) halogen,

   (vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,

   (vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,

   (viii) aryl of 6-12 carbon atoms, or
(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(9) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with

5

(i) alkyl of 1-6 carbon atoms,

(ii) alkenyl of 2-6 carbon atoms,

(iii) alkynyl of 2-6 carbon atoms,

(iv) alkoxy of 1-6 carbon atoms,

(v) halogen,

10

(vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,

(vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,

(viii) aryl of 6-12 carbon atoms, or

15

(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

(10) $R^4R^5$,

(11) or $R^1$ and $R^2$ combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered monocyclic saturated ring, which optionally contains 1-2 additional heteroatoms selected from the group consisting of NH, NR$^6$, S and O, or combine to form, together with the nitrogen atom to which they are attached, a 6-10 membered fused polycyclic saturated ring, which optionally contains 1-2 additional heteroatoms selected from the group consisting of NH, NR$^6$, S and O, or combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered unsaturated ring, which optionally contains 1-2 additional heteroatoms selected from the group consisting of N, S and O, wherein said monocyclic saturated ring, polycyclic saturated ring or unsaturated ring may be substituted with 1-2 substituents selected from the group consisting of OH, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-7 carbon atoms, heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O, halogen,
haloalkyl of 1-2 carbon atoms and a number of halogen atoms up to the perhalo level, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, and $R^7 R^8$,

with the proviso that $R^1$ and $R^2$ do not combine to form, together with the nitrogen atom to which they are attached, a 6-membered monocyclic saturated ring that contains O,

(d) $R^3$ is selected from

(1) hydrogen,

(2) alkyl of 1-8 carbon atoms,

(3) alkenyl of 2-8 carbon atoms,

(4) alkynyl of 2-8 carbon atoms,

(5) cycloalkyl of 3-7 carbon atoms, and

(6) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with

(i) alkyl of 1-6 carbon atoms,

(ii) alkenyl of 2-6 carbon atoms,

(iii) alkynyl of 2-6 carbon atoms,

(iv) alkoxy of 1-6 carbon atoms,

(v) halogen,

(vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,

(vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,

(viii) aryl of 6-12 carbon atoms, or

(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

with the proviso that $R^3$ is not hydrogen

(i) when $X$ is Cl;

(ii) when $R^1$ is hydrogen and $R^2$ is unsubstituted aryl of 6 carbon atoms,

(iii) when $R^1$ is hydrogen and $R^2$ is alkyl of 4 carbon atoms,

(iv) when $R^1$ and $R^2$ are both alkyl of 1 carbon atom,
(v) when \( R^1 \) is hydrogen and \( R^2 \) is areyl of 6 carbon atoms substituted with Cl, or

(vi) when \( R^1 \) is hydrogen and \( R^2 \) is alkyl of 1 carbon atom, with the further proviso that \( R^3 \) is not methyl or hydrogen when \( R^1 \) is hydrogen and \( R^2 \) is areyl of 6 carbon atoms substituted with Br,

\( R^4 \) is selected from

1. alkyl of 1-8 carbon atoms,
2. alkenyl of 2-8 carbon atoms,
3. alkynyl of 2-8 carbon atoms,
4. \( \text{C}(=\text{O}) \),
5. \( \text{S}(=\text{O})_2 \), and
6. \( \text{C}(=\text{O})\text{O}^- \),

\( R^5 \) is selected from

1. hydrogen,
2. \( \text{OH} \),
3. alkyl of 1-8 carbon atoms,
4. alkenyl of 2-8 carbon atoms,
5. alkynyl of 2-8 carbon atoms,
6. alkoxy of 1-8 carbon atoms,
7. thioxy of 1-8 carbon atoms,
8. areyl of 6-12 carbon atoms, which may be substituted with
   i. alkyl of 1-6 carbon atoms,
   ii. alkenyl of 2-6 carbon atoms,
   iii. alkynyl of 2-6 carbon atoms,
   iv. alkoxy of 1-6 carbon atoms,
   v. halogen,
   vi. haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
   vii. haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
   viii. areyl of 6-12 carbon atoms, or
   ix. heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,
(9) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with
   (i) alkyl of 1-6 carbon atoms,
   (ii) alkenyl of 2-6 carbon atoms,
   (iii) alkynyl of 2-6 carbon atoms,
   (iv) alkoxy of 1-6 carbon atoms,
   (v) halogen,
   (vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
   (vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
   (viii) aryl of 6-12 carbon atoms, or
(8) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,
(13) cycloalkyl of 3-7 carbon atoms,
(14) heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O, and
(15) NR^8R^{10},
   with the proviso that R^5 is not alkoxy of 4 carbon atoms when R^1 is hydrogen,
   R^2 is R^4R^5, R^1 is hydrogen, and R^4 is alkyl of 3 carbon atoms,
   with the further proviso that R^5 is not unsubstituted aryl of 6 carbon atoms
   when R^1 is hydrogen, R^2 is R^4R^5, R^1 is hydrogen, and R^4 is alkyl of 1 carbon atom,
   (g) R^6 and R^7 are independently selected from
   (1) alkyl of 1-8 carbon atoms,
   (2) alkenyl of 2-8 carbon atoms, and
   (1) alkynyl of 2-8 carbon atoms,
   (h) R^8 is selected from
   (1) OH,
   (2) aryl of 6-12 carbon atoms, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(i) \( R^9 \) and \( R^{10} \) are independently selected from

(1) hydrogen,
(2) alkyl of 1-8 carbon atoms,
(3) alkenyl of 2-8 carbon atoms, and
(4) alkynyl of 2-8 carbon atoms,
(5) or \( R^9 \) and \( R^{10} \) combine together with the nitrogen atom to which they are attached to form

(i) a 5-7 membered, unsaturated ring which may contain 1-2 additional heteroatoms selected from N, S and O, or to form

(ii) a 5-7 membered, saturated ring which may contain 1-2 additional heteroatoms selected from NH, NR\(^{11} \), S and O;

with the proviso that \( R^9 \) and \( R^{10} \) are not both alkyl of 1 carbon atom when \( R^1 \) is hydrogen, \( R^2 \) is \( R^9 R^5 \), \( R^3 \) is hydrogen, \( R^4 \) is alkyl of 2 carbon atoms, and \( R^5 \) is \( NR^9 R^{10} \), and

(j) \( R^{11} \) is selected from

(1) alkyl of 1-8 carbon atoms,
(2) alkenyl of 2-8 carbon atoms, and
(3) alkynyl of 2-8 carbon atoms,

and pharmaceutically acceptable salts thereof.

2. The compound of claim 1, wherein

(a) \( X \) is \( NR^1 R^2 \),

(b) \( Y \) is selected from the group consisting of S and O, and
(c) R¹ and R² are independently selected from the group consisting of
(1) hydrogen,
(2) alkyl of 1-8 carbon atoms,
(3) alkenyl of 2-8 carbon atoms,
(4) alkynyl of 2-8 carbon atoms,
(5) cycloalkyl of 3-7 carbon atoms,
(6) polycycloalkyl of 5-9 carbon atoms,
(7) heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O,
(8) aryl of 6-12 carbon atoms, which may be substituted with
   (i) alkyl of 1-6 carbon atoms,
   (ii) alkenyl of 2-6 carbon atoms,
   (iii) alkynyl of 2-6 carbon atoms,
   (iv) alkoxy of 1-6 carbon atoms,
   (v) halogen,
   (vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
   (vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(8) aryl of 6-12 carbon atoms, or
(9) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,
   (i) alkyl of 1-6 carbon atoms,
   (ii) alkenyl of 2-6 carbon atoms,
   (iii) alkynyl of 2-6 carbon atoms,
   (iv) alkoxy of 1-6 carbon atoms,
   (v) halogen,
(9) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with
   (vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
   (vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(viii) aryl of 6-12 carbon atoms, or
(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

5 (10) \( R^4-R^8 \),

or \( R^1 \) and \( R^2 \) combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered monocyclic saturated ring, or combine to form, together with the nitrogen atom to which they are attached, a 6-10 membered fused polycyclic saturated ring, or combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered unsaturated ring, wherein said monocyclic saturated ring, polycyclic saturated ring or unsaturated ring may be substituted with 1-2 substituents selected from the group consisting of OH, alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, cycloalkyl of 3-7 carbon atoms, heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O,

10 halogen, haloalkyl of 1-2 carbon atoms and a number of halogen atoms up to the perhalo level, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, and \( R^7-R^8 \), and pharmaceutically acceptable salts thereof.

20

3. A method of treating or preventing a PDE7B-mediated disease or condition comprising administering to a mammal in need thereof an effective amount of the compound of claim 1.

25

4. The method of claim 3 wherein the disease or condition is osteoporosis.

5. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable adjuvant.

30

6. A method of treating or preventing a PDE7B-mediated disease or condition comprising administering to a mammal in need thereof an effective amount of the compound of claim 2.
7. The method of claim 6 wherein the disease or condition is osteoporosis.

8. A pharmaceutical composition comprising the compound of claim 2 and a pharmaceutically acceptable adjuvant.

9. A method of treating or preventing a PDE7B-mediated disease or condition comprising administering to a mammal in need thereof an effective amount of a compound of formula II:

   (II)

wherein

(a) X is selected from halogen and NR\(^1\)R\(^2\),
(b) Y is selected from NR\(^3\), S and O,
(c) R\(^1\) and R\(^2\) are independently selected from
   (1) hydrogen,
   (2) alkyl of 1-8 carbon atoms,
   (3) alkenyl of 2-8 carbon atoms,
   (4) alkynyl of 2-8 carbon atoms,
   (5) cycloalkyl of 3-7 carbon atoms,
   (6) polycycloalkyl of 5-9 carbon atoms,
   (7) heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O,
   (8) aryl of 6-12 carbon atoms, which may be substituted with
      (i) alkyl of 1-6 carbon atoms,
      (ii) alkenyl of 2-6 carbon atoms,
      (iii) alkynyl of 2-6 carbon atoms,
      (iv) alkoxy of 1-6 carbon atoms,
      (v) halogen,
(vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,

(vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,

(viii) aryl of 6-12 carbon atoms, or

(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with

(i) alkyl of 1-6 carbon atoms,

(ii) alkenyl of 2-6 carbon atoms,

(iii) alkynyl of 2-6 carbon atoms,

(iv) alkoxy of 1-6 carbon atoms,

(v) halogen,

(vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,

(vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,

(viii) aryl of 6-12 carbon atoms, or

(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

(10) $R^4.R^5$,

(11) or $R^1$ and $R^2$ combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered monocyclic saturated ring, which optionally contains 1-2 additional heteroatoms selected from the group consisting of NH, $NR^6$, S and O, or combine to form, together with the nitrogen atom to which they are attached, a 6-10 membered fused polycyclic saturated ring, which optionally contains 1-2 additional heteroatoms selected from the group consisting of NH, $NR^6$, S and O, or combine to form, together with the nitrogen atom to which they are attached, a 5-7 membered unsaturated ring, which optionally contains 1-2 additional heteroatoms selected from the group consisting of N, S and O, wherein said monocyclic saturated ring, polycyclic
saturated ring or unsaturated ring may be substituted with 1-2
substituents selected from the group consisting of OH, alkyl of 1-6
carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon
atoms, cycloalkyl of 3-7 carbon atoms, heterocycloalkyl of 2-6 carbon
atoms and 1-2 heteroatoms selected from NH, S and O, halogen,
haloalkyl of 1-2 carbon atoms and a number of halogen atoms up to the
perhalo level, alkoxy of 1-6 carbon atoms, haloalkoxy of 1-6 carbon
atoms and a number of halogen atoms up to the perhalo level, and
R²R⁸,

R³ is selected from the group consisting of

(1) hydrogen,
(2) alkyl of 1-8 carbon atoms,
(3) alkenyl of 2-8 carbon atoms,
(4) alkynyl of 2-8 carbon atoms,
(5) cycloalkyl of 3-7 carbon atoms,
(6) aryl of 6-12 carbon atoms, which may be substituted with
   (i) alkyl of 1-6 carbon atoms,
   (ii) alkenyl of 2-6 carbon atoms,
   (iii) alkynyl of 2-6 carbon atoms,
   (iv) halogen,
   (v) haloalkyl of 1-6 carbon atoms and a number of halogen atoms
       up to the perhalo level,
   (vi) haloalkoxy of 1-6 carbon atoms and a number of halogen
        atoms up to the perhalo level,
   (vii) haloalkoxy of 1-6 carbon atoms and a number of halogen
        atoms up to the perhalo level,
   (viii) aryl of 6-12 carbon atoms, or
   (ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected
        from N, S and O,

(7) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N,
S and O, which may be substituted with
   (i) alkyl of 1-6 carbon atoms,
   (ii) alkenyl of 2-6 carbon atoms,
(iii) alkynyl of 2-6 carbon atoms,  
(iv) alkoxy of 1-6 carbon atoms,  
(v) halogen,  
(vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,  
(vi) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,  
(vii) aryl of 6-12 carbon atoms, or  
(viii) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,

(e) $R^4$ is selected from  
(1) alkyl of 1-8 carbon atoms,  
(2) alkenyl of 2-8 carbon atoms,  
(3) alkynyl of 2-8 carbon atoms,  
(4) C(=O),  
(5) S(=O)$_2$, and  
(6) C(=O)O$^{-}$,

(f) $R^5$ is selected from  
(1) hydrogen,  
(2) OH,  
(3) alkyl of 1-8 carbon atoms,  
(4) alkenyl of 2-8 carbon atoms,  
(5) alkynyl of 2-8 carbon atoms,  
(6) alkoxy of 1-8 carbon atoms,  
(7) thioxy of 1-8 carbon atoms,  
(8) aryl of 6-12 carbon atoms, which may be substituted with  
(i) alkyl of 1-6 carbon atoms,  
(ii) alkenyl of 2-6 carbon atoms,  
(iii) alkynyl of 2-6 carbon atoms,  
(iv) alkoxy of 1-6 carbon atoms,  
(v) halogen,  
(vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(viii) aryl of 6-12 carbon atoms, and
(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,
(9) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with
(i) alkyl of 1-6 carbon atoms,
(ii) alkenyl of 2-6 carbon atoms,
(iii) alkynyl of 2-6 carbon atoms,
(iv) alkoxy of 1-6 carbon atoms,
(v) halogen,
(vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(viii) aryl of 6-12 carbon atoms, and
(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O,
(10) cycloalkyl of 3-7 carbon atoms,
(11) heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O, and
(12) NR^9R^{10},
(g) R^6 and R^7 are independently selected from
(1) alkyl of 1-8 carbon atoms,
(2) alkenyl of 2-8 carbon atoms, and
(3) alkynyl of 2-8 carbon atoms;
(h) R^8 is selected from
(1) OH,
(2) aryl of 6-12 carbon atoms, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

(3) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with alkyl of 1-6 carbon atoms, alkenyl of 2-6 carbon atoms, alkynyl of 2-6 carbon atoms, alkoxy of 1-6 carbon atoms, halogen, haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level, aryl of 6-12 carbon atoms or heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

(i) $R^9$ and $R^{10}$ are independently selected from

(1) hydrogen,
(2) alkyl of 1-8 carbon atoms,
(3) alkenyl of 2-8 carbon atoms, and
(4) alkynyl of 2-8 carbon atoms,

(5) or $R^9$ and $R^{10}$ combine together with the nitrogen atom to which they are attached to form

(i) a 5-7 membered, unsaturated ring which may contain 1-2 additional heteroatoms selected from N, S and O, or to form

(ii) a 5-7 membered, saturated ring which may contain 1-2 additional heteroatoms selected from NH, NR$^{11}$, S and O; and

(j) $R^{11}$ is selected from

(1) alkyl of 1-8 carbon atoms,
(2) alkenyl of 2-8 carbon atoms, and
(3) alkynyl of 2-8 carbon atoms;

and pharmaceutically acceptable salts thereof.

10. The method of claim 9, wherein Y is S or NH.

11. The method of claim 9, wherein the disease or condition is osteoporosis.
12. A method of treating or preventing a PDE7B-mediated disease or condition comprising administering to a mammal in need thereof an effective amount of a compound of formula III:

\[
\begin{align*}
\text{III}
\end{align*}
\]

wherein
(a) Y is selected from NR², S, and O and
(b) R¹ and R² are independently selected from
(1) hydrogen,
(2) alkyl of 1-8 carbon atoms,
(3) alkenyl of 2-8 carbon atoms,
(4) alkynyl of 2-8 carbon atoms,
(5) cycloalkyl of 3-7 carbon atoms,
(6) polycycloalkyl of 5-9 carbon atoms,
(7) heterocycloalkyl of 2-6 carbon atoms and 1-2 heteroatoms selected from NH, S and O,
(8) aryl of 6-12 carbon atoms, which may be substituted with
(i) alkyl of 1-6 carbon atoms,
(ii) alkenyl of 2-6 carbon atoms,
(iii) alkynyl of 2-6 carbon atoms,
(iv) alkoxy of 1-6 carbon atoms,
(v) halogen,
(vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(viii) aryl of 6-12 carbon atoms, or
(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, and

(9) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O, which may be substituted with

(i) alkyl of 1-6 carbon atoms,
(ii) alkenyl of 2-6 carbon atoms,
(iii) alkynyl of 2-6 carbon atoms,
(iv) alkoxy of 1-6 carbon atoms,
(v) halogen,

(vi) haloalkyl of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(vii) haloalkoxy of 1-6 carbon atoms and a number of halogen atoms up to the perhalo level,
(viii) aryl of 6-12 carbon atoms, or

(ix) heteroaryl of 4-11 carbon atoms and 1-2 heteroatoms selected from N, S and O;

and pharmaceutically acceptable salts thereof.

13. The method of claim 12, wherein the disease or condition is osteoporosis.