BENZIMIDAZOLE, BENZTHIAZOLE AND BENZOXAZOLE DERIVATIVES AND THEIR USE AS LTA4H MODULATORS

Field of the Invention

This invention relates to leukotriene A4 hydrolase (LTA4H) inhibitors for the treatment of inflammation. More particularly, this invention relates to certain benzooxazol-2-yl, benzothiazol-2-yl and 1*H*-benzoimidazol-2-yl compounds useful as selective inhibitors of the LTA4H enzyme for the treatment of inflammatory conditions.

Background of the Invention

Inflammation is normally an acute response by the immune system to invasion by microbial pathogens, chemicals or physical injury. In some cases, however, the inflammatory response can progress to a chronic state, and be the cause of inflammatory disease. Therapeutic control of this chronic inflammation in diverse diseases is a major medical need.

Leukotrienes (LT) are biologically active metabolites of arachidonic acid (B. Samuelsson, Science 1983, 220(4597):568–575) that have been implicated in inflammatory diseases, including asthma (D.A. Munafo et al., J. Clin. Invest. 1994, 93(3):1042–1050), inflammatory bowel disease (IBD) (P. Sharon and W.F. Stenson, Gastroenterology 1984, 86(3):453–460), chronic obstructive pulmonary disease (COPD) (P.J. Barnes, Respiration 2001, 68(5):441–448), arthritis (R.J. Griffiths et al., Proc. Natl. Acad. Sci. U.S.A. 1995, 92(2):517–521; F. Tsuji et al., Life Sci. 1998, 64(3):L51–L56), psoriasis (K. Ikai, J. Dermatol. Sci. 1999, 21(3):135–146; Y.I. Zhu and M.J. Stiller, Skin Pharmacol. Appl. Skin Physiol. 2000, 13(5):235–245) and atherosclerosis (Friedrich, E. B. et al. *Arterioscler Thromb Vasc Biol* **23**, 1761-7 (2003); Subbarao, K. et al. *Arterioscler Thromb Vasc Biol* **24**, 369-75 (2004); Helgadottir, A. et al. *Nat Genet* **36**, 233-9 (2004); Jala, V.R. et al *Trends in Immun.* 25, 315-322 (2004)). The synthesis of leukotrienes is initiated by the conversion of arachidonic acid to an unstable epoxide intermediate, leukotriene A4 (LTA4), by 5-lipoxygenase (5-LO) (A.W. Ford-Hutchinson et al., Annu. Rev. Biochem. 1994, 63:383–347).

This enzyme is expressed predominantly by cells of myeloid origin, particularly neutrophils, eosinophils, monocytes/macrophages and mast cells (G.K. Reid et al., J. Biol. Chem. 1990, 265(32):19818–19823). LTA4 can either be conjugated with glutathione by leukotriene C4 (LTC4) synthase to produce the cysteinyl leukotriene, LTC4, or hydrolyzed to the diol, leukotriene B4 (LTB4) (B. Samuelsson, Science 1983, 220(4597):568–575). LTC4 and its metabolites, LTD4 and LTE4, induce smooth muscle contraction, broncho-constriction and vascular permeability, while LTB4 is a potent chemo-attractant and activator of neutrophils.

The stereospecific hydrolysis of LTA4 to LTB4 is catalyzed by leukotriene A4 hydrolase (LTA4H), a zinc-containing, cytosolic enzyme. This enzyme is ubiquitously expressed, with high levels in small intestinal epithelial cells, lung, and aorta (B. Samuelsson and C.D. Funk, J. Biol. Chem. 1989, 264(33):19469–19472). Moderate expression of LTA4H is observed in leukocytes, particularly neutrophils (T. Yokomizo et al., J. Lipid Mediators Cell Signalling 1995, 12(2,3):321–332).

Leukotriene B4 is a key pro-inflammatory mediator, able to recruit inflammatory cells, such as neutrophils and eosinophils, as well as activate neutrophils (F.A. Fitzpatrick et al., Ann. N. Y. Acad. Sci. 1994, 714:64–74; S.W. Crooks and R.A. Stockley, Int. J. Biochem. Cell Biol. 1998, 30(2):173–178; A. Klein et al., J. Immunol. 2000, 164:4271–4276). LTB4 mediates its pro-inflammatory effects by binding to G protein-coupled receptors, leukotriene B4 receptor 1 (BLT1) and leukotriene B4 receptor 2 (BLT2) (T. Yokomizo et al., Arch. Biochem. Biophys. 2001, 385(2):231–241). The receptor first identified, BLT1, binds LTB_4 with high affinity, leading to intracellular signaling and chemotaxis. BLT1 is expressed mainly in peripheral leukocytes, particularly neutrophils, eosinophils, macrophages (Huang, W. W. et al. *J Exp Med* **188**, 1063-74 (1998)) and monocytes (Yokomizo, T., Izumi, T. & Shimizu, T. *Life Sci* **68**, 2207-12 (2001)). The murine receptor is also expressed on effector T cells and was recently shown to mediate LTB_4-dependent migration of effector $CD8^+$ T cells (Goodarzi, K., Goodarzi, M., Tager, A. M., Luster, A. D. & von Andrian, U. H. *Nat Immunol* **4**, 965-73 (2003).Ott, V. L., Cambier, J. C., Kappler, J., Marrack, P. & Swanson, B. J. *Nat Immunol* **4**, 974-81 (2003)), early effector

$CD4^+$ T helper type 1 (T_H1) and T_H2 chemotaxis and adhesion to endothelial cells, as well as early effector $CD4^+$ and $CD8^+$ T cell recruitment in an asthma animal model (Tager, A. M. et al.. *Nat Immunol* **4**, 982-90 (2003)).LTB4 receptor BLT2 (S. Wang et al., J. Biol. Chem. 2000, 275(52):40686–40694; T. Yokomizo et al., J. Exp. Med. 2000, 192(3):421–431) shares 42% amino acid homology with BLT1, but is more broadly expressed, including in peripheral tissues such as the spleen, ovary and liver, as well as in leukocytes. BLT2 binds LTB4 with lower affinity than BLT1 does, mediates chemotaxis at higher concentrations of LTB4, and differs from BLT1 in its affinity for certain antagonists. While LTB4 receptor antagonists may differ in their affinity for BLT1 versus BLT2, blocking the production of LTB4 using LTA4H inhibitors would be expected to inhibit the downstream events mediated through both BLT1 and BLT2.

Studies have shown that introduction of exogenous LTB4 into normal tissues can induce inflammatory symptoms (R.D.R. Camp et al., Br. J. Pharmacol. 1983, 80(3):497–502; R. Camp et al., J. Invest. Dermatol. 1984, 82(2):202–204). Elevated levels of LTB4 have been observed in a number of inflammatory diseases including IBD, COPD, psoriasis, rheumatoid arthritis (RA), cystic fibrosis and asthma (S.W. Crooks and R.A. Stockley, Int. J. Biochem. Cell Biol. 1998, 30(2):173–178). Therefore, reduction of LTB4 production by an inhibitor of LTA4H activity would be predicted to have therapeutic potential in a wide range of diseases.

This idea is supported by a study of LTA4H-deficient mice that, while otherwise healthy, exhibited markedly decreased neutrophil influx in arachidonic acid-induced ear inflammation and zymosan-induced peritonitis models (R.S. Byrum et al., J. Immunol. 1999, 163(12): 6810–6819). LTA4H inhibitors have been shown to be effective anti-inflammatory agents in pre-clinical studies. For example, oral administration of LTA4H inhibitor SC57461 caused inhibition of ionophore-induced LTB4 production in mouse blood ex vivo, and in rat peritoneum in vivo (J.K. Kachur et al., J. Pharm. Exp. Ther. 2002, 300(2), 583–587). Eight weeks of treatment with the same inhibitor compound significantly improved colitis symptoms in cotton top tamarins (T.D. Penning, Curr. Pharm. Des. 2001, 7(3):163–179). The spontaneous colitis that

develops in these animals is very similar to human IBD. The results therefore indicate that LTA4H inhibitors would have therapeutic utility in this and other human inflammatory diseases.

Events that elicit the inflammatory response include the formation of the pro-inflammatory mediator leukotriene B4. Hydrolase LTA4H catalyzes the formation of this mediator, and LTA4H inhibitors block the production of the pro-inflammatory mediator LTB4, thus providing the ability to prevent and/or treat leukotriene-mediated conditions, such as inflammation. The inflammatory response is characterized by pain, increased temperature, redness, swelling, or reduced function, or by a combination of two or more of these symptoms. Regarding the onset and evolution of inflammation, inflammatory diseases or inflammation-mediated diseases or conditions include, but are not limited to, acute inflammation, allergic inflammation, and chronic inflammation.

Examples of textbooks on the subject of inflammation include J. I. Gallin and R. Snyderman, *Inflammation: Basic Principles and Clinical Correlates*, 3rd Edition, (Lippincott Williams & Wilkins, Philadelphia, 1999); V. Stvrtinova, J. Jakubovsky and I. Hulin, "Inflammation and Fever", *Pathophysiology Principles of Diseases* (Textbook for Medical Students, Academic Press, 1995); Cecil et al., *Textbook Of Medicine*, 18th Edition (W.B. Saunders Company, 1988); and Steadmans Medical Dictionary.

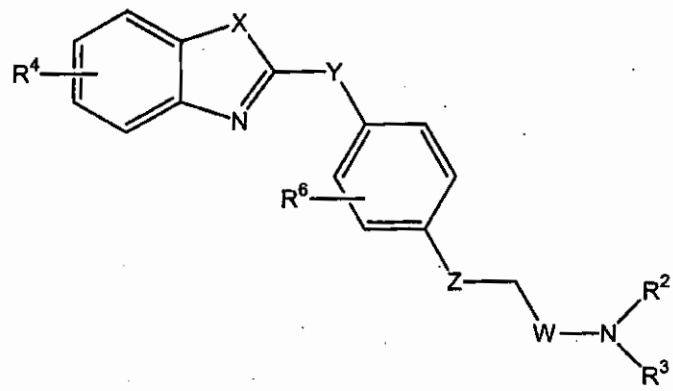
Background and review material on inflammation and conditions related with inflammation can be found in articles such as the following: C. Nathan, Points of control in inflammation, *Nature* 2002, 420:846-852; K.J. Tracey, The inflammatory reflex, *Nature* 2002, 420:853-859; L.M. Coussens and Z. Werb, Inflammation and cancer, *Nature* 2002, 420:860-867; P. Libby, Inflammation in atherosclerosis, *Nature* 2002, 420:868-874; C. Benoist and D. Mathis, Mast cells in autoimmune disease, *Nature* 2002, 420:875-878; H.L. Weiner and D.J. Selkoe, Inflammation and therapeutic vaccination in CNS diseases, *Nature* 2002, 420:879-884; J. Cohen, The immunopathogenesis of sepsis, *Nature* 2002, 420:885-891; D. Steinberg, Atherogenesis in perspective: Hypercholesterolemia and inflammation as partners in crime, *Nature Medicine* 2002, 8(11):1211-1217. Cited references are incorporated herein by reference.

Inflammation is due to any one of a plurality of conditions, such as asthma, chronic obstructed pulmonary disease (COPD), atherosclerosis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases (including Crohn's disease and ulcerative colitis), or psoriasis, which are each characterized by excessive or prolonged inflammation at some stage of the disease.

Applicants have discovered benzooxazol-2-yl, benzothiazol-2-yl and 1*H*-benzoimidazol-2-yl compounds and derivatives thereof; their use as inhibitors of enzymes, such as the LTA4H enzyme, in the formation of pro-inflammatory mediators, such as the LTB4 mediator; also their use for the treatment of inflammatory conditions; and the preparation of pharmaceutical compositions for the treatment of inflammation.

Summary of the Invention

There are provided by the present invention LTA4H enzyme inhibitors, which have the following general formula (I):



(I)

wherein

X is selected from the group consisting of NR^5, O, and S, with R^5 being one of H and CH_3;

Y is selected from the group consisting of CH_2, and O;

Z is selected from the group consisting of O and bond;

W is selected from the group consisting of CH_2 and CHR^1-CH_2, with R^1 being one of H and OH, wherein the R^1-attached carbon member in said CHR^1-CH_2 is not directly attached to the nitrogen member to which said W is attached;

R^4 is selected from the group consisting of H, OCH_3, Cl, F, Br, I, OH, NH_2, CN, CF_3 and CH_3;

R^6 is H or F; and

R^2 and R^3 are each independently selected from the group consisting of

A) H, C_{1-7}alkyl, C_{3-7}alkenyl, wherein the carbon in said alkenyl that is attached to the nitrogen member has only single bonds, C_{3-7}alkynyl, wherein the carbon in said alkynyl that is attached to the nitrogen member has only single bonds, C_{3-7}cycloalkyl optionally benzofused, C_{5-7}cycloalkenyl, -C_{3-7}cycloalkylC_{1-7}alkyl, -C_{1-7}alkylC_{3-7}cycloalkyl and phenyl, wherein each of the substituents A) is independently substituted

with 0, 1, or 2 R^Q, and each of said R^Q is a substituent at a carbon member that is at least one carbon member removed from the nitrogen member;

B) a substituent $HetR^a$;

C) -C_{1-7}alkylC(O)R^X, optionally substituted with CH_2R^{Ar} or $CH_2R^{Ar'}$;

D) -C_{2-5}alkylC(O)R^X, wherein two valence allowed carbon members in the C_{2-5}alkyl of said -C_{2-5}alkylC(O)R^X are part of a saturated C_{3-6}carbocycle;

E) -C_{2-5}alkylOH wherein two valence allowed carbon members in the C_{2-5}alkyl of said -C_{2-5}alkylOH are part of a saturated C_{3-6}carbocycle;

F) -C_{0-4}alkylphenyl, wherein the phenyl in said -C_{0-4}alkylphenyl is fused at two adjacent carbon members in said phenyl to R^f, or is benzofused;

G) -C_{0-4}alkylAr^6, where Ar^6 is a 6-membered heteroaryl having a carbon member point of attachment and having one or two –N= heteroatom members, and benzofused;

H) -C_{0-4}alkylAr^5, where Ar^5 is a 5-membered heteroaryl, having one heteroatom member selected from the group consisting of O, S, and >NR^Y, and having 0 or 1 –N= additional heteroatom member, optionally containing two carbonyl groups, and optionally benzofused;

I) -C_{1-4}alkyl$Ar^{5'}$, where $Ar^{5'}$ is a 5-membered heteroaryl containing 3 or 4 nitrogen members, optionally substituted with R^Y, and having a valence allowed site as a point of attachment;

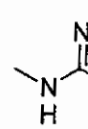
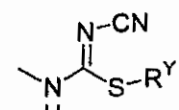
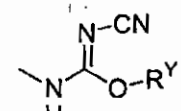
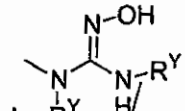
J) -C_{0-4}alkylAr^{6-6}, where Ar^{6-6} is a C_{0-4}alkyl-attached phenyl fused at valence allowed sites to a 6-membered heteroaryl, wherein said 6-membered heteroaryl has one or two –N= heteroatom members;

K) -C_{0-4}alkylAr^{6-5}, where Ar^{6-5} is a C_{0-4}alkyl-attached phenyl fused at valence allowed sites to a 5-membered heteroaryl, said 5-membered heteroaryl having one heteroatom member selected from the group consisting of O, S, and >NR^Y, and said 5-membered heteroaryl having 0 or 1 additional heteroatom member which is –N=; and

L) one of 2-(4-ethyl-phenoxy)-benzothiazole, 2-(4-ethyl-phenoxy)-benzooxazole, and 2-(4-ethyl-phenoxy)-1*H*-benzoimidazole;

M) SO_2C_{1-4}alkyl;

alternatively R^2 and R^3 are taken together with the nitrogen to which they are attached to form a heterocyclic ring that contains at least one heteroatom member that is said attachment nitrogen, said heterocyclic ring being selected from the group consisting of

i) a 4-7 membered heterocyclic ring $HetR^b$, said 4-7 membered heterocyclic ring $HetR^b$ having one heteroatom member that is said attachment nitrogen, and being substituted with 0, 1, or 2 substituents at the same or at different substitution members, said substituents being selected from the group consisting of $-R^Y$, -CN, $-C(O)R^Y$, $-C_{0-4}alkylCO_2R^Y$, $-C_{0-4}alkylC(O)CO_2R^Y$, $-C_{0-4}alkylOR^Y$, $-C_{0-4}alkylC(O)NR^YR^Z$, $-C_{0-4}alkylNR^YC(O)R^Z$, $-C(O)NR^ZOR^Y$, $-C_{0-4}alkylNR^YC(O)CH_2OR^Y$, $-C_{0-4}alkylNR^YC(O)CH_2C(O)R^Y$, $-C_{0-4}alkylNR^YCO_2R^Y$, $-C_{0-4}alkylNR^YC(O)NR^YR^Z$, $-C_{0-4}alkylNR^YC(S)NR^YR^Z$, $-NR^YC(O)CO_2R^Y$,$-NR^YR^Z$, $-C_{0-4}alkylNR^WSO_2R^Y$,1,3-dihydro-indol-2-one-1-yl, 1,3-dihydro-benzoimidazol-2-one-1-yl, tetrazol-5-yl, 1-R^Y-1*H*-tetrazol-5-yl, R^Y-triazolyl, 2-R^Y-2*H*-tetrazol-5-yl, pyrrolidine-2-thion-1-yl, piperidine-2-thion-1-yl, $-C_{0-4}alkylC(O)N(R^Y)(SO_2R^Y)$, $-C_{0-4}alkylN(R^Y)(SO_2)NR^YR^Y$, $-C_{0-4}alkylN(R^Y)(SO_2)NR^YCO_2R^Y$, halo,  ,  ,  , and  ;

ii) a 5-7 membered heterocyclic ring $HetR^c$, said 5-7 heterocyclic ring $HetR^c$ having one additional heteroatom member separated from said attachment nitrogen by at least one carbon members, said additional heteroatom member being selected from the group consisting of O, $S(=O)_{0-2}$, and $>NR^M$, said 5-7 membered heterocyclic ring $HetR^c$ having 0 or 1 carbonyl members, and being substituted with 0, 1, or 2 substituents at the same or at different carbon substitution members, said substituents being selected from the group consisting of $-C(O)R^Y$, $-CO_2R^Y$ $-C_{3-4}alkylCO_2R^Y$ and R^Z;

iii) one of imidazolidin-1-yl, 2-imidazolin-1-yl, pyrazol-1-yl, imidazol-1-yl, 2*H*-tetrazol-2-yl, 1*H*-tetrazol-1-yl, pyrrol-1-yl, 2-pyrrolin-1-yl, and 3-pyrrolin-1-yl, wherein each of said 2*H*-tetrazol-2-yl and 1*H*-tetrazol-1-yl is substituted at the carbon member with 0 or 1 of $-C_{0-4}alkylR^Z$, $-C_{0-4}alkylSR^Y$, $-C_{0-4}alkylCO_2R^Y$, and substituent $HetR^a$; and

iv) one of 1,2,3,4-tetrahydro-quinolin-1-yl, 1,2,3,4-tetrahydro-isoquinolin-2-yl, indol-1-yl, isoindol-2-yl, indolin-1-yl, benzimidazol-1-yl, 2,8-diaza-spiro[4.5]decan-1-one-8-yl, 4-{[(2-tert-butoxycarbonylamino-cyclobutanecarbonyl)-amino]-methyl}-piperidin-1-yl, 4-{[(2-amino-cyclobutanecarbonyl)-amino]-methyl}-piperidin-1-yl, 3,9-diaza-spiro[5.5]undecane-3-carboxylic acid-9-yl tert-butyl ester, 4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-8-yl, and 4-oxo-1,3,8-triaza-spiro[4.5]dec-8-yl;

wherein

substituent $HetR^a$ is a 4-7 membered heterocyclic ring having a carbon member point of attachment and containing a member $>NR^M$ as a heteroatom member, and said heteroatom member being separated from said carbon member point of attachment by at least 1 additional carbon member;

R^K is selected from the group consisting of H, $-C_{1-4}alkyl$, $-C_{0-4}alkylR^{Ar}$ each optionally substituted with 1, 2, or 3 substituents R^N

R^L is selected from the group consisting of $-CO_2R^S$ and $-C(O)NR^SR^{S'}$;

R^M is selected from the group consisting of R^Z, indol-7-yl, $-SO_2R^Y$, $-C_{3-4}alkylCO_2R^Y$, $-CO_2R^Y$, $-C(O)NR^ZOR^Y$, $-C(O)R^Y$, $-C(O)C_{1-4}alkylOR^Y$, $-C_{0-4}alkylC(O)NR^SR^{S'}$, $C_{0-4}alkylC(O)CO_2R^Y$, 1,3-dihydro-indol-2-one-1-yl, 1,3-dihydro-benzoimidazol-2-one-1-yl, tetrazol-5-yl, 1-R^Y-1*H*-tetrazol-5-yl, R^Y-triazolyl, 2-R^Y-2*H*-tetrazol-5-yl and $-C_{0-4}alkylC(O)N(R^Y)(SO_2R^Y)$, each optionally substituted with 1, 2 or 3 substituents R^N;

R^N is selected from the group consisting of OCH_3, Cl, F, Br, I, OH, NH_2, CN, CF_3, CH_3, $OC(O)CH_3$, and NO_2;

R^P is selected from the group consisting of R^Y, $-C_{2-4}alkylOR^Y$, R^{Ar}, $-C_{1-2}alkylCO_2R^Y$, $-C_{1-2}alkylCONR^SR^{S'}$, indol-7-yl, and $-SO_2C_{1-4}alkyl$;

R^Q is selected from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, trichloromethyl, -CN, -C_{1-4}alkyl, -C_{0-4}alkylR^{Ar}, -C_{0-4}alkyl$R^{Ar'}$, -C_{0-4}alkylOR^Y, -C_{0-4}alkylCO_2R^Y, -C_{0-4}alkylNR^YR^Z, -C_{0-4}alkylNR^YCOR^Y, -C_{0-4}alkyl$NR^YCONR^YR^Z$, -C_{0-4}alkyl$NR^YSO_2R^Y$, and -C_{0-4}alkylSR^Y;

R^S and $R^{S'}$ are independently selected from the group consisting of H, -C_{1-4}alkyl, and -C_{0-4}alkylphenyl; alternatively, R^S and $R^{S'}$ are taken together with the nitrogen member to which said R^S and $R^{S'}$ are attached to form a 4-7 membered heterocyclic ring having 0 or 1 additional heteroatom member selected from the group consisting of O, S, and $>NR^Y$, provided that said additional heteroatom member is separated by at least two carbon members from said nitrogen member to which said R^S and $R^{S'}$ are attached, and provided that where R^Y is C_{0-4}alkylR^{Ar}, then R^{Ar} is not substituted with R^L;

R^W is selected from the group consisting of R^Y, and -C_{3-7}cycloalkyl;

R^X is selected from the group consisting of -OR^Y, -NR^YR^Z, -C_{1-4}alkyl, and -C_{0-4}alkylR^{Ar};

R^Y is selected from the group consisting of H, -C_{1-4}alkyl, -C_{0-4}alkylR^{Ar} and -C_{0-4}alkyl$R^{Ar'}$, each optionally substituted with 1, 2, or 3 substituents R^N;

R^Z is selected from the group consisting of R^Y, -C_{2-4}alkylOR^Y, -C_{1-2}alkylCO_2R^Y, -C_{1-2}alkylC(O)$NR^SR^{S'}$, and -C_{2-4}alkyl$NR^SR^{S'}$;

when R^Y and R^Z are attached to a nitrogen member, R^Y and R^Z are selected as defined above, or R^Y and R^Z are taken together with the R^Y- and R^Z-attached nitrogen member to form a 4-7 membered heterocyclic ring HetR^d having 0 or 1 additional heteroatom members selected from the group consisting of O, S, and $>NR^M$, said 4-7 membered heterocyclic ring HetR^d having 0 or 1 carbonyl members, and said 4-7 membered heterocyclic ring HetR^d having 0 or 1 valence allowed carbon members substituted with at least one of R^M, -CO_2H, and -C_{0-1}alkylOR^Y;

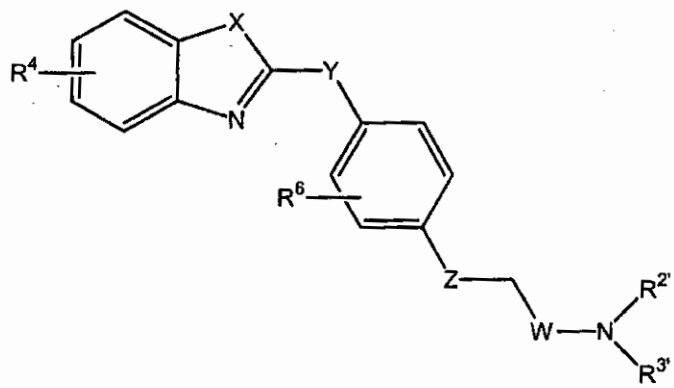
R^{Ar} is a moiety with a carbon member attachment point and said moiety is selected from the group consisting of phenyl, pyridyl, pyrimidyl, and pyrazinyl, wherein each valence allowed carbon member in each of said moieties is independently substituted with at least one of 0, 1, 2 or 3 R^N, and 0 or 1 R^L;

$R^{Ar'}$ is a 3-8 membered ring, having 0, 1 or 2 heteroatom members selected from the group consisting of O, S, N, and >NR^Y, having 0, 1, or 2 unsaturated bonds, having 0 or 1 carbonyl members, wherein each valence allowed member in each of said rings is independently substituted with 0, 1, or 2 R^K; and

R^f is a linear 3- to 5-membered hydrocarbon moiety having 0 or 1 unsaturated carbon-carbon bonds and having 0 or 1 carbonyl members;

or an enantiomer, diasteromer, racemic, tautomer, hydrate, solvate, or a pharmaceutically acceptable salt, ester, or amide thereof.

Embodiments of the present invention comprise new compounds that are LTA4H enzyme inhibitors and have the general formula (II):



(II)

or an enantiomer, diasteromer, racemic, tautomer, hydrate, solvate, or a pharmaceutically acceptable salt, ester, or amide thereof,

wherein

R^4, R^6, X, Y, Z, and W are defined as in compound of formula (I), $R^{2'}$ is defined as R^2 in compound of formula (I), and $R^{3'}$ is defined as R^3 in compound of formula (I), provided that

(a) at least one of said $R^{2'}$ and $R^{3'}$ is not ethyl when one selection in the group consisting of selections (s1), (s2), (s3), and (s4), is satisfied, and each of said selections is specified as

(s1): R^4 is H, Z is O, W is CH_2, Y is CH_2, and X is S;

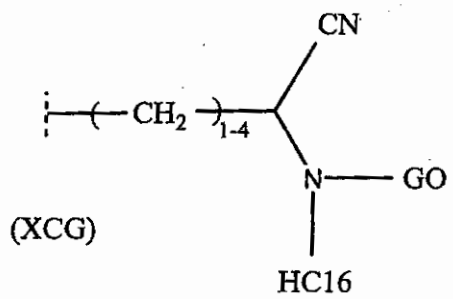
(s2): R^4 is H, Z is O, W is CH_2, Y is CH_2, and X is NH;

(s3): R^4 is H, Z is O, W is CH_2, Y is O, and X is S;

(s4): R^4 is 5-chloro, Z is O, W is CH_2, Y is CH_2, and X is S;

(b) further provided that when Z is bond, Y is CH_2, W is CHR^1-CH_2, R^1 is H, and one of $R^{2'}$ and $R^{3'}$ is 1*H*-imidazol-2-yl, then the other of $R^{2'}$ and $R^{3'}$ is selected from A1), B)-L), wherein B)-L) are as defined above for compound of formula (I), and A1) consists of H, C_{3-7}alkenyl, wherein the carbon in said C_{3-7}alkenyl that is attached to the nitrogen member has only single bonds, C_{3-7}alkynyl, wherein the carbon in said alkynyl that is attached to the nitrogen member has only single bonds, C_{3-7}cycloalkyl optionally benzofused, C_{5-7}cycloalkenyl, -C_{3-7}cycloalkylC_{1-7}alkyl, -C_{1-7}alkylC_{3-7}cycloalkyl; and

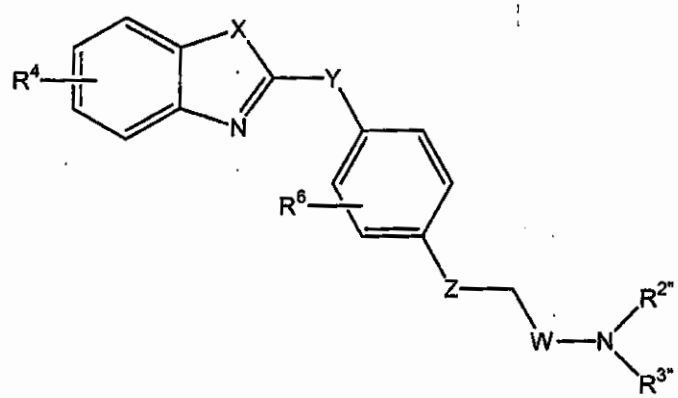
(c) further provided that when X is S, Y is O, Z is bond, and W is CH_2, then one of $R^{2'}$ and $R^{3'}$ Is not XCG when the other is C_{1-6}alkyl, wherein XCG is the group



(XCG)

wherein HC16 is one of H, C_{1-6}alkyl, haloC_{1-6}alkyl, allyl, and C_{1-6}alkoxymethyl, and GO is a group attached by a carbon member that has a =O substituent forming an amido group (>N-C(O)-) with the nitrogen member to wich said GO group is attached.

Other embodiments of the present invention comprise new compounds that are LTA4H enzyme inhibitors and have the general formula (III):



(III)

or an enantiomer, diasteromer, racemic, tautomer, hydrate, solvate, or a pharmaceutically acceptable salt, ester, or amide thereof,

wherein

R^4, R^6, X, Y, Z, and W are defined as in compound of formula (I), $R^{2"}$ is defined as R^2 in compound of formula (I), and $R^{3"}$ is defined as R^3 in compound of formula (I), provided that

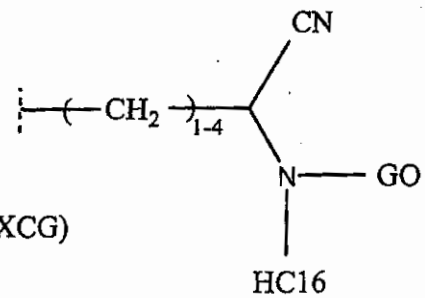
(a) said $R^{2"}$ and $R^{3"}$ further satisfy one of the following:

(e1): at least one of said $R^{2"}$ and $R^{3"}$ is not C_{1-5}alkyl , when Z is O and X is S;

(e2): none of $R^{2"}$ and $R^{3"}$ is C_{1-4}alkylC(O)R^X, with R^X being one of C_{1-4}alkyl, OH, -OC_{1-4}alkyl, -OC_{0-4}alkylR^{Ar}, or –NR^YR^Y, when Y is O, Z is bond, and $R^{2"}$ is different from $R^{3"}$; and

(e3): none of $R^{2"}$ and $R^{3"}$ is -C_{1-6}alkylCN, when Y is O, Z is bond, and $R^{2"}$ is different from $R^{3"}$; and

(b) further provided that when X is S, Y is O, Z is bond, and W is CH_2, then one of $R^{2"}$ and $R^{3"}$ is not XCG when the other is C_{1-6}alkyl, wherein XCG is the group



(XCG)

HC16

wherein HC16 is one of H, C_{1-6}alkyl, haloC_{1-6}alkyl, allyl, and C_{1-6}alkoxymethyl, and GO is a group attached by a carbon member that has a =O substituent forming an amido group (>N-C(O)-) with the nitrogen member to which said GO group is attached.

Isomeric forms of the compounds of the foregoing formulae, and of their pharmaceutically acceptable salts, amides and esters, are encompassed within the present invention, and reference herein to one of such isomeric forms is meant to refer to at least one of such isomeric forms. One of ordinary skill in the art will recognize that compounds according to this invention may exist, for example in a single isomeric form whereas other compounds may exist in the form of a regioisomeric mixture.

Whether stated explicitly or not in any part of the written description and claims, it is understood that each substituent and member assignment in the context of this invention is made independently of any other member and substituent assignment, unless stated otherwise. By way of a first example on substituent terminology, if substituent $S^1_{example}$ is one of S_1 and S_2, and substituent $S^2_{example}$ is one of S_3 and S_4, then these assignments refer to embodiments of this invention given according to the choices $S^1_{example}$ is S_1 and $S^2_{example}$ is S_3; $S^1_{example}$ is S_1 and $S^2_{example}$ is S_4; $S^1_{example}$ is S_2 and $S^2_{example}$ is S_3; $S^1_{example}$ is S_2 and $S^2_{example}$ is S_4; and equivalents of each one of such choices. The shorter terminology "$S^1_{example}$ is one of S_1 and S_2, and $S^2_{example}$ is one of S_3 and S_4" is accordingly used herein for the sake of brevity, but not by way of limitation. The foregoing first example on substituent terminology, which is stated in generic terms, is meant to illustrate the various substituent R assignments described herein. The foregoing convention given herein for substituents extends, when applicable, to members such as X, Y, Z, and W, and the index n.

Furthermore, when more than one assignment is given for any member or substituent, embodiments of this invention comprise the various groupings that can be made from the listed assignments, taken independently, and

equivalents thereof. By way of a second example on substituent terminology, if it is herein described that substituent $S_{example}$ is one of S_1, S_2, and S_3, this listing refers to embodiments of this invention for which $S_{example}$ is S_1; $S_{example}$ is S_2; $S_{example}$ is S_3; $S_{example}$ is one of S_1 and S_2; $S_{example}$ is one of S_1 and S_3; $S_{example}$ is one of S_2 and S_3; $S_{example}$ is one of S_1, S_2 and S_3; and $S_{example}$ is any equivalent of each one of these choices. The shorter terminology "$S_{example}$ is one of S_1, S_2, and S_3" is accordingly used herein for the sake of brevity, but not by way of limitation. The foregoing second example on substituent terminology, which is stated in generic terms, is meant to illustrate the various substituent R assignments described herein. The foregoing convention given herein for substituents extends, when applicable, to members such as X, Y, Z, and W, and the index n.

The nomenclature "C_{i-j}" with $j > i$, when applied herein to a class of substituents, is meant to refer to embodiments of this invention for which each and every one of the number of carbon members, from i to j including i and j, is independently realized. By way of example, the term C_{1-3} refers independently to embodiments that have one carbon member (C_1), embodiments that have two carbon members (C_2), and embodiments that have three carbon members (C_3).

The term C_{n-m}alkyl refers to an aliphatic chain, whether straight or branched, with a total number N of carbon members in the chain that satisfies $n \leq N \leq m$, with $m > n$.

When any variable referring to a substituent, compound member or index, occurs more than once, the full range of assignments is meant to apply to each occurrence, independently of the specific assignment(s) to any other occurrence of such variable.

According to the foregoing interpretive considerations on assignments and nomenclature, it is understood that explicit reference herein to a set implies, where chemically meaningful and unless indicated otherwise, independent reference to embodiments of such set, and reference to each and every one of the possible embodiments of subsets of the set referred to explicitly.

The present invention also features methods for inhibiting LTA4H enzyme activity with such compounds, and pharmaceutical compositions containing such compounds and methods of using such compositions in the treatment or prevention of conditions that are mediated by LTA4H enzyme activity.

Pharmaceutical compositions according to the present invention include at least one of the compounds of the present invention. If more than one of such compounds is included in a composition, the therapeutically effective amount may be a jointly effective amount. As such inhibitors of the LTA4H enzyme, compounds and compositions according to the present invention are useful in the prevention, inhibition, or treatment of inflammation.

The invention also features a pharmaceutical composition for treating or preventing an LTA4H-mediated condition in a subject, comprising a therapeutically effective amount of at least one LTA4H modulator selected from compounds of formulae (I), (II), and (II), enantiomers, diastereomers, racemates thereof, pharmaceutically acceptable salts, amides and esters thereof. In addition, the invention features a pharmaceutical composition for inhibiting inflammatory response in a subject, comprising a therapeutically effective amount of at least LTA4H inhibitor selected from compounds of formulae (I), (II), and (III), enantiomers, diastereomers, racemates thereof, pharmaceutically acceptable salts, amides and esters thereof. The invention additionally features an anti-inflammatory composition, comprising a therapeutically effective amount of at least one anti-inflammatory compound selected from compounds of formulae (I), (II), and (III), enantiomers, diastereomers, racemates thereof, pharmaceutically acceptable salts, amides and esters thereof.

The invention features methods for treating or preventing inflammation in a subject, comprising administering to the subject in connection with an inflammatory response a pharmaceutical composition that comprises a therapeutically effective amount of at least one anti-inflammatory compound selected from compounds of formulae (I), (II), and (III), enantiomers, diastereomers, racemates thereof, pharmaceutically acceptable salts, amides and esters thereof. The invention also features methods for treating or

preventing an LTA4H-mediated condition in a subject, comprising administering to the subject a pharmaceutical composition that comprises a therapeutically effective amount of at least one LTA4H modulator selected from compounds of formulae (I), (II), and (III), enantiomers, diastereomers, racemates thereof, pharmaceutically acceptable salts, amides and esters thereof. Furthermore, the invention features methods for inhibiting inflammation in a subject, comprising administering to the subject a pharmaceutical composition that comprises a therapeutically effective amount of at least one LTA4H inhibitor selected from compounds of formulae (I), (II), and (III), enantiomers, diastereomers, racemates thereof, pharmaceutically acceptable salts, amides and esters thereof.

This invention features methods for the treatment, prevention and/or inhibition of conditions that are associated with and/or cause inflammation, such as any one or a plurality of the followoing conditions: Asthma, chronic obstructed pulmonary disease (COPD), atherosclerosis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel diseases (including Crohn's disease and ulcerative colitis), or psoriasis, which are each characterized by excessive or prolonged inflammation at some stage of the disease.

Additional features and advantages of the invention will become apparent from the detailed description below, including examples, and the appended claims.

Detailed Description of the Invention

The present invention is directed to compounds of formula (I), (II), or (III) as herein defined, enantiomers, diastereomers, racemates thereof, pharmaceutically acceptable salts, amides and esters thereof, pharmaceutical compositions that contain at least one of such compounds, methods of using, including treatment and/or prevention of conditions such as those that are mediated by LTA4H, and methods of making such pharmaceutical compositions.

The following terms are defined below, and by their usage throughout the disclosure.

"Alkyl" includes straight chain and branched hydrocarbons with at least one hydrogen removed to form a radical group. Alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, 1-methylpropyl, pentyl, isopentyl, sec-pentyl, hexyl, heptyl, octyl, and so on. Alkyl does not include cycloalkyl.

"Alkenyl" includes straight chain and branched hydrocarbon radicals as above with at least one carbon-carbon double bond (sp^2). Unless indicated otherwise by the prefix that indicates the number of carbon members, alkenyls include ethenyl (or vinyl), prop-1-enyl, prop-2-enyl (or allyl), isopropenyl (or 1-methylvinyl), but-1-enyl, but-2-enyl, butadienyls, pentenyls, hexa-2,4-dienyl, and so on.

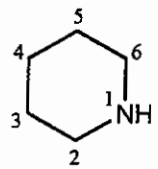
"Alkynyl" includes straight chain and branched hydrocarbon radicals as above with at least one carbon-carbon triple bond (sp). Unless indicated otherwise by the prefix that indicates the number of carbon members, alkynyls include ethynyl, propynyls, butynyls, and pentynyls. Hydrocarbon radicals having a mixture of double bonds and triple bonds, such as 2-penten-4-ynyl, are grouped as alkynyls herein.

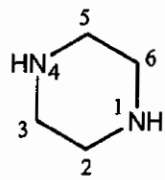
"Alkoxy" includes a straight chain or branched alkyl group with a terminal oxygen linking the alkyl group to the rest of the molecule. Alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy and so on. "Aminoalkyl", "thioalkyl", and "sulfonylalkyl" are analogous to alkoxy, replacing the terminal oxygen atom of alkoxy with, respectively, NH (or NR), S, and SO_2.

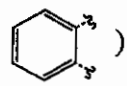
Unless indicated otherwise by the prefix that indicates the number of carbon members, "cycloalkyl" includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and so on.

Unless indicated otherwise by the prefix that indicates the number of members in the cyclic structure, "heterocyclyl", "heterocyclic" or "heterocycle" is a 3- to 8-member aromatic, saturated, or partially saturated single or fused ring system that comprises carbon atoms wherein the heteroatoms are selected from N, O, and S. Examples of heterocyclyls include thiazoylyl, furyl, pyranyl, isobenzofuranyl, pyrrolyl, imidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolyl, furazanyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, indolinyl, and morpholinyl. For example, preferred heterocyclyls or heterocyclic radicals include morpholinyl, piperazinyl, pyrrolidinyl, pyridyl, cyclohexylimino, cycloheptylimino, and more preferably, piperidyl.

Substitution positions are referred to in conventional terms. For example, piperidine and piperazine group substitution positions are numberd as follows:





"Carbocycle" is a cycloalkyl or a partially saturated cycloalkyl that is not benzo  .

"Aryl" includes phenyl, naphthyl, biphenylyl, tetrahydronaphthyl, and so on, any of which may be optionally substituted. Aryl also includes arylalkyl groups such as benzyl, phenethyl, and phenylpropyl. Aryl includes a ring system containing an optionally substituted 6-membered carbocyclic aromatic ring, said system may be bicyclic, bridge, and/or fused. The system may include rings that are aromatic, or partially or completely saturated. Examples of ring systems include indenyl, pentalenyl, 1-4-dihydronaphthyl, indanyl, benzimidazolyl, benzothiophenyl, indolyl, benzofuranyl, isoquinolinyl, and so

on. Examples illustrating heteroaryl are thienyl, furanyl, pyrrolyl, imidazolyl, oxazolyl, thiazolyl, benzothienyl, benzofuranyl, benzimidazolyl, benzoxazolyl, benzothiazolyl.

"Halo" includes fluoro, chloro, bromo, and iodo, and is preferably fluoro or chloro.

The term "carbonyl" refers to a >C=O moiety, such that when this term is characterized as being part of a chain or cyclic structure, the carbon member in the carbonyl group is taken as being one of the carbon members of such chain or cyclic structure.

As in standard chemical nomenclature, the group phenyl is herein referred to as "phenyl" or as "Ph".

It is understood that substitutions and combinations of substitutions recited herein, whether stated explicitly or not, refer to substitutions that are consistent with the valency of the member being substituted. Terms such as "valence allowed site", "valence allowed member" and morphological variations thereof are used herein in this sense. For example, "valence allowed" when applied to a carbon member refers to the tetravalency of C; it refers to the trivalency of N when applied to a nitrogen member; and it refers to the four bonds of a nitrogen member that is conventionally characterized with a positive electric charge. Valence allowed options are part of the ordinary skill in the art.

"Patient" or "subject" includes mammals such as human beings and animals (*e.g.*, dogs, cats, horses, rats, rabbits, mice, non-human primates) in need of observation, experiment, treatment or prevention in connection with the relevant disease or condition. Preferably, the patient is a human being.

"Composition" includes a product comprising the specified ingredients in the specified amounts, including in the effective amounts, as well as any product that results directly or indirectly from combinations of the specified ingredients in the specified amounts.

"Therapeutically effective amount" or "effective amount" and grammatically related terms mean that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian,

medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

Table of Acronyms

Term	Acronym
Tetrahydrofuran	THF
N,N-Dimethylformamide	DMF
N,N-Dimethylacetamide	DMA
Dimethyl sulfoxide	DMSO
tert-Butylcarbamoyl	BOC
Bovine serum albumin	BSA
High-pressure liquid chromatography	HPLC
Thin layer chromatography	TLC

Compounds of formula (I), (II), or (III) comprise compounds that satisfy any one of the combinations of definitions given herein and equivalents thereof.

It is understood that some compounds refered to herein are chiral and/or have geometric isomeric centers, for example E- and Z- isomers. The present invention encompasses all such optical isomers, including diasteroisomers and racemic mixtures, and geometric isomers that possess the activity that characterizes the compounds of this invention. In addition, certain compounds referred to herein can exist in solvated as well as unsolvated forms. It is understood that this invention encompasses all such solvated and unsolvated forms that possess the activity that characterizes the compounds of this invention. Compounds according to the present invention that have been modified to be detectable by some analytic technique are also within the scope of this invention. An example of such compounds is an isotopically labeled compound, such as an ^{18}F isotopically labeled compound that may be used as a probe in detection and/or imaging techniques, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT). Another example of such compounds is an isotopically labeled

compound, such as a deuterium and/or tritium labeled compound that may be used in reaction kinetic studies.

It is understood that substitutions and combinations of substitutions recited herein, whether stated explicitly or not, refer to substitutions that are consistent with the valency of the member being substituted. For example, a substitution applied to a carbon member refers to the tetravalency of C; it refers to the trivalency of N when applied to a nitrogen member; and it refers to the four bonds of a nitrogen member that is conventionally characterized with a positive electric charge. Valence allowed options are part of the ordinary skill in the art.

The "pharmaceutically acceptable salts, amides or and esters thereof" refer to those salts, amides and ester forms of the compounds of the present invention that would be apparent to the pharmaceutical chemist, *i.e.*, those that are non-toxic and that would favorably affect the pharmacological properties of said compounds of the present invention. Those compounds having favorable pharmacological properties would be apparent to the pharmaceutical chemist, *i.e.*, those that are non-toxic and that possess such pharmacological properties to provide sufficient palatability, absorption, distribution, metabolism and excretion. Other factors, more practical in nature, that are also important in the selection are cost of raw materials, ease of crystallization, yield, stability, hygroscopicity, and flowability of the resulting bulk drug.

Representative acids and bases that may be used in the preparation of pharmaceutically acceptable salts include the following:

acids including acetic acid, 2,2-dichlorolactic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, α-oxo-glutaric acid, glycolic acid, hipuric acid, hydrobromic acid, hydrochloric acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic

acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid; and

bases including ammonia, L-arginine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylenediamine, N-methyl-glucamine, hydrabamine, 1H-imidazole, L-lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, secondary amine, sodium hydroxide, triethanolamine, tromethamine and zinc hydroxide.

See, for example, S.M. Berge, *et al.*, "Pharmaceutical Salts", *J. Pharm. Sci.* 1977, 66:1–19, which is incorporated herein by reference. Examples of suitable esters include C_{1-7}alkyl, C_{5-7}cycloalkyl, phenyl, substituted phenyl, and phenylC_{1-6}alkyl- esters. Preferred esters include methyl esters.

The present invention includes within its scope prodrugs of the compounds of this invention. In general, such prodrugs will be functional derivatives of the compounds that are readily convertible *in vivo* into the required compound. Thus, in the methods of treatment of the present invention, the term "administering" shall encompass the treatment of the various disorders described with the compound specifically disclosed or with a compound that may not be specifically disclosed, but that converts to the specified compound *in vivo* after administration to the patient. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Embodiments of this invention, where X is O, are made according to the synthetic methods outlined in Schemes A–D and F–L, have demonstrated LTA4H inhibitory activity, and are selected from the group consisting of:

Example	Compound
11	2-[4-(2-Piperidin-1-yl-ethoxy)-phenoxy]-benzooxazole;
13	(1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]ethyl}-piperidin-4-yl)-methanol;
14	1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-ol;
16	{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-dibutyl-amine;
21	(1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidin-2-yl)-methanol;
27	1-{3-[4-(Benzooxazol-2-yloxy)-phenoxy]-propyl}-4-phenyl-piperidin-4-ol;
28	1-{3-[4-(Benzooxazol-2-yloxy)-phenoxy]-propyl}-4-benzyl-piperidin-4-ol;
29	2-[4-(2-Piperidin-1-yl-ethyl)-phenoxy]-benzooxazole;
35	{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-cyclohexyl-ethyl-amine;
36	1-{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-piperidin-4-ol;
40	1-{3-[4-(Benzooxazol-2-yloxy)-phenoxy]-2-hydroxy-propyl}-4-phenyl-piperidin-4-ol;
41	1-[2-(4-Benzooxazol-2-ylmethyl-phenoxy)-ethyl]-piperidine-4-carboxylic acid ethyl ester;
44	2-[4-(2-Pyrrolidin-1-yl-ethoxy)-phenoxy]-benzooxazole;
45	{3-[4-(Benzooxazol-2-yloxy)-phenoxy]-propyl}-dimethyl-amine;
46	{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-dimethyl-amine;
47	2-[4-(2-Azepan-1-yl-ethoxy)-phenoxy]-benzooxazole;
53	1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidin-4-ol;
54	{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-cyclohexyl-ethyl-amine;
55	2-{4-[2-(2-Ethyl-piperidin-1-yl)-ethoxy]-phenoxy}-benzooxazole;
56	1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidine-4-carbonitrile;
57	1-(1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidin-4-yl)-ethanone;

58 2-{4-[2-(4-Methyl-piperidin-1-yl)-ethoxy]-phenoxy}-benzooxazole;

59 1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-(4-chloro-phenyl)-piperidin-4-ol;

60 1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-(4-bromo-phenyl)-piperidin-4-ol;

61 1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-(4-chloro-3-trifluoromethyl-phenyl)-piperidin-4-ol;

62 1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-benzyl-piperidin-4-ol;

63 {2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-cyclohexyl-methyl-amine;

64 {2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-cyclopropylmethyl-propyl-amine;

65 {2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-butyl-ethyl-amine;

66 2-({2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-benzyl-amino)-ethanol;

67 2-{4-[2-(4-Benzyl-piperidin-1-yl)-ethoxy]-phenoxy}-benzooxazole;

68 (1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidin-3-yl)-methanol;

69 2-({2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-propyl-amino)-ethanol;

77 2-[4-(2-Azetidin-1-yl-ethoxy)-phenoxy]-benzooxazole;

78 *N*-(1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-2-phenyl-acetamide;

79 1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidine-3-carboxylic acid ethyl ester;

86 2-{4-[3-(4-Phenyl-piperidin-1-yl)-propoxy]-phenoxy}-benzooxazole;

88 1-{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-4-phenyl-piperidin-4-ol;

89 {2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-cyclohexyl-ethyl-amine;

90 2-[4-(2-Pyrrolidin-1-yl-ethyl)-phenoxy]-benzooxazole;

91 2-[4-(2-Azepan-1-yl-ethyl)-phenoxy]-benzooxazole;

92	{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-propyl-amine;
93	{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-dibutyl-amine;
94	1-{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ol;
96	1-{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid methyl ester;
116	1-{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-4-phenyl-piperidin-4-ol;
120	2-[4-(3-Piperidin-1-yl-propyl)-phenoxy]-benzooxazole;
121	{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-dibutyl-amine;
122	{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-cyclopropylmethyl-propyl-amine;
135	1-[4-(Benzooxazol-2-yloxy)-phenoxy]-3-pyrrolidin-1-yl-propan-2-ol;
136	1-[2-(4-Benzooxazol-2-ylmethyl-phenoxy)-ethyl]-4-phenyl-piperidin-4-ol;
137	1-[2-(4-Benzooxazol-2-ylmethyl-phenoxy)-ethyl]-piperidine-4-carboxylic acid amide;
271	2-(4-Piperidin-1-ylmethyl-phenoxy)-benzooxazole;
481	2-[4-(2-Morpholin-4-yl-ethoxy)-phenoxy]-benzooxazole; and
484	{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-diethyl-amine.

Other embodiments of this invention, where X is S, are made according to the synthetic methods outlined in Schemes A–G, and I-L, have demonstrated LTA4H inhibitory activity, and are selected from the group consisting of:

Example	Compound
12	{2-[4-(6-Chloro-benzothiazol-2-yloxy)-phenoxy]-ethyl}-diethyl-amine;
15	1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-ol;
17	1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carboxylic acid ethyl ester;

18 1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carboxylic acid;

19 (1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-pyrrolidin-1-yl-methanone;

20 3-[(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carbonyl)-amino]-propionic acid ethyl ester;

22 1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carboxylic acid amide;

23 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-pyrrolidin-2-one;

24 1'-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-[1,4']bipiperidinyl-2-one;

25 8-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-2,8-diaza-spiro[4.5]decan-1-one;

26 2-[4-(3-Pyrrolidin-1-yl-propoxy)-phenoxy]-benzothiazole;

30 {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclohexyl-ethyl-amine;

31 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-3-carboxylic acid amide;

32 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one;

33 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid methyl ester;

34 (1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-(4-methyl-piperazin-1-yl)-methanone;

42 1-[2-(4-Benzothiazol-2-ylmethyl-phenoxy)-ethyl]-piperidine-4-carboxylic acid methyl ester;

43 3-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropyl-amino)-propionic acid;

48 {2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-dimethyl-amine;

49 2-[4-(2-Pyrrolidin-1-yl-ethoxy)-phenoxy]-benzothiazole;

50 {3-[4-(Benzothiazol-2-yloxy)-phenoxy]-propyl}-dimethyl-amine;

51 2-[4-(2-Azepan-1-yl-ethoxy)-phenoxy]-benzothiazole;

52 2-[4-(2-Azepan-1-yl-ethoxy)-phenoxy]-6-methoxy-benzothiazole;

70 1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidin-4-ol;

71 {2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclohexyl-ethyl-amine;

72 1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-(4-chloro-phenyl)-piperidin-4-ol;

73 {2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-dibutyl-amine;

74 1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-(4-bromo-phenyl)-piperidin-4-ol;

75 1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-(4-chloro-3-trifluoromethyl-phenyl)-piperidin-4-ol;

76 1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-benzyl-piperidin-4-ol;

80 1'-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-[1,4']bipiperidine;

81 (1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-methanol;

82 *N*-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-2-phenyl-acetamide;

83 1'-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-[1,4']bipiperidinyl-2-one;

84 2-(4-{2-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-yl]-ethoxy}-phenoxy)-benzothiazole;

85 2-(4-{2-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-yl]-ethyl}-phenoxy)-benzothiazole;

87 1-{3-[4-(Benzothiazol-2-yloxy)-phenoxy]-propyl}-4-phenyl-piperidin-4-ol;

95 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-4-phenyl-piperidin-4-ol;

97 2-[4-(2-Pyrrolidin-1-yl-ethyl)-phenoxy]-benzothiazole;

98 2-[4-(2-Azepan-1-yl-ethyl)-phenoxy]-benzothiazole;

99 {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-propyl-amine;

100 {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-dibutyl-amine;

101 2-[4-(2-Piperidin-1-yl-ethyl)-phenoxy]-benzothiazole;

102 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ol;

103 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid methyl ester;

104 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid amide;

105 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-3-carboxylic acid ethyl ester;

106 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-4-phenyl-piperidine-4-carboxylic acid ethyl ester;

107 (1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-acetic acid ethyl ester;

108 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one;

109 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-pyrrolidin-2-one;

110 *N*-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-2-phenyl-acetamide;

111 8-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-2,8-diaza-spiro[4.5]decan-1-one;

112 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-3-ol;

113 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid ethyl ester;

114 1'-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-[1,4']bipiperidine;

115 2-{4-[2-(4-Methyl-piperazin-1-yl)-ethyl]-phenoxy}-benzothiazole;

143 2-(4-{2-[4-(1-Benzyl-1*H*-tetrazol-5-yl)-piperidin-1-yl]-ethoxy}-phenoxy)-benzothiazole;

144 4-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carbonyl)-piperazine-1-carboxylic acid *tert*-butyl ester;

146 2-(4-{2-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-yl]-ethyl}-phenoxy)-benzothiazole;

147 1-[2-(4-Benzothiazol-2-ylmethyl-phenoxy)-ethyl]-piperidine-4-carboxylic acid amide;

148 1-{1-[2-(4-Benzothiazol-2-ylmethyl-phenoxy)-ethyl]-piperidin-4-yl}-pyrrolidin-2-one;

149 1-[4-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carbonyl)-piperazin-1-yl]-ethanone;

150 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid;

151 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-pyrrolidine-2-thione;

152 2-(4-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperazin-1-yl)-ethanol;

153 2-(4-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperazin-1-yl)-1-pyrrolidin-1-yl-ethanone;

154 2-(4-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperazin-1-yl)-1-morpholin-4-yl-ethanone;

155 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-3-carboxylic acid;

156 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-2-carboxylic acid;

157 (1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-3-yl)-acetic acid;

158 (1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-acetic acid ethyl ester;

159 (1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-carbamic acid tert-butyl ester;

160 (1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-acetic acid;

161 (1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-3-yl)-methanol;

162 ({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclohexyl-amino)-acetic acid methyl ester;

163 (4-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperazin-1-yl)-acetic acid;

164 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester;

166 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-5-oxo-pyrrolidine-2-carboxylic acid;

167 4-(4-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperazin-1-yl)-phenol;

168 *N*-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-4-chloro-*N*-cyclopropyl-benzene sulfonamide;

170 3-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropylmethyl-amino)-propionic acid;

171 3-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-isopropyl-amino)-propionic acid;

172 1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-ylamine;

173 3-[{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-(1-methyl-piperidin-4-yl)-amino]-propionic acid;

174 3-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-benzyl-amino)-propionic acid;

175 3-((1-Acetyl-piperidin-4-yl)-{2-[4-(benzothiazol-2-yloxy)-phenoxy]-ethyl}-amino)-propionic acid;

176 4-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-1H-tetrazol-5-yl)-piperidine-1-carboxylic acid tert-butyl ester;

177 3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propionic acid;

178 3-((1-Acetyl-piperidin-4-yl)-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-amino)-propionic acid;

179 3-[{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-(1-methyl-piperidin-4-yl)-amino]-propionic acid;

180 3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propionic acid;

181 3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-isopropyl-amino)-propionic acid;

182 2-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-1-pyrrolidin-1-yl-ethanone;

183 (*R*)-1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-3-carboxylic acid;

184 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one;

185 2-(4-{2-[4-(6-Methyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-phenoxy)-benzothiazole;

186 2-{4-[2-(4-Ethanesulfonyl-piperazin-1-yl)-ethyl]-phenoxy}-benzothiazole;

187 2-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-1-morpholin-4-yl-ethanone;

188 3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-methyl-amino)-propionic acid;

189 3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopentyl-amino)-propionic acid;

190 3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclobutyl-amino)-propionic acid;

192 3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-benzyl-amino)-propionic acid;

193 (1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-(4-hydroxymethyl-piperidin-1-yl)-methanone;

194 {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amine;

195 (1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;

196 (1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone;

197 2-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-ethanol;

198 3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propan-1-ol;

199 4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-butyric acid;

200 3-[(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carbonyl)-amino]-propionic acid;

201 4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-butyronitrile;

202 3-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-propionic acid;

203 [(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carbonyl)-methyl-amino]-acetic acid;

204 3-(4-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperazin-1-yl)-phenol;

205 2-(4-{2-[4-(4-Methoxy-phenyl)-piperazin-1-yl]-ethoxy}-phenoxy)-benzothiazole;

206 2-{4-[2-(5-Piperidin-4-yl-tetrazol-1-yl)-ethoxy]-phenoxy}-benzothiazole;

207 (*S*)-1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one;

208 {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amine;

209 2-[({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-methyl]-cyclopropanecarboxylic acid ethyl ester;

210 4-(4-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperazine-1-carbonyl)-benzoic acid ethyl ester;

211 2-[({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-methyl]-cyclopropanecarboxylic acid;

212 1-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propan-2-ol;

213 3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-1,1,1-trifluoro-propan-2-ol;

214 3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propionamide;

215 3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propane-1,2-diol;

216 2-{4-[2-(5-Phenyl-tetrazol-2-yl)-ethoxy]-phenoxy}-benzothiazole;

217 2-{4-[2-(5-Phenyl-tetrazol-1-yl)-ethoxy]-phenoxy}-benzothiazole;

218 *N*-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-*N*-cyclopropyl-2-(2H-tetrazol-5-yl)-acetamide;

219 (S)-3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-2-methyl-propan-1-ol;

220 (*R*)-3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-2-methyl-propan-1-ol;

221 2-{4-[2-(5-Methylsulfanyl-tetrazol-2-yl)-ethoxy]-phenoxy}-benzothiazole;

222 2-{4-[2-(5-Methylsulfanyl-tetrazol-1-yl)-ethoxy]-phenoxy}-benzothiazole;

223 2-[4-(2-Tetrazol-2-yl-ethoxy)-phenoxy]-benzothiazole;

224 2-[4-(2-Tetrazol-1-yl-ethoxy)-phenoxy]-benzothiazole;

225 (1*R*,2*R*)-2-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-cyclohexanecarboxylic acid;

226 (1*S*,2*R*)-2-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-cyclohexanecarboxylic acid;

227 (1*R*,2*R*)-2-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-cyclohexanol;

228 (1*S*,2*R*)-2-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-cyclohexanol;

229 4-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-butyric acid;

250 1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidine-4-carboxylic acid;

251 1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-pyrrolidin-2-one;

252 2-(2-Fluoro-4-piperidin-1-ylmethyl-phenoxy)-benzothiazole;

253 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-2-hydroxy-acetamide;

254 1-(2-{[4-(Benzothiazol-2-yloxy)-benzyl]-cyclopropyl-amino}-ethyl)-4-hydroxy-pyrrolidin-2-one;

255 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-N-methyl-methanesulfonamide;

256 2-{4-[4-(1H-Tetrazol-5-yl)-piperidin-1-ylmethyl]-phenoxy}-benzothiazole;

257 1-{4-[4-(Benzothiazol-2-yloxy)-benzyl]-piperazin-1-yl}-2-hydroxy-ethanone;

258 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-methanesulfonamide;

259 3-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-oxazolidin-2-one;

260 4-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-morpholin-3-one;

261 (*R*) 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one;

262 2-(4-{2-[4-(1H-Tetrazol-5-yl)-piperidin-1-yl]-ethyl}-phenoxy)-benzothiazole;

263 (1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-2-yl)-methanol;

264 (1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-1H-tetrazol-5-yl)-acetic acid ethyl ester;

265 (1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-1H-tetrazol-5-yl)-acetic acid ethyl ester;

266 2-{4-[2-(5-Piperidin-4-yl-tetrazol-2-yl)-ethoxy]-phenoxy}-benzothiazole hydrochloride;

267 7-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-spiro-[3-phthalide]-piperidine;

268 1-{3-[4-(Benzothiazol-2-yloxy)-phenyl]-propyl}-piperidine-4-carboxylic acid ethyl ester;

269 2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamine hydrochloride;

270 2-(4-{2-[4-(1H-Tetrazol-5-yl)-piperidin-1-yl]-ethoxy}-phenoxy)-benzothiazole;

271 2-(4-Piperidin-1-ylmethyl-phenoxy)-benzooxazole;

272 [4-(Benzothiazol-2-yloxy)-benzyl]-cyclohexyl-ethyl-amine;

273 [4-(Benzothiazol-2-yloxy)-benzyl]-cyclopropylmethyl-propyl-amine;

274 1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidine-4-carboxylic acid amide;

275 1'-[4-(Benzothiazol-2-yloxy)-benzyl]-[1,4']bipiperidinyl-2-one;

276 {4-[4-(Benzothiazol-2-yloxy)-benzyl]-piperazin-1-yl}-pyridin-3-yl-methanone;

277 {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-carbamic acid tert-butyl ester;

278 {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-carbamic acid methyl ester;

279 N-{C-[[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl]-methylamino sulfonyl}-carbamic acid tert-butyl ester,

280 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-sulfamide hydrochloride,

281 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-acetamide;

282 {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-acetic acid;

283 Acetic acid ({1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-carbamoyl)-methyl ester;

284 [2-({1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-carbamoyl)-cyclobutyl]-carbamic acid tert-butyl ester;

285 2-Amino-cyclobutanecarboxylic acid {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-amide dihydrochloride;

286 2-(4-Pyrrolidin-1-ylmethyl-phenoxy)-benzothiazole;

287 2-{[4-(Benzothiazol-2-yloxy)-benzyl]-ethyl-amino}-ethanol;

288 2-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-2-yl}-ethanol;

289 1-{4-[4-(Benzothiazol-2-yloxy)-benzyl]-piperazin-1-yl}-ethanone;

290 8-[4-(Benzothiazol-2-yloxy)-benzyl]-2,8-diaza-spiro[4.5]decan-1-one;

291 Spiro[isobenzofuran-1(3H), 4'-piperidin]-3-one, 1'-[4-(Benzothiazol-2-yloxy)-benzyl]

292 (*R*)-1-[4-(Benzothiazol-2-yloxy)-benzyl]-pyrrolidin-3-ol;

293 2-[4-(2-Methyl-piperidin-1-ylmethyl)-phenoxy]-benzothiazole;

294 [4-(Benzothiazol-2-yloxy)-benzyl]-diethyl-amine;

295 [4-(Benzothiazol-2-yloxy)-benzyl]-butyl-methyl-amine;

296 2-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-ethanol;

297 1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ol;

298 {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-2-yl}-methanol;

299 (*R*)-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-pyrrolidin-2-yl}-methanol;

300 2-(4-Azetidin-1-ylmethyl-phenoxy)-benzothiazole;

301 1-[4-(Benzothiazol-2-yloxy)-benzyl]-[1,4]diazepan-5-one;

302 {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-3-yl}-methanol;

303 1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidine-3-carboxylic acid amide;

304 9-[4-(Benzothiazol-2-yloxy)-benzyl]-3,9-diaza-spiro[5.5]undecane-3-carboxylic acid tert-butyl ester;

305 2-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-3-yl}-ethanol;

306 cis-4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-cyclohexanecarboxylic acid trifluoromethanesulfonate salt;

307 (4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(tetrahydro-furan-2-yl)-methanone;

308 Propane-2-sulfonic acid (1-{2-[4-(benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carbonyl)-amide;

309 (4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-oxo-acetic acid methyl ester;

310 N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carbonyl)-benzenesulfonamide trifluoromethanesulfonate salt;

311 N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carbonyl)-methanesulfonamide trifluoromethanesulfonate salt;

312 (4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-oxo-acetic acid trifluoromethanesulfonate salt;

313 (4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-morpholin-4-yl-methanone;

314 1-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-2-thiophen-2-yl-ethanone;

315 (4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-pyridin-3-yl-methanone;

316 (4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-cyclopropyl-methanone;

317 1-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-2-methoxy-ethanone;

318 1-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-2,2,2-trifluoro-ethanone;

319 4-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazine-1-carbonyl)-benzoic acid;

320 (4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-pyridin-4-yl-methanone;

321 (4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(5-methyl-pyrazin-2-yl)-methanone;

322 (*R*)-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(tetrahydro-furan-2-yl)-methanone;

323 (*S*)-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(tetrahydro-furan-2-yl)-methanone;

324 (4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(tetrahydro-furan-3-yl)-methanone;

325 1-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-2-hydroxy-ethanone;

326 2-[2-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-2-oxo-ethyl]-cyclopentanone;

327 3-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-propionic acid trifluoromethanesufonate salt;

328 3-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-oxazolidin-2-one;

329 4-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-morpholin-3-one;

330 4-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-morpholin-3-one;

331 3-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-oxazolidin-2-one;

332 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid benzyloxy-amide;

333 (1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-acetic acid;

334 (*R*)-1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one;

335 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid hydroxyamide;

336 (*S*)-1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one;

337 (1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-carbamic acid tert-butyl ester;

338 2-{4-[2-(4-Fluoro-piperidin-1-yl)-ethyl]-phenoxy}-benzothiazole;

339 2-{4-[2-(4,4-Difluoro-piperidin-1-yl)-ethyl]-phenoxy}-benzothiazole;

340 (*R*)-1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-pyrrolidin-3-ol;

341 N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-formamide;

342 (1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-urea;

343 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-3-cyano-2-phenyl-isourea;

344 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-3-cyano-2-methyl-isothiourea;

345 N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-methanesulfonamide;

346 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-3-cyano-2-methyl-guanidine;

347 8-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one;

348 8-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-1,3,8-triaza-spiro[4.5]decane-2,4-dione;

349 (1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-methyl-carbamic acid tert-butyl ester;

350 N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-N-methyl-acetamide;

351 N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-N-methyl-methanesulfonamide;

352 Acetic acid [(1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-methyl-carbamoyl]-methyl ester;

353 N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-N-acetamide;

354 Acetic acid (1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ylcarbamoyl)-methyl ester;

355 2-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-methyl-amino)-3-(1H-imidazol-2-yl)-propionic acid;

356 2-(4-{2-[4-(3-Nitro-pyridin-2-yl)-[1,4]diazepan-1-yl]-ethyl}-phenoxy)-benzothiazole;

357 2-(4-Piperidin-1-ylmethyl-phenoxy)-benzothiazole;

358 1-[4-(Benzothiazol-2-yloxy)-benzyl]-4-phenyl-piperidin-4-ol;

359 1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ol;

360 {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-methanol;

361 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-methanesulfonamide;

362 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-2-hydroxy-acetamide;

363 {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-carbamic acid methyl ester;

364 {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-urea;

365 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-2,2,2-trifluoro-acetamide;

366 {4-[4-(Benzothiazol-2-yloxy)-benzyl]-piperazin-1-yl}-acetic acid;

367 2-[4-(4-Methanesulfonyl-piperazin-1-ylmethyl)-phenoxy]-benzothiazole;

368 1-{4-[4-(Benzothiazol-2-yloxy)-benzyl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone;

369 2-(4-Morpholin-4-ylmethyl-phenoxy)-benzothiazole;

370 {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-carbamic acid phenyl ester;

371 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-benzenesulfonamide;

372 3-[4-(Benzothiazol-2-yloxy)-benzylamino]-propionic acid ethyl ester;

373 3-[4-(Benzothiazol-2-yloxy)-benzylamino]-propionic acid;

374 [(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carbonyl)-methyl-amino]-acetic acid ethyl ester;

376 1'-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-[1,4']bipiperidinyl-4-carboxylic acid ethyl ester;

377 1'-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-[1,4']bipiperidinyl-4-carboxylic acid;

378 {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-ethyl-amine;

379 3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-2-methyl-propionic acid trifluoromethansulfonic acid salt;

380 2-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-ethanol;

381 2-[2-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-ethoxy]-ethanol;

382 3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propan-1-ol;

383 {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-(3-tetrazol-2-yl-propyl)-amine;

384 {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-(3-pyrrol-1-yl-propyl)-amine;

385 4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-butyronitrile;

386 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid (2-cyano-ethyl)-amide;

387 {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-[3-(2H-tetrazol-5-yl)-propyl]-amine;

388 3-[5-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-tetrazol-1-yl]-propionitrile;

389 {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-[3-(2H-tetrazol-5-yl)-propyl]-amine;

390 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide;

391 {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-[3-(1H-[1,2,4]triazol-3-yl)-propyl]-amine;

392 {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-[3-(5-methyl-1H-[1,2,4]triazol-3-yl)-propyl]-amine;

393 {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-[3-(5-phenyl-1H-[1,2,4]triazol-3-yl)-propyl]-amine;

394 2-(4-{2-[4-(1-Methyl-1H-tetrazol-5-yl)-piperidin-1-yl]-ethyl}-phenoxy)-benzothiazole;

395 2-(4-{2-[4-(2-Methyl-2H-tetrazol-5-yl)-piperidin-1-yl]-ethyl}-phenoxy)-benzothiazole;

396 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carbonitrile;

397 2-(4-{2-[4-(1H-[1,2,3]Triazol-4-yl)-piperidin-1-yl]-ethyl}-phenoxy)-benzothiazole;

398 4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-butyric acid ethyl ester;

399 4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-butyric acid ethyl ester;

400 2-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-isoindole-1,3-dione;

401 4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-butyric acid;

402 1-(3-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-propyl)-pyrrolidin-2-one;

403 N-1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-N1-cyclopropylmethyl-propane-1,3-diamine;

404 5-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-pentanoic acid methyl ester;

405 N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-acetamide;

406 Morpholine-4-carboxylic acid [3-({2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-amide;

407 N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-methanesulfonamide

408 5-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-pentanoic acid;

409 1-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-isopropyl-amino)-propyl]-pyrrolidin-2-one;

410 1-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-pyrrolidin-2-one;

411 1-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-pyrrolidin-2-one;

412 1-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-propyl-amino)-propyl]-pyrrolidin-2-one;

413 4-((1-Acetyl-piperidin-4-yl)-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-amino)-butyric acid ethyl ester;

414 4-((1-Acetyl-piperidin-4-yl)-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-amino)-butyric acid ethyl ester;

415 4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-methanesulfonyl-amino)-butyric acid;

416 ({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-acetic acid;

417 6-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-hexanoic acid ethyl ester;

418 7-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-heptanoic acid ethyl ester;

419 6-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-hexanoic acid;

420 7-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-heptanoic acid;

421 N-1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-N1-cyclopropyl-propane-1,3-diamine;

422 N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-acetamide;

423 N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-isobutyramide;

424 N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-benzamide;

425 N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-4-chloro-benzamide;

426 N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-methanesulfonamide;

427 Propane-2-sulfonic acid [3-({2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-amide trifluoromethansulfonic acid salt;

428 8-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-octanoic acid ethyl ester;

429 1-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-3-phenyl-urea;

430 8-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-octanoic acid;

431 Tetrahydro-furan-2-carboxylic acid [3-({2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-amide;

432 N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-2-hydroxy-acetamide;

433 4-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropyl-amino)-butyric acid;

434 1-{3-[4-(Benzothiazol-2-yloxy)-benzylamino]-propyl}-pyrrolidin-2-one;

435 1-(3-{[4-(Benzothiazol-2-yloxy)-benzyl]-methyl-amino}-propyl)-pyrrolidin-2-one;

436 1-(3-{[4-(Benzothiazol-2-yloxy)-benzyl]-isopropyl-amino}-propyl)-pyrrolidin-2-one;

437 1-(3-{[4-(Benzothiazol-2-yloxy)-benzyl]-ethyl-amino}-propyl)-pyrrolidin-2-one;

438 [4-(Benzothiazol-2-yloxy)-benzyl]-cyclopropyl-amine;

439 N-1-[4-(Benzothiazol-2-yloxy)-benzyl]-N1-cyclopropyl-propane-1,3-diamine;

440 N-(3-{[4-(Benzothiazol-2-yloxy)-benzyl]-cyclopropyl-amino}-propyl)-isobutyramide;

441 1-(3-{[4-(Benzothiazol-2-yloxy)-benzyl]-cyclopropyl-amino}-propyl)-3-isopropyl-urea;

442 1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-3-isopropyl-urea;

443 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-oxalamic acid methyl ester;

444 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-isobutyramide;

445 Tetrahydro-furan-2-carboxylic acid {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-amide;

446 1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-4-hydroxy-pyrrolidin-2-one;

447 1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-4-hydroxy-pyrrolidin-2-one;

448 {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-urea;

449 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-oxalamic acid;

450 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-2-hydroxy-acetamide;

451 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-2,2,2-trifluoro-acetamide;

452 2-[4-(1,1-Dioxo-1l6-thiomorpholin-4-ylmethyl)-phenoxy]-benzothiazole;

453 N-{1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-amino sulfonyl}-carbamic acid tert-butyl ester;

454 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-acetamide;

455 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-N,N-dimethylsulfamide;

456 1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-3-ethyl-urea;

457 1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-3-ethyl-thiourea;

458 Propane-1-sulfonic acid {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-amide;

459 Propane-2-sulfonic acid {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-amide;

460 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-sulfamide;

461 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-formamide;

462 {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-carbamic acid ethyl ester;

463 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-propionamide;

464 N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-butyramide;

465 1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-3-propyl-urea;

466 {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-carbamic acid propyl ester;

467 1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-3-methyl-urea;

469 1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-1,3-dimethyl-urea;

470	1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-1-methyl-urea;
471	N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-N-methyl-acetamide;
472	{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-methyl-carbamic acid methyl ester;
473	N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-N-methyl-oxalamic acid methyl ester;
474	N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-N-methyl-oxalamic acid;
475	Guanidine, N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-N'-hydroxy;
476	{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-carbamic acid isopropyl ester;
477	3-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-1,1-dimethyl-urea;
478	Acetic acid {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylcarbamoyl}-methyl ester;
479	{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-thiourea;
482	2-[4-(2-Morpholin-4-yl-ethoxy)-phenoxy]-benzothiazole; and
483	2-[4-(2-Piperidin-1-yl-ethoxy)-phenoxy]-benzothiazole.

Additional embodiments of this invention, where X is NR^5 with R^5 being one of H and CH_3, are made according to the synthetic methods outlined in Schemes A–C, F, G and J-L, have demonstrated LTA4H inhibitory activity, and are selected from the group consisting of:

Example	Compound
37	1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidin-4-ol;
38	{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-propyl-amine;

39	Cyclohexyl-ethyl-{2-[4-(1-methyl-1*H*-benzoimidazol-2-yloxy)-phenyl]-ethyl}-amine;
117	1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-4-(4-bromo-phenyl)-piperidin-4-ol;
118	1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-4-(4-chloro-phenyl)-piperidin-4-ol;
119	1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-4-benzyl-piperidin-4-ol;
123	{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-cyclohexyl-ethyl-amine;
124	2-[4-(2-Pyrrolidin-1-yl-ethyl)-phenoxy]-1*H*-benzoimidazole;
125	2-[4-(2-Azepan-1-yl-ethyl)-phenoxy]-1*H*-benzoimidazole;
126	{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-dibutyl-amine;
127	1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ol;
128	1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid methyl ester;
129	{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-cyclohexyl-ethyl-amine;
130	2-{4-[2-(4-Methyl-piperidin-1-yl)-ethoxy]-phenoxy}-1*H*-benzoimidazole;
131	2-{4-[2-(2-Ethyl-piperidin-1-yl)-ethoxy]-phenoxy}-1*H*-benzoimidazole;
132	2-[4-(2-Piperidin-1-yl-ethoxy)-phenoxy]-1*H*-benzoimidazole;
133	(1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-methanol;
134	1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-ol;
138	2-[4-(2-Azepan-1-yl-ethoxy)-phenoxy]-1*H*-benzoimidazole amide;
139	{3-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-propyl}-dimethyl-amine;
140	2-[4-(2-Pyrrolidin-1-yl-ethoxy)-phenoxy]-1*H*-benzoimidazole;
141	{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-diethyl-amine;
142	2-[4-(2-Morpholin-4-yl-ethoxy)-phenoxy]-1*H*-benzoimidazole;
230	2-[4-(2-Piperidin-1-yl-ethyl)-phenoxy]-1*H*-benzoimidazole;

231 1-(1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-pyrrolidin-2-one;

480 (1-{2-[4-(1H-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-methanol; and

485 1-{2-[4-(1H-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carboxylic acid ethyl ester.

Compounds of the present invention may be prepared according to the reaction schemes described below. The schemes represent two basic approaches to target compound synthesis, both in a linear fashion, commencing from either end of the molecule. Persons skilled in the art will recognize that certain compounds are more advantageously produced by one scheme over another.

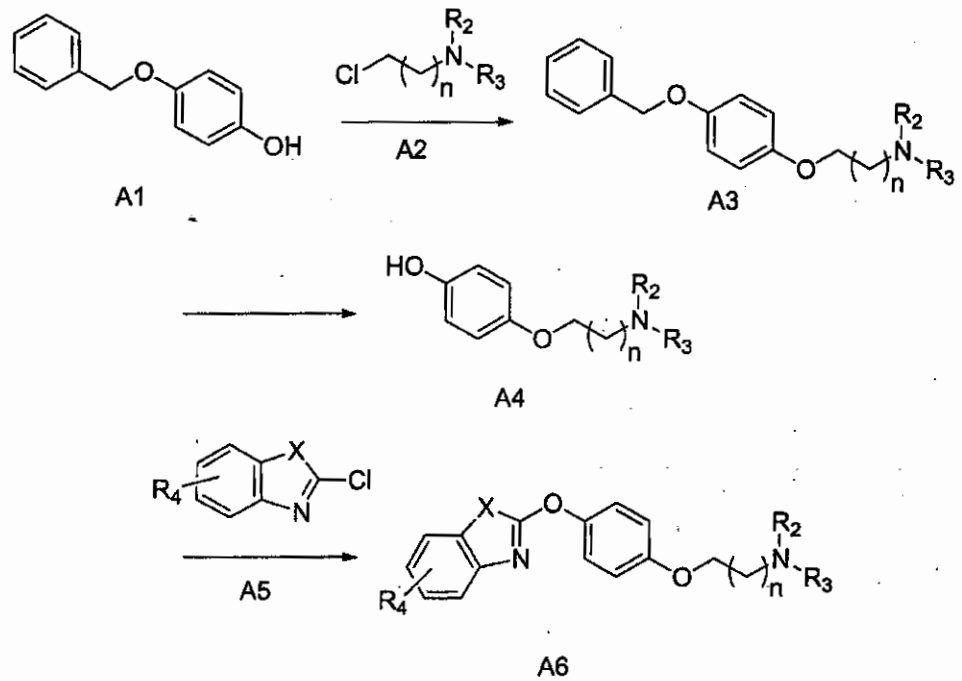
To obtain the various compounds herein, starting materials may be employed which carry the ultimately desired substituents though the reaction scheme with or without protection as appropriate. Starting materials may be obtained from commercial sources or synthesized by methods known to one skilled in the art. Alternatively, it may be necessary to employ, in the place of the ultimately desired substituent, a suitable group, which may be carried through the reaction scheme and replaced as appropriate with the desired substituent. Any product containing a chiral center may be separated into its enantiomers by conventional techniques.

Embodiments of processes illustrated herein include, when chemically meaningful, one or more steps such as hydrolysis, halogenation, protection, and deprotection. These steps can be implemented in light of the teachings provided herein and the ordinary skill in the art.

During any of the processes for preparation of the compounds of the present invention, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. In addition, compounds of the invention may be modified by using protecting groups; such compounds, precursors, or prodrugs are also within the scope of the invention. This may be achieved by means of conventional protecting groups, such as those described in "Protective Groups in Organic Chemistry", ed. J.F.W. McOmie, Plenum

Press, 1973; and T.W. Greene & P.G.M. Wuts, "Protective Groups in Organic Synthesis", 3rd ed., John Wiley & Sons, 1999. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

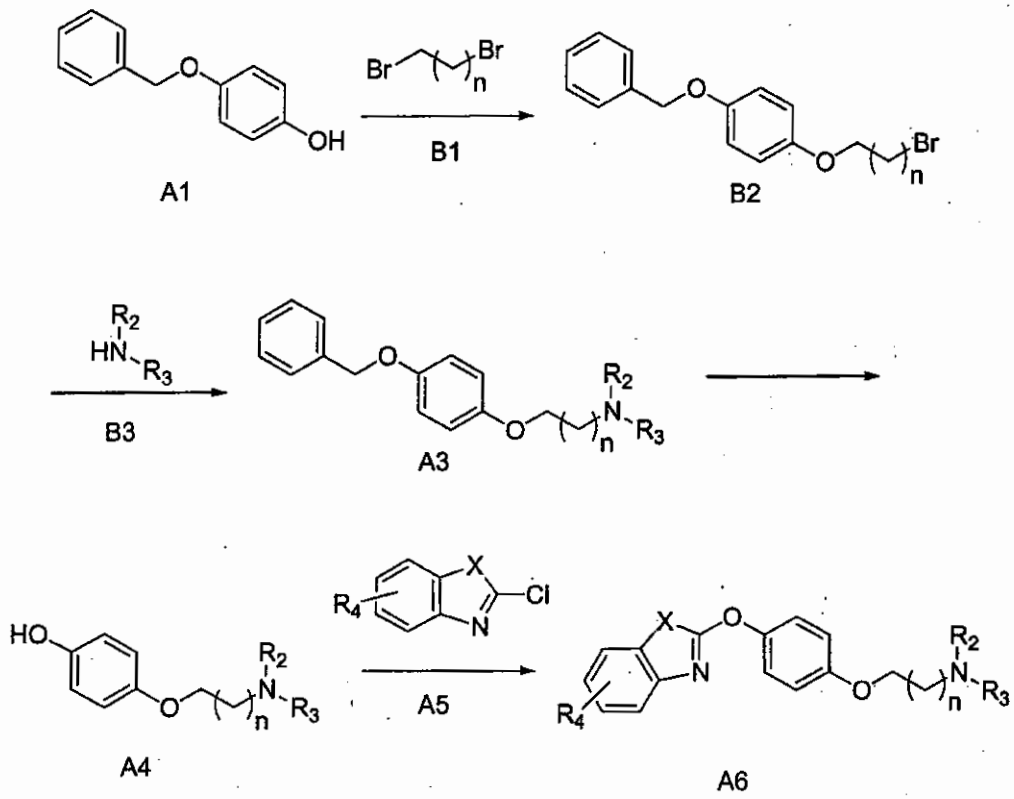
Scheme A



Referring to Scheme A, n is 1 or 2 commercially available 4-benzyloxyphenol, A1, is alkylated with amino alkyl halides, A2; several amino alkyl chlorides are commercially available. The reactions can be run under a wide range of temperatures, including room temperature and more elevated temperatures, in the presence of an inorganic base known to facilitate O-alkylation, such as, but not limited to, K_2CO_3, Cs_2CO_3 and mixtures thereof (*J. Med. Chem*, 1997, 40, 1407-1416). Suitable solvents include but are not limited to DMF. Removal of the benzyl group on A3 may be accomplished using catalytic hydrogenation conditions well known to those skilled in the art (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999.). Suitable catalysts include but are not limited to Pd on carbon (Pd/C), in solvents such as ethyl acetate, alcohols and mixtures thereof. Examples of alcohols include but are not limited to CH_3OH, ethanol, *i*-PrOH. These reactions are typically run at room temperature. Removal of the benzyl group on A3 may be accomplished in some

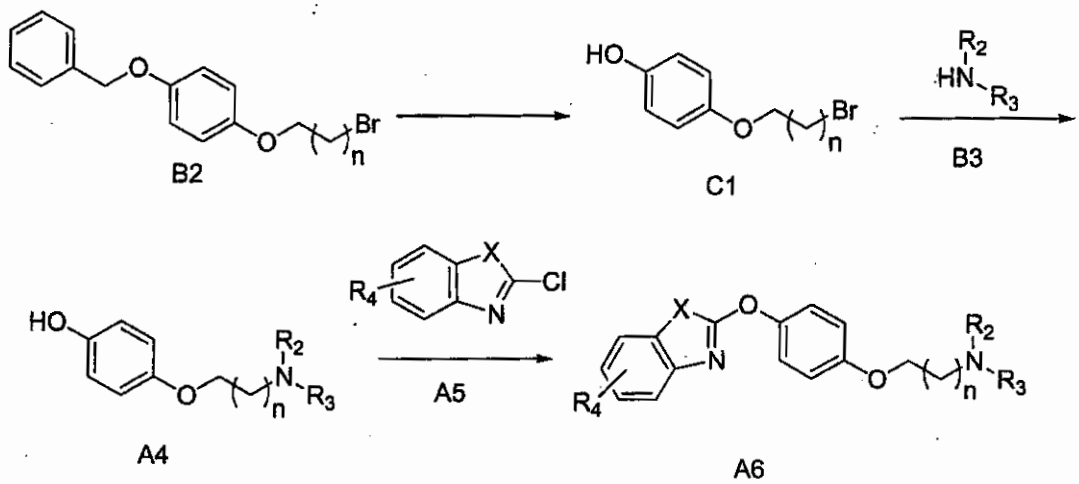
embodiments by using dissolving metal reductions or transfer hydrogenation conditions at suitable temperatures. For example, dissolving metal reductions are typically performed at temperatures below room temperature (-33 °C). Reaction of A4 with the aromatic bicyclic ring system, A5, suitably protected if appropriate, may be accomplished within a wide range of temperatures including room temperature and more elevated temperatures in the presence of a suitable base including but not limited to amine or inorganic base as defined above. Suitable amine bases include but are not limited to triethylamine (TEA), *N,N*-diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), resin-bound amine bases and mixtures thereof. When X is oxygen or sulfur, protecting groups are not applicable. Suitable solvents include but are not limited to DMF, CH_3CN, acetone and mixtures thereof. When X is NR^5, and R^5 is a suitable silicon based protecting group, such as SEM (trimethylsilylethoxymethyl), removal of the silicon-based protecting group on NR^5 can be accomplished using conditions well known to those skilled in the art (Greene et. al. as cited above). Typical reaction conditions include but are not limited to the use of tetrabutylammonium fluoride (TBAF), in suitable solvents such as THF at elevated temperatures.

Scheme B



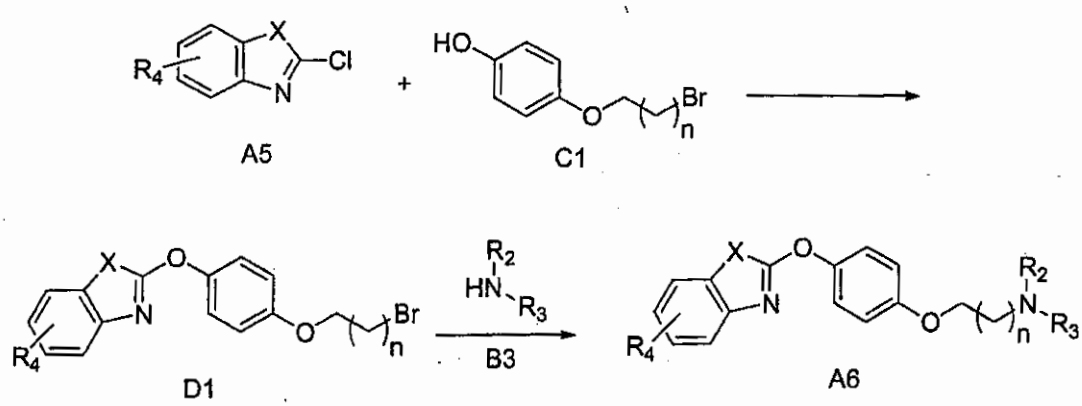
Referring to Scheme B, commercially available 4-benzyloxyphenol, A1, is alkylated with dihaloalkanes, preferably dibromoalkanes such as 1,2-dibromoethane and 1,3-dibromopropane, B1, both of which are commercially available, under a wide range of temperatures with elevated temperatures preferred (*Zhou, Z. –L. et al.*, J. Med. Chem. 1999, 42:2993-3000). The reactions are conducted in the presence of an inorganic base known to facilitate O-alkylation such as, but not limited to, K_2CO_3, Cs_2CO_3 and mixtures thereof. Suitable solvents include but are not limited to CH_3CN and DMF. Compounds of structure B2 are treated with amines, B3, either in the presence or absence of a suitable amine base as described above under a wide range of temperatures with elevated temperatures preferred. Suitable solvents include CH_3CN, CH_2Cl_2 and DMF. Further conversion of the resulting products, of structure A3, to compounds of structure A6, is as detailed above for Scheme A.

Scheme C



Referring to Scheme C, the benzyl group of compounds of structure B2 can be removed using catalytic hydrogenation conditions well known to those skilled in the art (Greene et. al. as cited above). Suitable catalysts include but are not limited to Pd/C, in solvents such as THF and THF/ethanol mixtures. These reactions are typically run at room temperature. Removal of the benzyl group on B2 can be accomplished in some embodiments using transfer-hydrogenation conditions using suitable solvents and temperatures. Compounds of general structure C1 are treated with amines of structure B3 either in the presence or absence of a suitable amine base as described above under a wide range of temperatures with elevated temperatures preferred. Suitable solvents include but are not limited to CH_3CN, CH_2Cl_2 and DMF. Further conversion of the resulting products, A4, to compounds A6, is as detailed above for Scheme A.

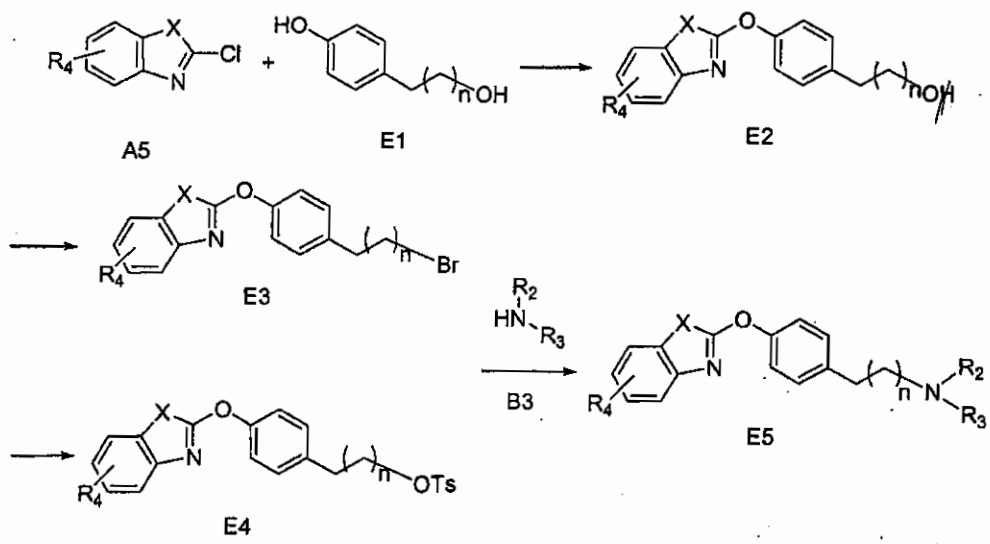
Scheme D



Referring to Scheme D, the compounds of structure A6 can also be prepared by treatment of compounds of structure C1 with aromatic bicyclic compounds, A5, where X = S and O, in the presence of a suitable inorganic base, as defined above, under a wide range of temperatures with elevated temperatures preferred. Suitable solvents include but are not limited to DMF, CH_3CN and mixtures thereof. Conversion of compounds of structure D1 to compounds of structure A6 can be accomplished by treatment with compounds of structure B3. These reactions can be performed either in the presence or absence of a suitable amine base as defined above or an inorganic base such as, but not limited to, K_2CO_3, Cs_2CO_3 and mixtures thereof as described above, under a wide range of temperatures with elevated temperatures preferred. Suitable solvents include but are not limited to CH_3CN and DMF.

It is envisaged that when X is NR^5, and R^5 is a suitable silicon-based protecting group that the synthesis would follow that described above. The removal of the silicon-based protecting group at the end of the synthetic sequence is further envisaged to occur using conditions as described by texts such as (Greene et. al. as cited above).

Scheme E

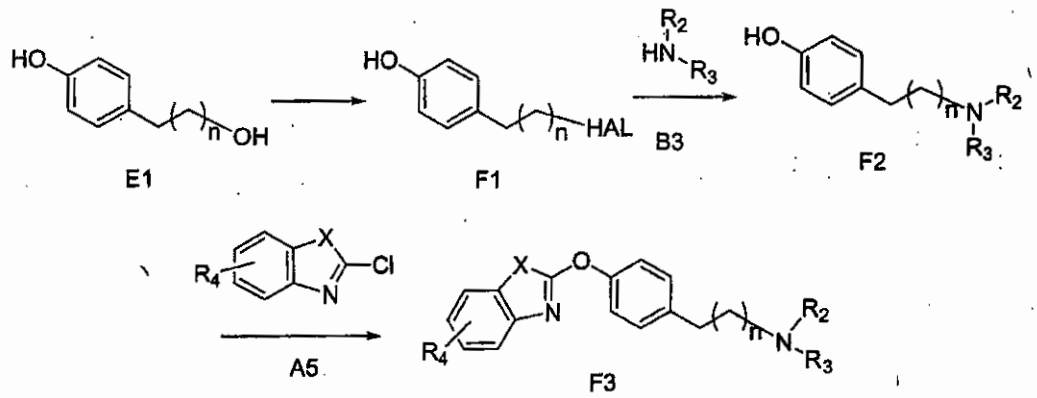


Referring to Scheme E, treatment of compounds of structure E1 with aromatic bicyclic compounds, A5, where X is Swhy not O also?, in the presence of a suitable inorganic base, as defined above, under a wide range of temperatures with elevated temperatures are preferred. Suitable solvents

include but are not limited to DMF, CH_3CN and mixtures thereof. Compounds of structure E2 can be converted to compounds of structure E3 using typical brominating conditions including but not limited to the use of PBr_3 at elevated temperatures. Suitable solvents include but are not limited to benzene. Compounds of structure E2 can also be converted to compounds of structure E4 using standard conditions for sulphonylation well known to those skilled in the art. These include but are not limited to the use of TsCl to prepare tosylates, as denoted in the scheme, in the presence of an amine base at room temperature in CH_2Cl_2. Conversion of compounds of structure E3 to compounds of structure E5 can be accomplished by treatment with compounds of structure B3. These reactions can be performed either in the presence or absence of a suitable amine base as described above or an inorganic base such as, but not limited to, K_2CO_3, Cs_2CO_3 and mixtures thereof under a wide range of temperatures with elevated temperatures preferred. Suitable solvents include but are not limited to CH_3CN and DMF. Compounds of structure E4 can be converted to the compounds of the structure E5 by treatment with compounds of structure B3. These reactions can be performed either in the presence or absence of a suitable amine base as described above under a wide range of temperatures. Suitable solvents include but are not limited to CH_3CN and DMF.

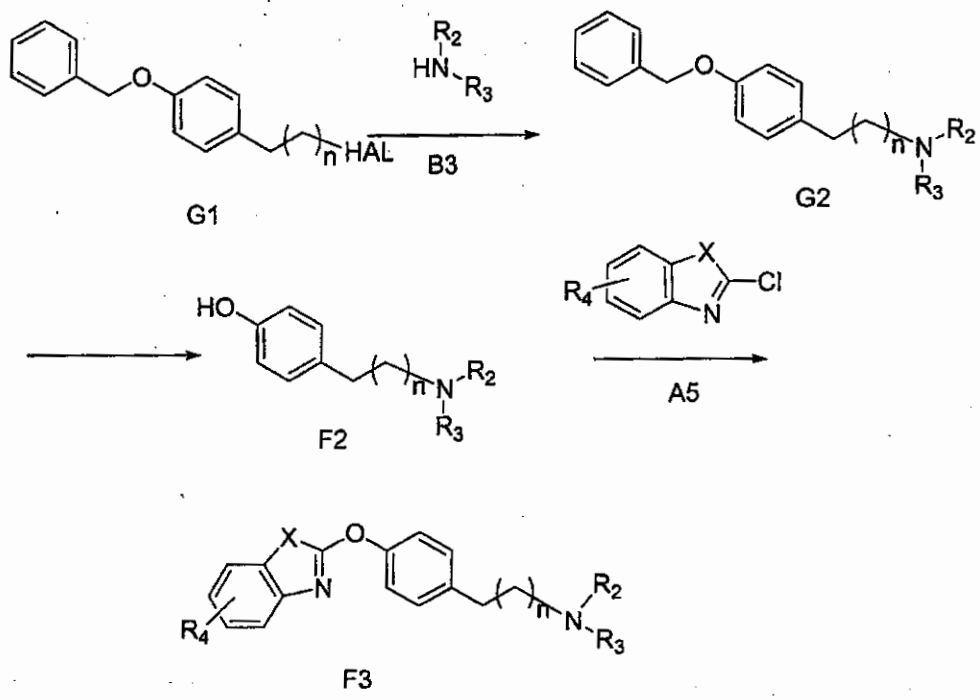
It is envisaged that when X is NR^5, and R^5 is a suitable silicon-based protecting group that the synthesis would follow that described above. The removal of the silicon-based protecting group at the end of the synthetic sequence is further envisaged to occur using conditions as described by texts such as Greene et. al. (as cited above).

Scheme F



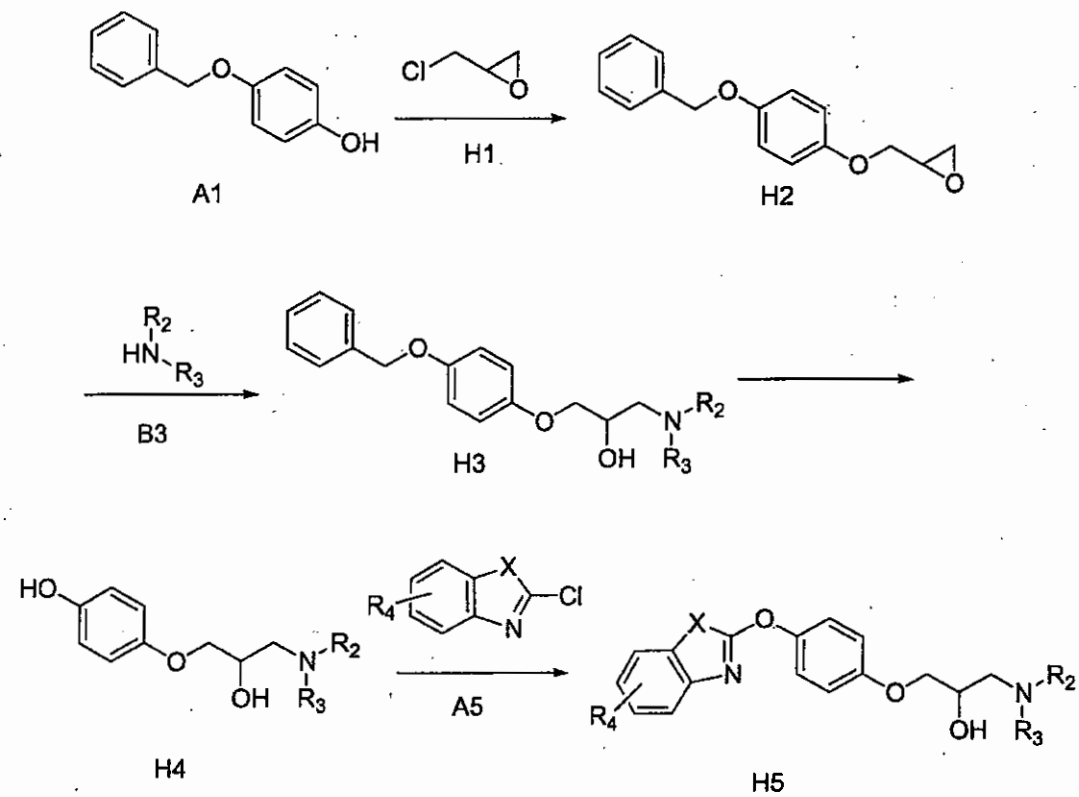
Referring to Scheme F, commercially available 4-(2-hydroxy-ethyl)-phenol and 4-(2-hydroxy-propyl)-phenol are converted to the corresponding alkyl halides F1, where HAL is chloride or bromide, using typical brominating or chlorinating conditions. These conditions include but are not limited to treatment with 48% HBr solutions at elevated temperatures. The resulting bromophenols of structure F1 can then be treated with amines of the structure of B3 either in the presence or absence of a suitable amine base as described above under a wide range of temperatures. Suitable solvents include but are not limited to CH_3CN and DMF. Reaction of F2 with the aromatic bicyclic ring system, A5, suitably protected if appropriate, may be accomplished within a wide range of temperatures including room temperature and more elevated temperatures, in the presence of a suitable amine or inorganic base as defined above. Suitable solvents include but are not limited to DMF, CH_3CN, acetone and mixtures thereof. When X is O or S, protecting groups are not applicable. When X is NR^5, and R^5 is a suitable silicon-based protecting group, such as SEM (trimethylsilylethoxymethyl), removal of the silicon-based protecting group on NR^5 can be accomplished using conditions well known to those skilled in the art (Greene et. al. as cited above). Typical reaction conditions include but are not limited to the use of TBAF, in suitable solvents such as THF at elevated temperatures.

Scheme G



Referring to Scheme G, G1, where n is 0 or 2 and HAL is bromide or chloride, are commercially available materials or may be obtained from **, and G1, where n is 1, is envisaged to be available using standard alkylation conditions starting from 4-(2-hydroxy-ethyl)-phenol and benzyl bromide. The benzyl group in G1 serves as a protecting group. Other compatible protecting groups known to one skilled in the art may be employed in this sequence. Compounds with the general structure G2 can be obtained by treatment with amines of the general structure B3, either in the presence or absence of a suitable amine base as described above under a wide range of temperatures. Suitable solvents include but are not limited to CH_3CN and DMF. Removal of the benzyl may be accomplished using catalytic hydrogenation conditions well known to those skilled in the art (Greene et. al. as cited above). Suitable catalysts include but are not limited to Pd/C, in solvents such as ethyl acetate, alcohols and mixtures thereof. Examples of alcohols include but are not limited to CH_3OH, ethanol, *i*-PrOH. These reactions are typically run at room temperature. Removal of the benzyl group on G2 may be accomplished in some embodiments using transfer-hydrogenation conditions at suitable temperatures. Further conversion of the resulting products, F2, to the final target compounds F3 is as detailed above for Scheme F.

Scheme H



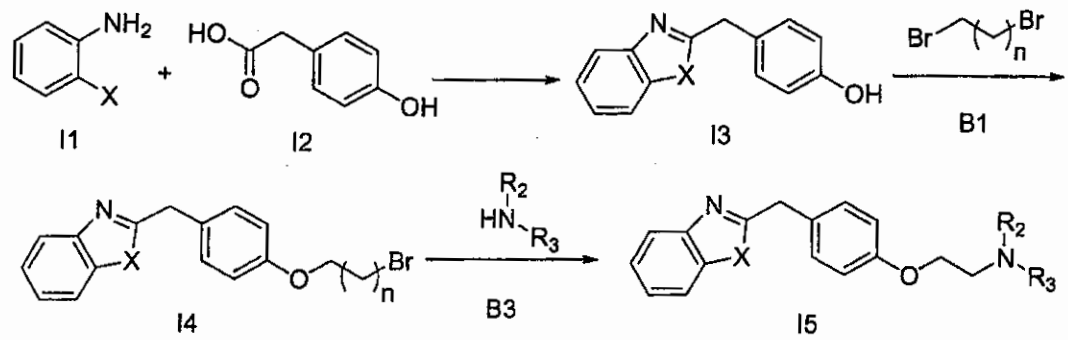
Referring to Scheme H, commercially available 4-benzyloxyphenol, A1, is treated with epichlorohydrin, H1, both of which are commercially available. The reaction can be run under a wide range of temperatures, with elevated temperatures preferred, in the presence of an inorganic base such as, but not limited to, K_2CO_3, Cs_2CO_3 and mixtures thereof. Suitable solvents include but are not limited to DMF. Conversion of compounds of structure H2 to compounds of structure H3 can be accomplished by treatment with amines of general structure B3 either in the presence or absence of a suitable amine base as described above or an inorganic base such as, but not limited to, K_2CO_3, Cs_2CO_3 and mixtures thereof under a wide range of temperatures with elevated temperatures preferred. Suitable solvents include but are not limited to CH_3CN and DMF. Removal of the benzyl group on H3 may be accomplished using catalytic-hydrogenation conditions well known to those skilled in the art (Greene et. al. as cited above). Suitable catalysts include but are not limited to Pd/C, in solvents such as ethyl acetate, alcohols and mixtures thereof. Examples of alcohols include but are not limited to ethanol, CH_3OH, *i*-

PrOH. These reactions are typically run at room temperature. Removal of the benzyl group on B2 can be accomplished in some embodiments using transfer-hydrogenation conditions using suitable solvents and temperatures.

Conversion of compounds of structure H4 to final target compounds H5 can be accomplished by treatment with the aromatic bicyclic ring system, A5, where X is O, in the presence of a suitable inorganic base, as defined above, under a wide range of temperatures with lower temperatures preferred. Suitable solvents include but are not limited to acetone.

It is envisaged that when X is NR^5, and R^5 is a suitable silicon-based protecting group that the synthesis would follow that described above. The removal of the silicon-based protecting group at the end of the synthetic sequence is further envisaged to occur using conditions as described by texts such as Greene et. al. (as cited above).

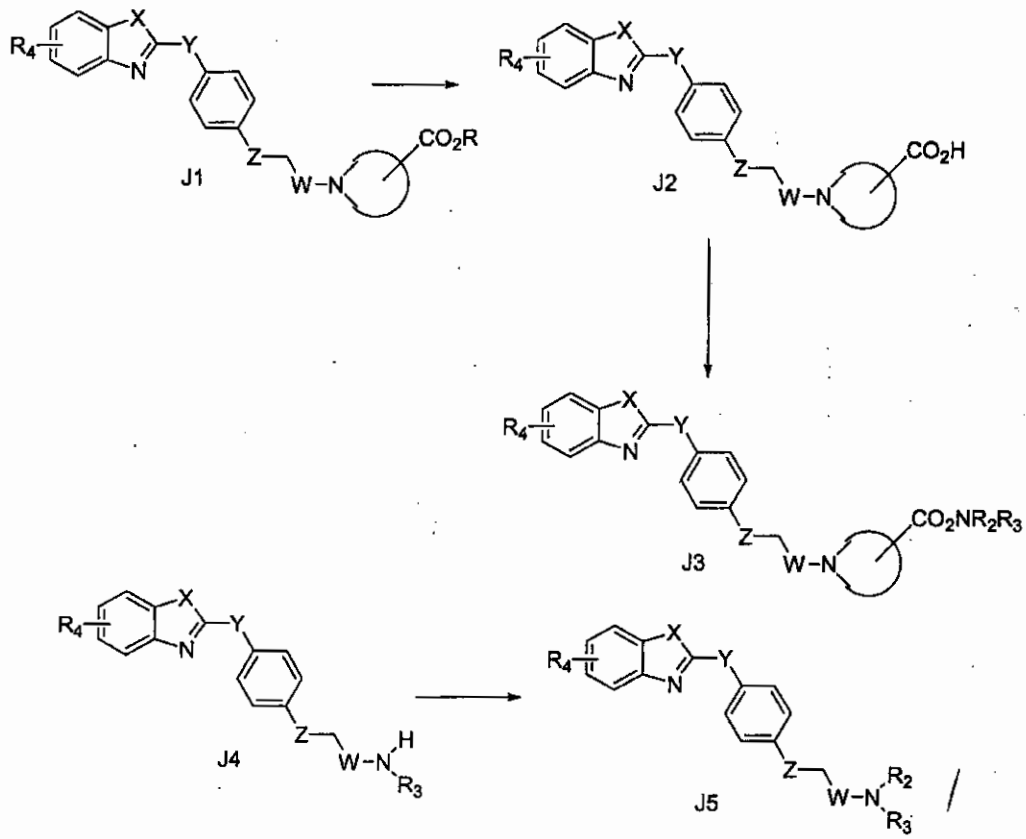
Scheme I



Referring to Scheme I, compounds of type I5 are prepared by heating commercially available 4-hydroxyphenyl acetic acid with, in the case of X is S, 2-aminothiophenol. In the case of X is O, 2-aminophenol is used. The two starting materials are heated in the absence of solvent, and the resulting phenols, I3, are treated with dihaloalkanes, preferably dibromoalkanes such as 1,2-dibromoethane and 1,3-dibromopropane, B1, both of which are commercially available, under a wide range of temperatures with elevated temperatures preferred (*Zhou, Z. –L. et al.* as cited above). The reactions are conducted in the presence of an inorganic base known to facilitate O-alkylation such as, but not limited to, K_2CO_3, Cs_2CO_3 and mixtures thereof. Suitable solvents include but are not limited to CH_3CN and DMF. Compounds of

structure I4 are treated with amines, B3, either in the presence or absence of a suitable amine base as described above under a wide range of temperatures with elevated temperatures preferred. Suitable solvents include CH_3CN, CH_2Cl_2 and DMF.

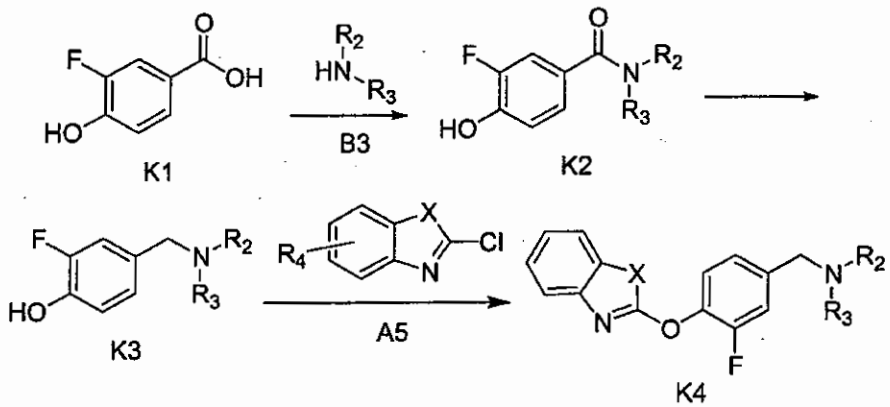
Scheme J



Referring to Scheme J, compounds of the structure J1 can be further elaborated within the limits of the claims to give more highly functionalized target compounds. For example, hydrolysis using methods well known to those skilled in the art such as but not limited to the use of aqueous solutions of LiOH, KOH or NaOH, or aqueous solutions of HCl or CH_3CO_2H, or the use of $(CH_3)_3SiOK$. Furthermore, persons skilled in the art will recognize that certain compounds are more advantageously produced by one method as compared to another and that salts of the desired compounds may initially result. Compounds of the structure J2 can be further modified to give amides using methods well known to those skilled in the art including but not limited to using $(COCl_2)_2$ to convert to the intermediary acid chloride followed by

exposure to amines of the structure B3. Alternatively, standard amide bond-forming conditions may be utilized, including but not limited to the use of 1,(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), with or without additives such as HOBT, and amines of the structure B3. Compounds of the structure J4 can be further modified by reductive amination using standard conditions well known to those skilled in the art, including but not limited to the use of an amine of the structure B3 and $NaBH(OAc)_3$ in an appropriate solvent such as CH_2Cl_2, $ClCH_2CH_2Cl$ or CF_3CH_2OH.

Scheme K

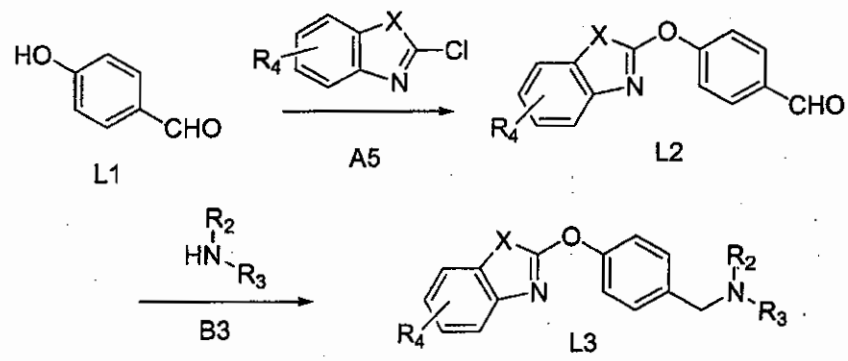


Referring to Scheme K, commercially available 3-fluoro-4-hydroxy-benzoic acid, K11, is converted to amides K2, with amines of structure B3, using standard peptide coupling conditions well known to those skilled in the art such as, but not limited to, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), 1,3-dicyclohexylcarbodiimide (DCC), *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophoshate (HATU), *O*-benzotriazol-1-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HBTU) and mixtures thereof. Suitable solvents include, but are not limited to, CH_2Cl_2 and THF. The resulting amides of structure K2 are reduced to amines of formula K3 under reducing conditions well known to those skilled in the art, including but not limited to, lithium aluminum hydride in an appropriate solvent such as, but not limited to, THF. Conversion of benzyl amines K3 to the final target compounds, K4, can be accomplished by treatment with the aromatic bicyclic ring system, A5, where X is S or O, in the presence of a suitable inorganic base under a wide range of temperatures with elevated temperatures

preferred. Suitable inorganic bases include, but are not limited to, K_2CO_3, Cs_2CO_3 and mixtures thereof. Suitable solvents include, but are not limited to, acetone and CH_3CN.

It is envisaged that when X is NR^5, and R^5 is a suitable silicon-based protecting group that the synthesis would follow that described above. The removal of the silicon-based protecting group at the end of the synthetic sequence is further envisaged to occur using conditions as described by texts such as Greene et. al. (as cited above).

Scheme L



Referring to Scheme L, an alternate embodiment toward the preparation of compounds of formula (I) where n is 0 is described. The starting material L1, 4-hydroxybenzaldehyde, is converted to ethers of formula L2 by treatment with the aromatic bicyclic ring system, A5, where X is S or O, in the presence of a suitable inorganic base under a wide range of temperatures with elevated temperatures preferred. Suitable inorganic bases include, but are not limited to, K_2CO_3, Cs_2CO_3 and mixtures thereof. Suitable solvents include, but are not limited to, acetone and CH_3CN. It is envisaged that when X is NR^5, and R^5 is a suitable silicon-based protecting group that the synthesis would follow that described above. The removal of the silicon-based protecting group at the end of the synthetic sequence is further envisaged to occur using conditions as described by texts such as Greene et. al. (as cited above). Aldehydes of formula L2 are converted to amines of formula L3 under reductive amination conditions with amines of formula B3. Suitable reducing agents include $Na(OAc)_3BH$ and $NaCNBH_3$, with or without the addition of activating agents such as acetic acid or $ZnCl_2$. Suitable solvents include THF and methanol, and

reaction temperatures may range from 0 °C to 70 °C. Preferred reaction conditions are $Na(OAc)_3BH$ in THF at room temperature.

Pharmaceutically acceptable salts, esters, and amides of compounds according to the present invention refer to those salt, ester, and amide forms of the compounds of the present invention which would be apparent to the pharmaceutical chemist, *i.e.*, those which are non-toxic and which would favorably affect the pharmacokinetic properties of said compounds of the present invention. Those compounds having favorable pharmacokinetic properties would be apparent to the pharmaceutical chemist, *i.e.*, those which are non-toxic and which possess such pharmacokinetic properties to provide sufficient palatability, absorption, distribution, metabolism and excretion. Other factors, more practical in nature, which are also important in the selection, are cost of raw materials, ease of crystallization, yield, stability, hygroscopicity and flowability of the resulting bulk drug.

In addition, acceptable salts of carboxylates include sodium, potassium, calcium and magnesium. Examples of suitable cationic salts include hydrobromic, hydroiodic, hydrochloric, perchloric, sulfuric, maleic, fumaric, malic, tartaric, citric, benzoic, mandelic, methanesulfonic, hydroethanesulfonic, benzenesulfonic, oxalic, palmitic, 2-naphthalenesulfonic, p-toluenesulfonic, cyclohexanesulfamic and saccharic.

More extensive sets of examples of acids and bases that may be used in the preparation of pharmaceutically acceptable salts include the following: Acids such as acetic acid, 2,2-dichloroactic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid, α-oxo-glutaric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, (+)-L-lactic acid, (±)-DL-lactic acid, lactobionic acid, maleic acid, (-)-L-malic acid, malonic acid, (±)-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-

disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitric acid, pamoic acid, phosphoric acid, L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebacic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid; and bases such as ammonia, L-arginine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylenediamine, N-methyl-glucamine, hydrabamine, 1H-imidazole, L-lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, secondary amines, sodium hydroxide, triethanolamine, tromethamine and zinc hydroxide. *See, e.g.*, S.M. Berge, *et al.*, "Pharmacetuical Salts", J. Pharm. Sci., 1977, 66:1-19, which is incorporated herein by reference.

Examples of suitable esters include such esters where one or more carboxyl substituents is replaced with p-methoxybenzyloxycarbonyl, 2,4,6-trimethylbenzyloxycarbonyl, 9-anthryloxycarbonyl, CH_3SCH_2COO-, tetrahydrofur-2-yloxycarbonyl, tetrahydropyran-2-yloxycarbonyl, fur-2-yloxycarbonyl, benzoylmethoxycarbonyl, p-nitrobenzyloxycarbonyl, 4-pyridylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, t-butyloxycarbonyl, t-amyloxycarbonyl, diphenylmethoxycarbonyl, triphenylmethoxycarbonyl, adamantyloxycarbonyl, 2-benzyloxyphenyloxycarbonyl, 4-methylthiophenyloxycarbonyl, or tetrahydropyran-2-yloxycarbonyl.

Compounds of the present invention may be used in pharmaceutical compositions to treat patients (humans and other mammals) with disorders involving the action of the LTA4H enzyme. In particular, compounds of the present invention may be used in pharmaceutical compositions to treat inflammation. More particularly, compounds of the present invention may be used in pharmaceutical compositions to treat inflammatory conditions such as inflammatory bowel disease (IBD) (such as Crohn's disease and ulcerative colitis), chronic obstructive pulmonary disease (COPD), arthritis, psoriasis, asthma, cystic fibrosis, atherosclerosis, rheumatoid arthritis, and multiple sclerosis.

The present invention features pharmaceutical compositions containing such compounds and methods of using such compositions in the treatment or prevention of conditions that are mediated by LTA4H enzyme activity. Accordingly, the present invention also contemplates a pharmaceutical composition that comprises at least one compound according to this invention, preferably dispersed in a pharmaceutically acceptable carrier. The at least one compound according to this invention is present in such composition in an amount sufficient to inhibit LTA4H enzyme activity. More particularly, the at least one compound according to this invention is present in such composition in an anti-inflammatory amount.

Accordingly, a pharmaceutical composition that comprises an anti-inflammatory amount of at least one compound according to the present invention in a pharmaceutically acceptable carrier is also contemplated herein. The composition comprises a unit dosage of the at least one compound according to this invention. In preferred practice, the at least one compound according to the present invention that is comprised in the pharmaceutical composition is capable of inhibiting LTA4H enzyme activity in the amount at which that compound is present in the pharmaceutical composition, when that pharmaceutical composition is introduced as a unit dose into an appropriate patient or subject.

The terms "unit dose" and their grammatical equivalent forms are used herein to refer to physically discrete units suitable as unitary dosages for human patients and other animals, each unit containing a predetermined effective, pharmacologic amount of the active ingredient calculated to produce the desired pharmacological effect. The specifications for the novel unit dosage forms of this invention are determined by, and are directly dependent on, the characteristics of the active ingredient, and on the limitations inherent in the art of compounding such an active ingredient for therapeutic use in humans and other animals.

The pharmaceutical compositions can be prepared using conventional pharmaceutical excipients and compounding techniques. Examples of suitable unit dosage forms are tablets, capsules, pills, powder packets, granules, wafers, and the like, segregated multiples of any unit dosage form, as well as

liquid solutions, and suspensions. Oral dosage forms may be elixirs, syrups, capsules tablets and the like. Examples of solid carriers include those materials usually employed in the manufacture of pills or tablets, such as lactose, starch, glucose, methylcellulose, magnesium stearate, dicalcium phosphate, mannitol and the like, thickeners such as tragacanth and methylcellulose USP, finely divided SiO_2, polyvinylpyrrolidone, magnesium stearate, and the like. Typical liquid oral excipients include ethanol, glycerol, water and the like. All excipients may be mixed as needed with inert diluents (for example, sodium and calcium carbonates, sodium and calcium phosphates, and lactose), disintegrants (for example, cornstarch and alginic acid), diluents, granulating agents, lubricants (for example, magnesium stearate, stearic acid, and talc), binders (for example, starch and gelatin), thickeners (for example, paraffin, waxes, and petrolatum), flavoring agents, coloring agents, preservatives, and the like by conventional techniques known to those of ordinary skill in the art of preparing dosage forms. Coatings can be present and include, for example, glyceryl monostearate and/or glyceryl distearate. Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules, in which the active ingredient is mixed with water or oil, such as peanut oil, liquid paraffin, or olive oil.

Parenteral dosage forms may be prepared using water or another sterile carrier. For intramuscular, intraperitoneal, subcutaneous, and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone, and gum tragacanth, and a wetting agent, such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

Physiologically acceptable carriers are well known in the art. Examples of liquid carriers are solutions in which compounds according to the present invention form solutions, emulsions, and dispersions. Compatible antioxidants,

such as methlyparaben and propylparaben, can be present in solid and liquid compositions, as can sweeteners.

Pharmacetuical compositions according to the present invention may include suitable emulsifiers typically used in emulsion compositions. Such emulsifiers are described in standard publications such as H.P. Fiedler, 1989, Lexikon der Hilfsstoffe für Pharmazie, Kosmetic und agrenzende Gebiete, Cantor ed., Aulendorf, Germany, and in Handbook of Pharmacetutical Excipients, 1986, American Pharmaceutical Association, Washington, DC, and the Pharmaceutical Society of Great Britain, London, UK, which are incorporated herein by reference. Gelling agents may also be added to compositions according to this invention. Polyacrylic acid derivatives, such as carbomers, are examples of gelling agents, and more particularly, various types of carbopol, which are typically used in amounts from about 0.2% to about 2%. Suspensions may be prepared as a cream, an ointment, including a water-free ointment, a water-in-oil emulsion, an oil-in-water emulsion, an emulsion gel, or a gel.

It is anticipated that the compounds of the invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, rectal, and topical administration, and inhalation. For oral administration, the compounds of the invention will generally be provided in the form of tablets, capsules, or as a solution or suspension.

"Therapeutically effective amount" or "effective amount" and grammatically related terms mean that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a subject that is being sought by a researcher, veterinarian, medical doctor, or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. "Subject" or "patient" includes mammals such as human beings and animals (*e.g.*, dogs, cats, horses, rats, rabbits, mice, non-human primates) in need of observation, experiment, treatment or prevention in connection with the relevant disease or condition. Preferably, the patient or subject is a human being.

Effective doses of the compounds of the present invention may be ascertained by conventional methods. The specific dosage level required for any particular patient will depend on a number of factors, including severity of the condition, the route of administration, and the weight of the patient.

In general, it is anticipated that the daily dose (whether administered as a single dose or as divided doses) will be in the range from about 0.01 mg to about 1000 mg per day, more usually from about 1 mg to about 500 mg per day, and most usually form about 10 mg to about 200 mg per day. Expressed as dosage per unit body weight, a typical dose will be expected to be between about 0.0001 mg/kg and about 15 mg/kg, especially between about 0.01 mg/kg and about 7 mg/kg, and most especially between about 0.15 mg/kg and 2.5 mg/kg.

Anticipated oral dose ranges include from about 0.01 to 500 mg/kg, daily, more preferably from about 0.05 to about 100 mg/kg, taken in 1-4 separate doses. Some compounds of the invention may be orally dosed in the range of about 0.05 to about 50 mg/kg daily, while others may be dosed at 0.05 to about 20 mg/kg daily. Infusion doses can range from about 1.0 to about 1.0×10^4 µg/(kg.min) of inhibitor, admixed with a pharmaceutical carrier over a period ranging from several minutes to several days. For topical administration, compounds of the present invention may be mixed with a pharmaceutical carrier at a concentration from about 0.1 to about 10% of drug to vehicle.

A method for treating inflammation in a patient exhibiting or susceptible to an inflammatory condition is also contemplated. A method for treating an LTA4H-mediated condition is also contemplated. The methods comprise administering to that patient an effective amount of a pharmaceutical composition that includes a unit dose of an active ingredient that is at least one of the compounds according to this invention dispersed in a pharmaceutically acceptable carrier.

To provide a more concise description, some of the quantitative expressions given herein are not qualified with the term "about". It is understood that, whether the term "about" is used explicitly or not, every quantity given herein is meant to refer to the actual given value, and it is also

meant to refer to the approximation to such given value that would reasonably be inferred based on the ordinary skill in the art, including approximations due to the experimental and/or measurement conditions for such given value. Whenever a yield is given as a percentage, such yield refers to a mass of the entity for which the yield is given with respect to the maximum amount of the same entity that could be obtained under the particular stoichiometric conditions. Concentrations that are given as percentages refer to mass ratios, unless indicated differently.

EXAMPLES

In order to illustrate the invention, the following examples are included. These examples do not limit the invention. They are only meant to suggest a method of practicing the invention. Those skilled in the art may find other methods of practicing the invention that are obvious to them. However, those methods are deemed to be within the scope of this invention.

General Experimental Procedures:

NMR spectra were obtained on either a Bruker model DPX400 (400 MHz) or DPX500 (500 MHz) spectrometer. The format of the ^{1}H NMR data below is: chemical shift in ppm down field of the tetramethylsilane reference (multiplicity, coupling constant *J* in Hz, integration).

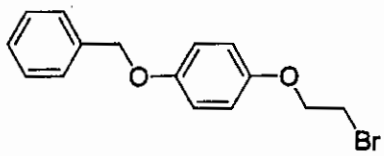
Mass spectra were obtained on an Agilent series 1100 MSD using electrospray ionization (ESI) in either positive or negative mode as indicated. The "mass calculated" for a molecular formula is the monoisotopic mass of the compound.

Reversed-Phase HPLC retention times are reported in minutes, using the methods and conditions reported below.

Instrument:	Gilson 215
Solvent:	CH_3CN (0.05% trifluoroacetic acid, TFA)/H_2O (0.05% TFA)
Flow rate:	25 mL/min
Gradient:	0 min at 10% CH_3CN; 20 min linear ramp to 99% CH_3CN;
Column:	YMC-Pack ODS-A AA 12505-1530WT SH-362-5 (S-5 um, 12 nM, 150x30 mm)
Temperature:	25 °C
Wavelength:	Dual detection at 220 and 254 nM

Flash column chromatography was accomplished using ISCO Foxy 200 or ISCO OPTIX 10X systems employing one of the following commercially available prepacked columns: Biotage 40S (SiO_2 40 g), Biotage 40M (SiO_2 90 g), Biotage 40L (SiO_2 120 g), Biotage 65M (SiO_2 300 g) or ISCO Redisep (SiO_2, 10 g, 12 g, 35 g, 40 g, or 120 g).

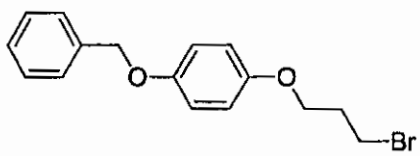
EXAMPLE 1



2-(4-Benzyloxy-phenoxy)-ethyl bromide.

To a stirring solution of 4-benzyloxyphenol (72 g, 359.6 mmol) in CH_3CN (600 mL) was added dibromoethane (155 mL, 1.80 mol) and K_2CO_3 (105 g, 759.9 mmol). This brown suspension was heated at reflux and allowed to stir for 96 h. The resulting suspension was cooled to room temperature, diluted with acetone (250 mL), and filtered through diatomaceous earth, which was then rinsed with additional acetone. The filtrate was concentrated under reduced pressure. The resulting oil was dissolved in CH_3OH (500 mL), and the solution was stirred for 2 h. The title compound was obtained by filtration and air-dried to give 70 g (228 mmol, 63% yield) as a tan solid. ^1H NMR (400 MHz, $CDCl_3$): 7.60-7.30 (m, 5H), 6.88 (d, J = 8.4, 2H), 6.80 (d, J = 8.4, 2H), 4.70 (s, 2H), 3.79 (t, J = 5.8, 2H), 3.07 (t, J = 5.8, 2H).

EXAMPLE 2

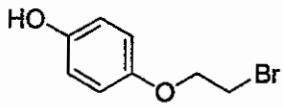


1-[3-(4-Benzyloxy-phenoxy)-propyl]-bromide.

To a stirring solution of 4-benzyloxyphenol (25 g, 124.9 mmol) in CH_3CN (125 mL) was added dibromopropane (63 mL, 624 mmol) and K_2CO_3 (34.5 g, 250 mmol). This brown suspension was heated at reflux and allowed to stir for 66 h. The suspension was then cooled to room temperature and filtered twice through diatomaceous earth pads. The pads were rinsed with CH_3CN, and the combined filtrates were concentrated under reduced pressure. The resultant oil was purified on SiO_2 (300 g; 33% CH_2Cl_2/hexanes) to give 35.4 g (110 mmol, 88% yield) of a brown solid. ^1H NMR (400 MHz, $CDCl_3$): 7.46-7.29 (m,

5H), 6.85 (q, J = 8.1, 2H), 6.82 (q, J = 7.2, 2H), 5.03 (s, 2H), 4.06 (t, J = 5.8, 2H), 3.61 (t, J = 6.5, 2H), 2.39 (m, J = 6.2, 2H).

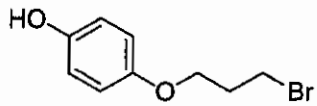
EXAMPLE 3



4-(2-Bromo-ethoxy)-phenol.

2-(4-Benzyloxy-phenoxy)-ethyl bromide (EXAMPLE 1; 70 g, 227 mmol) was dissolved in THF (500 mL). To this solution was added Pd on carbon (10 wt %, 7 g) as a suspension in ethanol (50 mL). The resulting suspension was placed on a Parr hydrogenator at 40 psi of H_2 and shaken overnight. The reaction mixture was filtered through a pad of diatomaceous earth, and the filtrate was concentrated under reduced pressure to give 48.5 g (224 mmol, 99% yield) of a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$): 6.83 (d, J = 9.1, 2H), 6.77 (d, J = 9.1, 2H), 4.51 (s, 1H), 4.24 (t, J = 6.3, 2H), 3.62 (t, J = 6.3, 2H).

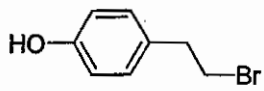
EXAMPLE 4



4-(3-Bromo-propoxy)-phenol.

[3-(4-Benzyloxy-phenoxy)-propyl]-bromide (10 g, 31.1 mmol) was dissolved in THF (100 mL). To this solution was added 10% palladium on carbon (1 g) as a suspension in THF (20 mL). The resulting suspension was placed on a Parr hydrogenator at 40 psi of H_2, and shaken overnight. The reaction mixture was filtered through a pad of diatomaceous earth, and the filtrate was concentrated under reduced pressure to give 7 g (30.5 mmol, 98% yield) of a tan solid. ^{1}H NMR: (400 MHz, $CDCl_3$) 6.76 (d, J = 9.1, 2H), 6.69 (d, 9.1, 2H), 4.00 (t, J = 5.9, 2H), 3.60 (t, J = 6.6, 2H), 2.23 (m, J = 6.1, 2H).

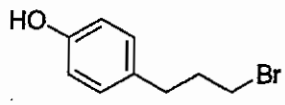
EXAMPLE 5



4-(2-Bromo-ethyl)-phenol.

4-(2-Hydroxy-ethyl)-phenol (50 g, 362 mmol) was dissolved in 48 wt % HBr (250 mL). This light yellow solution was heated to 80 °C and stirred for 16 h. The reaction mixture was allowed to cool to room temperature and was then extracted with CH_2Cl_2 (3 x 50 mL). The combined extracts were dried, filtered, and concentrated under reduced pressure to afford 72 g (100% crude yield) of a tan solid. ^{1}H NMR (400 MHz, $CDCl_3$): 9.25 (s, 1H), 7.04 (d, J = 8.4, 2H), 6.67 (d, J = 8.4, 2H), 3.62 (t, J = 7.4, 2H), 2.97 (t, J = 7.4, 2H).

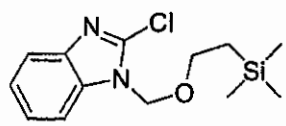
EXAMPLE 6



4-(3-bromo-propyl)-phenol.

A mixture of 4-(3-hydroxy-propyl)-phenol (52.7 g, 346.3 mmol) in 48 wt % HBr (265 mL) was stirred at 80 °C for 20 h and then cooled to room temperature. Water (400 mL) was added, and the product was extracted with CH_2Cl_2 (500 mL). The extract was dried ($MgSO_4$) and concentrated under reduced pressure to give the desired product as a beige solid (69 g, 92% yield). TLC (SiO_2, CH_2Cl_2): R_f = 0.37. ^{1}H NMR (400 MHz, DMSO-d_6): 9.18 (s, 1H), 6.99 (d, J = 8.3, 2H), 6.67 (d, J = 8.4, 2H), 3.47 (t, J = 6.6, 2H), 2.58 (t, J = 7.2, 2H), 2.05-1.95 (m, 2H).

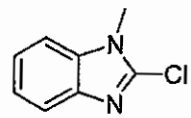
EXAMPLE 7



2-Chloro-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-benzoimidazole.

To a suspension of sodium hydride (6.2 g, 245 mmol) in DMF (275 mL) at 5 °C was added 2-chlorobenzimidazole (37 g, 243 mmol) via a solid-addition funnel over 30 min while maintaining the internal temperature of the mixture below 10 °C. An additional 25 mL of DMF was added, and the ice bath was removed. After 2 h, 2-(trimethylsilyl)ethoxymethyl chloride (SEM-Cl) was added dropwise over 5 min. A white precipitate formed. The reaction mixture was stirred at room temperature for 18 h. To the mixture was added H_2O (500 mL) and ethyl acetate (750 mL). The organic layer was washed with additional H_2O (500 mL), dried ($MgSO_4$), and concentrated under reduced pressure, giving 65.8 g (96% yield) of the desired product as a clear golden oil, which solidified upon standing to give a beige solid. TLC (SiO_2, 5% acetone/CH_2Cl_2): R_f = 0.64. MS (ESI): mass calculated for $C_{13}H_{19}ClN_2OSi$, 282.10; m/z found, 283.1. ^1H NMR (400 MHz, $CDCl_3$): 7.70 (d, J = 7.3, 1H), 7.46 (d, J = 7.6, 1H), 7.40-7.25 (m, 2H), 3.58 (t, J = 7.9, 2H), 0.92 (t, J = 8.3, 2H), 0.04 (s, 9H).

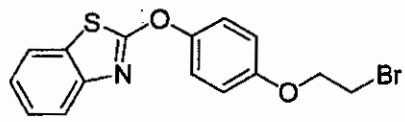
EXAMPLE 8



2-Chloro-1-methyl-1*H*-benzoimidazole.

Dimethyl sulfate (11.0 mL, 116 mmol) was added to a solution of 2-chlorobenzimidazole (10.6 g, 70 mmol) in 2.5 M NaOH (70 mL, 175 mmol), and the mixture was stirred at 23 °C for 2 h. The reaction mixture was filtered, and the solid product was washed with H_2O (6 x 50 mL) and dried in vacuo to afford a light brown solid (9.4 g, 81% yield). MS (ESI): mass calculated for $C_8H_7ClN_2$, 166.03; m/z found, 167.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.75-7.70 (m, 1H), 7.35-7.29 (m, 3H), 3.82 (s, 3H).

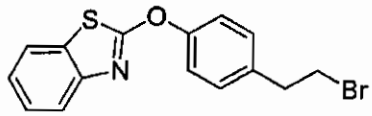
EXAMPLE 9



2-[4-(2-Bromo-ethoxy)-phenoxy]-benzothiazole.

A solution of 4-(2-bromo-ethoxy)-phenol (EXAMPLE 3; 8.7 g, 40.1 mmol) and 2-chlorobenzothiazole (12 mL, 92 mmol) in CH_3CN was treated with finely powdered Cs_2CO_3 (26 g, 80 mmol), and the resulting mixture was stirred at 23 °C for 30 h. The reaction mixture was filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure. The crude solid was purified on SiO_2 (100 g; 0–40% ethyl acetate/hexanes) to provide 6.7 g (47% yield) of a white solid. MS (ESI): mass calculated for $C_{15}H_{12}BrNO_2S$, 348.98; m/z found, 350.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.78, (dd, J = 8.0, 0.4, 1H), 7.70 (dd, J = 8.0, 0.7, 1H), 7.42 (dt, J = 7.5, 1.3, 1H), 7.34 (dd, J = 9.1, 2H), 7.01 (dd, J = 9.1, 2H), 4.34 (t, J = 6.2, 2H), 3.70 (t, J = 6.2, 2H).

EXAMPLE 10



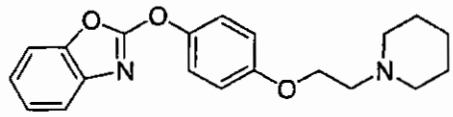
2-[4-(2-Bromo-ethyl)-phenoxy]-benzothiazole.

A. 2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethanol. A solution of 4-hydroxyphenethyl alcohol (867 mg, 6.3 mmol) and 2-chlorobenzothiazole 0.82 mL, 6.3 mmol) in CH_3CN was treated with finely powdered Cs_2CO_3 (4.1 g, 12.5 mmol), and the resulting suspension was stirred for 40 h at 70 °C. The reaction mixture was filtered through diatomaceous earth, and the filtrate was concentrated to a crude oil, which was purified on SiO_2 (40 g; 0–50% ethyl acetate/hexanes) to provide 940 mg (55% yield) of a clear oil. MS (ESI): mass calculated for $C_{15}H_{13}NO_2S$, 271.07; m/z found, 272.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.78 (dd, J = 7.9, 0.4, 1H), 7.75 (dd, J = 7.9, 0.7, 1H), 7.46 (dt, J

= 7.4, 1.3, 1H), 7.38-7.29 (m, 3H), 3.93 (q, J = 6.4, 2H), 2.94, (t, J = 6.5, 2H), 1.50 (m, 1H).

B. 2-[4-(2-Bromo-ethyl)-phenoxy]-benzothiazole. A solution of 2-[4-(benzothiazol-2-yloxy)-phenyl]-ethanol (174 mg, 0.64 mmol) in benzene (3 mL) was treated with PBr_3 (0.060 mL, 0.64 mmol), and the resulting suspension was heated to 70 °C for 90 min. The reaction mixture was cooled and diluted with ethyl acetate (30 mL). This solution was washed with H_2O (10mL) then brine (10 mL), dried, and concentrated under reduced pressure. The crude product was purified on SiO_2 (12 g; 0–50% ethyl acetate/hexanes) to provide 120 mg of a light yellow oil. MS (ESI): mass calculated for $C_{15}H_{12}BrNOS$, 332.98; m/z found, 335.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.79 (dd, J = 8.0, 0.3, 1H), 7.76 (dd, J = 8.0, 0.6, 1H), 7.42 (dt, J = 7.4, 1.2, 1H), 7.38-7.29 (m, 3H), 3.62 (t, J = 7.5, 2H), 3.25 (t, J =7.5, 2H).

EXAMPLE 11



2-[4-(2-Piperidin-1-yl-ethoxy)-phenoxy]-benzooxazole.

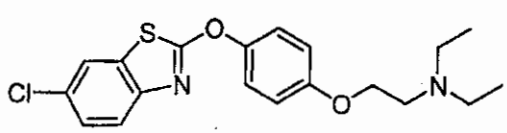
A. 1-[2-(4-Benzyloxy-phenoxy)-ethyl]-piperidine. To a mixture of 4-(benzyloxy)phenol (24.6 g, 123 mmol) and 1-(2-chloroethyl)piperidine hydrochloride (20.6 g, 112 mmol) in DMF (175 mL) was added K_2CO_3 (25 g,181 mmol) and Cs_2CO_3 (40 g, 123 mmol). The reaction mixture was stirred for 3 days at room temperature. To the mixture was added H_2O (300 mL) and CH_2Cl_2. The organic layer was washed with 10% NaOH then brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 33 g of a clear, dark purple liquid. The liquid was purified on SiO_2 (300 g; 0-50% ethyl acetate/hexanes) to give 23.4 g (67% yield) of a light yellow solid. TLC (SiO_2, 50% hexanes/ethyl acetate): R_f = 0.11. MS (ESI): mass calculated for $C_{20}H_{25}NO_2$, 311.19; m/z found, 312.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.50-7.26 (m, 5H), 6.91 (d, J = 9.2, 2H,), 6.85 (d, J = 9.2, 2H), 5.02 (s, 2H),

4.06 (t, J = 6.1, 2H), 2.76 (t, J = 6.1, 2H), 2.51 (br s, 4H), 1.65-1.55 (m, 4H), 1.45 (br s, 2H).

B. 4-(2-Piperidin-1-yl-ethoxy)-phenol. To a solution of 1-[2-(4-benzyloxy-phenoxy)-ethyl]-piperidine (15.0 g, 48.2 mmol) in 1:1 ethanol/ethyl acetate (400 mL) was added Pd on carbon (10 wt %, 1.5 g). The mixture was placed on a Parr hydrogenator at 40 psi of H_2 for 20 h. The reaction mixture was filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure to give 9.4 g (88% yield) of the desired product as a light gray solid. TLC (SiO_2, 50% acetone/CH_2Cl_2): R_f = 0.16. MS (ESI): mass calculated for $C_{13}H_{19}NO_2$, 221.14; m/z found, 222.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.88 (s, 1H), 6.73 (d, J = 6.6, 2H), 6.65 (d, J = 6.6, 2H), 3.93 (t, J = 6.0, 2H), 2.58 (t, J = 6.0, 2H), 2.40 (s, 4H), 1.51-1.45 (m, 4H), 1.35 (br s, 2H).

C. 2-[4-(2-Piperidin-1-yl-ethoxy)-phenoxy] benzooxazole. To a stirred solution of 4-(2-piperidin-1-yl-ethoxy)-phenol (1.5 g, 6.8 mmol) in acetone (20 mL) at 5 °C was added K_2CO_3 (1.0 g, 7.2 mmol). To the mixture was added 2-chloro-benzooxazole (0.5 mL, 4.4 mmol) at 5 °C. The resulting mixture was warmed to room termperature overnight. After 20 h the mixture was filtered, and the filtrate was concentrated under reduced pressure to a brown solid, which was purified on SiO_2 (35 g; 50% acetone/CH_2Cl_2). The desired fractions were combined and concentrated under reduced pressure to give 1.2 g (80% yield) of the desired product as a white solid. TLC (SiO_2, 50% acetone/CH_2Cl_2): R_f = 0.18. MS (ESI): mass calculated for $C_{20}H_{22}N_2O_3$, 338.16; m/z found, 339.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.52 (d, J =7.2, 1H), 7.41 (d, J = 7.2, 1H), 7.35-7.20 (m, 4H), 6.97 (d, J = 9.1, 2H), 4.12 (t, J = 6.1, 2H), 2.79 (t, J = 6.0, 2H), 2.52 (s, 4H), 1.67-1.55 (m, 4H), 1.50-1.40 (m, 2H).

EXAMPLE 12



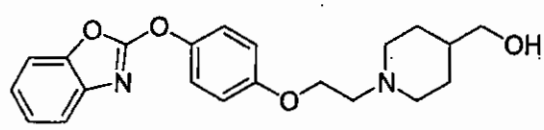
{2-[4-(6-Chloro-benzothiazol-2-yloxy)-phenoxy]-ethyl}-diethyl-amine.

A. [2-(4-Benzyloxy-phenoxy)-ethyl]-diethyl-amine. To a mixture of 4-(benzyloxy)phenol (51 g, 255 mmol) and (2-chloro-ethyl)-diethyl-amine hydrochloride (41.6 g, 242 mmol) in DMF (400 mL) was added K_2CO_3 (37 g, 268 mmol) and Cs_2CO_3 (87 g, 267 mmol). The reaction mixture was stirred at room temperature for 17 days. To the mixture was added H_2O (600 mL) and CH_2Cl_2. The organic layer was washed with H_2O, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 33 g of a clear, dark purple liquid, which was purified on SiO_2 (300 g; ethyl acetate) to give a light yellow oil (34.5 g, 48% yield). TLC (SiO_2, 50% hexanes/ethyl acetate): R_f = 0.10. MS (ESI): mass calculated for $C_{19}H_{25}NO_2$, 299.19; m/z found, 300.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.50-7.28 (m, 5H), 6.89 (d, J = 9.2, 2H), 6.85 (d, J = 9.2, 2H), 5.02 (s, 2H), 4.00 (t, J = 6.4, 2H), 2.86 (t, J = 6.4, 2H), 2.63 (q, J = 7.2, 4H), 1.08 (t, J = 7.1, 6H).

B. 4-(2-Diethylamino-ethoxy)-phenol. To a solution of [2-(4-benzyloxy-phenoxy)-ethyl]-diethyl-amine (21 g, 70 mmol) in 1:1 ethanol/ethyl acetate (500 mL) was added Pd on carbon (10 wt %, 1.5 g). The mixture was placed on a Parr hydrogenator at 40 psi of H_2 for 20 h. The reaction mixture was filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure to give 13.1 g (89% yield) of the desired product as a clear brown oil. MS (ESI): mass calculated for $C_{12}H_{19}NO_2$, 209.14; m/z found, 210.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 6.68 (s, 4H,), 3.99 (t, J = 6.2, 2H), 2.88 (t, J = 6.2, 2H), 2.69 (q, J = 7.2, 4H), 1.09 (t, J = 7.1, 6H).

C. {2-[4-(6-Chloro-benzothiazol-2-yloxy)-phenoxy]-ethyl}-diethyl-amine. To a solution of 4-(2-diethylamino-ethoxy)-phenol (500 mg, 2.39 mmol) in acetone (7 mL) containing Cs_2CO_3 (876 mg, 2.69 mmol) was added 2,6-dichlorobenzthiazole (365 mg, 1.79 mmol). The mixture was heated at reflux for 3 days. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a brown oil, which was purified on SiO_2 (35 g; acetone) to give 624 mg (76% yield) of the desired product. TLC (SiO_2, acetone): R_f = 0.23. MS (ESI): mass found for $C_{19}H_{21}ClN_2O_2S$, 376.10; m/z found, 377.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.64 (d, J = 8.5, 2H), 7.34 (d, J = 8.8, 1H), 7.25 (d, J = 6.8, 2H), 6.96 (d, J = 9.1, 2H).

EXAMPLE 13



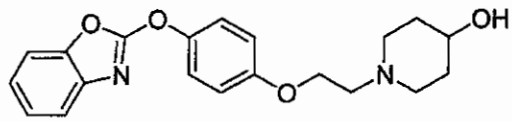
(1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]ethyl}-piperidin-4-yl)-methanol.

A. 4-[2-(4-Hydroxymethyl-piperidin-1-yl)-ethoxy]-phenol. A solution of 4-(2-bromo-ethoxy)-phenol (EXAMPLE 3; 7 g, 32.2 mmol), piperidinemethanol (5.2 g, 45.3 mmol), and *N*,*N*-diisopropylethylamine (7.9 mL, 45.3 mmol) in CH_3CN (100 mL) was stirred at 65 °C for 18 h. The reaction mixture was cooled to room temperature and stirred an additional 48 h. The solvent was removed under reduced pressure to yield a black semi-solid. This material was dissolved in CH_2Cl_2 (200 mL), and the solution was washed with H_2O (2 x 50 mL). The aqueous phase was back-extracted with 10% CH_3OH/CH_2Cl_2 (100 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to a black oil, which was purified on SiO_2 (120 g; 0–100% acetone/CH_2Cl_2) to give the desired product as a brown oil. Diethyl ether was added to the oil to precipitate the product. Filtration yielded the title compound as a tan solid (1.9 g, 23% yield). TLC (SiO_2, 5% 2 M NH_3 in CH_3OH/CH_2Cl_2): R_f = 0.09. MS (ESI): mass calculated for $C_{14}H_{21}NO_3$, 251.15; m/z found, 252.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 6.69 (s, 4H), 4.03 (t, *J* = 5.9, 2H,), 3.51 (d, *J* = 6.5, 2H), 3.09 (d, *J* = 11.6, 2H), 2.79 (t, *J* = 5.9, 2H), 2.18-2.11 (m, 2H), 1.79 (d, *J* = 16.2, 2H), 1.49-1.62 (m, 1H), 1.36 (dq, *J* = 3.6, 12.3, 2H), 1.23 (br s, 2H).

B. (1-{2-[4-Benzooxazol-2-loxy)-phenoxy]ethyl}-piperidin-4-yl)-methanol. A mixture of 4-[2-(4-hydroxymethyl-piperidin-1-yl)-ethoxy]-phenol (0.5 g, 1.98 mmol), 2-chloro-benzooxazole (205 µL, 1.8 mmol) and Cs_2CO_3 (1.35 g, 4.15 mmol) in acetone (8.0 mL) was stirred at room temperature for 48 h. The resulting mixture was filtered through diatomaceous earth, and the pad was washed with CH_2Cl_2. The combined filtrates were concentrated under reduced pressure to a yellow oil. The oil was purified on SiO_2 (40 g; 0–100% acetone/CH_2Cl_2) to provide a solid, which was dissolved in CH_2Cl_2 (100 mL). This solution was washed with 1 N NaOH (3 x 5 mL) then H_2O (5 mL), dried

(Na_2SO_4), filtered, and concentrated under reduced pressure to yield the title compound as a white solid (424 mg, 64% yield). TLC (SiO_2, 5% 2 M NH_3 in CH_3OH/CH_2Cl_2): R_f = 0.17. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_4$, 368.17; m/z found, 369.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.53-7.50 (m, 1H), 7.44-7.42 (m, 1H), 7.34-7.21 (m, 4H), 7.00-6.96 (m, 2H), 4.13 (t, *J* = 6.0, 2H,), 3.55-3.48 (m, 2H), 3.02-3.09 (m, 2H), 2.82 (t, *J* = 6.0, 2H), 2.13 (dt, *J* = 2.4, 11.8, 2H), 1.78-1.75 (m, 2H), 1.59-1.48 (m, 2H), 1.33 (dq, *J* = 3.7, 12.4, 2H).

EXAMPLE 14



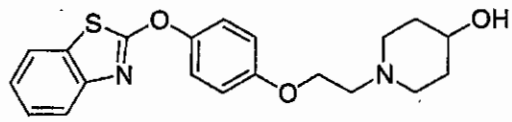
1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-ol.

A. 1-[2-(4-Hydroxy-phenoxy)-ethyl]-piperidin-4-ol. To a stirring solution of 4-(2-bromo-ethoxy)-phenol (EXAMPLE 3; 9 g, 42 mmol) in CH_3CN (150 mL) was added 4-hydroxypiperidine (5.3 g, 52.5 mmol), followed by *N,N*-diisopropylethylamine (6.7 g, 52.5 mmol). The resulting solution was stirred overnight at room temperature, yielding a suspension. The suspension was filtered, and the filtrate was concentrated under reduced pressure. Diethyl ether was added to the resultant oil, and the mixture was warmed to 45 °C for 2 min, forming a white precipitate. This suspension was stirred at room temperature for 2 h, then filtered, giving 7.9 g (33 mmol, 79% yield) of an off-white solid. MS (ESI): mass calculated for $C_{13}H_{19}NO_3$, 237.14; m/z found, 238.2 $[M+H]^{+1}$. ^1H NMR (400 MHz, CD_3OD): 7.10 and 7.02 (q, *J* = 32.3, 9.0, 2H), 4.35 (t, *J* = 5.7, 2H), 3.59 (m, 1H), 3.26-3.19 (m, 2H), 3.07 (t, *J* = 5.7, 2H), 2.60 (t, *J* = 9.9, 2H), 2.20-2.12 (m, 2H), 1.94-1.82 (m, 2H).

B. 1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-ol. To a stirring solution of 1-[2-(4-hydroxy-phenoxy)-ethyl]-piperidin-4-ol (500 mg, 2.1 mmol) in acetone (10 mL) was added Cs_2CO_3 (1.4 g, 4.41 mmol). This suspension was cooled to 0 °C, and 2-chloro-benzooxazole (388 mg, 2.5 mmol, 0.29 mL) was added dropwise. The reaction mixture was allowed to warm to room

temperature overnight, and was then filtered, and concentrated under reduced pressure. The resultant oil was purified on SiO_2 (40 g; 0–100% acetone/CH_2Cl_2) to give 400 mg (1.1 mmol, 54% yield) of a white solid. MS (ESI): mass calculated for $C_{20}H_{22}N_2O_4$, 354.16; m/z found, 355.2 $[M+H]^{+1}$. ^1H NMR: (400 MHz, $CDCl_3$) 7.55 (dd, J = 7.2, 1.8, 1H), 7.46 (dd, J = 7.3, 2.0, 1H), 7.36 (d, J = 9.1, 2H), 7.32-7.25 (m, 2H), 7.01 (d, J = 9.1, 2H), 4.18 (t, J = 5.4, 2H), 3.80 (m, 1H), 3.01-2.86 (m, 4H), 2.40 (br s, 1H), 1.99 (m, 2H), 1.74-1.65 (m, 2H), 1.48 (d, J = 4.1, 1H).

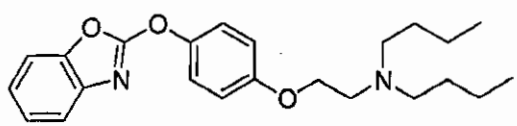
EXAMPLE 15



1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-ol.

To a stirring solution of 1-[2-(4-hydroxy-phenoxy)-ethyl]-piperidin-4-ol (EXAMPLE 14, step A; 500 mg, 1.25 mmol) in DMF (10 mL), was added Cs_2CO_3 (1.4 g, 4.41 mmol) and 2-chlorobenzothiazole (0.33 mL, 2.5 mmol). The suspension was heated to 80 °C and stirred overnight. The reaction mixture was allowed to cool to room temperature and then filtered through diatomaceous earth. The filtrate was concentrated under reduced pressure, and the residue was purified on SiO_2 (40 g; 0–100% acetone/CH_2Cl_2), giving 321 mg (0.86 mmol, 69% yield) of a tan solid. MS (ESI): mass calculated for $C_{20}H_{22}N_2O_3S$, 370.14; m/z found, 371.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.64 (d, J = 8.0, 1H), 7.56 (d, J = 7.8, 1H), 7.30 (t, J = 7.2, 1H), 7.21-7.14 (m, 3H), 6.87 (d, J = 9.1, 2H), 4.05 (t, J = 5.8, 2H), 3.67 (br s, 1H), 2.82 (m, 2H), 2.76 (t, J = 5.8, 2H), 2.27 (t, J = 9.5, 2H), 2.01 (br s, 1H), 1.90-1.82 (m, 2H), 1.64-1.52 (m, 2H).

EXAMPLE 16

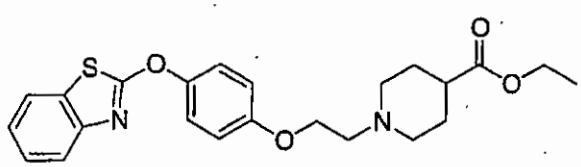


{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-dibutyl-amine.

A. 4-(2-Dibutylamino-ethoxy)-phenol. To a stirring solution of 4-(2-bromo-ethoxy)-phenol (EXAMPLE 3; 8.2 g, 37 mmol) in CH_3CN (150 mL), was added dibutylamine (5.98 g, 46.3 mmol) and *N,N*-diisopropylethylamine (5.98 g, 46.3 mmol). The mixture was stirred overnight at 75 °C. The resulting suspension was filtered, and the filtrate was concentrated under reduced pressure. The resultant oil was purified on SiO_2 (110 g; 0–100% acetone/CH_2Cl_2) to give 7.7 g (29 mmol, 78% yield) of a brown solid. MS (ESI): mass calculated for $C_{16}H_{27}NO_2$, 265.2; m/z found, 266.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 6.81 (d, J = 7.0, 2H), 6.63 (d, J = 6.0, 2H), 4.22 (br s, 2H), 3.25 (br s, 2H), 2.93 (br s, 4H), 2.16 (br s, 2H), 1.88 (br s, 1H), 1.68 (br s, 4H), 1.33 (d, J = 5.7, 4H), 0.94 (br s, 6H).

B. {2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-dibutyl-amine. To a stirring solution of 4-(2-dibutylamino-ethoxy)-phenol (500 mg, 1.9 mmol) in acetone (9.4 mL) was added Cs_2CO_3 (1.3 g, 3.9 mmol). This suspension was cooled to 0 °C, and 2-chloro-benzooxazole (346 mg, 2.2 mmol, 0.26 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature overnight, then was filtered. The filtrate was concentrated under reduced pressure. The resultant oil was dissolved in CH_2Cl_2 and purified on SiO_2 (40 g; 0–100% acetone/CH_2Cl_2) to give 180 mg (0.47 mmol, 25% yield) of a white solid. MS (ESI): mass calculated for $C_{23}H_{30}N_2O_3$, 382.23; m/z found, 383.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.50 (d, J = 7.2, 2H), 7.41 (d, J = 7.3, 2H), 7.31 (d, J = 9.1, 2H), 7.28-7.19 (m, 2H), 6.96 (d, J = 9.1, 2H), 4.13 (m, 2H), 2.88 (m, 2H), 2.54 (m, 4H), 1.47 (m, 4H), 1.32 (m, 4H), 0.92 (t, J = 7.3, 6H).

EXAMPLE 17

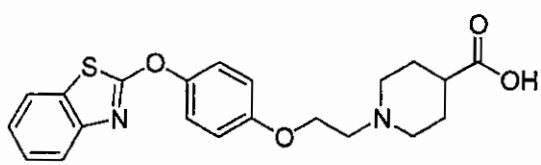


1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carboxylic acid ethyl ester.

A. 1-[2-(4-Hydroxy-phenoxy)-ethyl]-piperidine-4-carboxylic acid ethyl ester. To a stirring solution of 4-(2-bromo-ethoxy)-phenol (EXAMPLE 3; 5 g, 23.1 mmol) in CH_3CN (200 mL) was added ethyl isonipecotate (5.3 mL, 34.7 mmol). The reaction mixture was heated to 84 °C and stirred for 16 h, then cooled to room temperature and concentrated under reduced pressure. The resultant oil was dissolved in CH_2Cl_2 and purified on SiO_2 (300 g; 0–25% acetone/CH_2Cl_2) to give a white solid (6.3 g, 93% yield). MS (ESI): mass calculated for $C_{16}H_{23}NO_4$, 293.16; m/z found, 294.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 6.63 (m, 4H), 4.07 (q, J = 7.2, 2H), 3.96 (t, J = 5.7, 2H), 2.96 (m, 2H), 2.74 (t, J = 5.6, 2H), 2.26-2.23 (m, 3H), 1.88-1.77 (m, 5H), 1.17 (t, J = 7.2, 3H).

B. 1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carboxylic acid ethyl ester. To a stirring solution of 1-[2-(4-hydroxy-phenoxy)-ethyl]-piperidine-4-carboxylic acid ethyl ester (2.5 g, 6.8 mmol) in CH_3CN (34 mL) was added Cs_2CO_3 (5 g, 14.3 mmol) and 2-chlorobenzothiazole (1.26 mL, 10.2 mmol). The reaction mixture was heated to 75 °C for 3 h, then cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and purified on SiO_2 (40 g; 0–25% acetone/CH_2Cl_2) to give a white solid (2.94 g, 100% yield). MS (ESI): mass calculated for $C_{23}H_{26}N_2O_4S$, 426.16; m/z found, 427.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.76 (d, J = 8.0, 1H), 7.64 (t, J = 8.1, 1H), 7.41 (t, J = 8.4, 1H), 7.30 (d, J = 9.0, 3H), 7.05 (d, J = 6.8, 2H), 4.19 (t, J = 5.5, 2H), 4.12 (q, J = 7.1, 2H), 3.02 (m, 2H), 2.83 (t, J = 5.5, 2H), 2.37 (m, 1H), 2.25 (t, J = 11.6, 2H), 1.93 (m, 2H), 1.79 (m, 2H), 1.24 (t, J = 7.2, 3H).

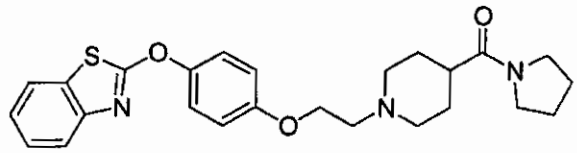
EXAMPLE 18



1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carboxylic acid potassium salt.

To a stirring solution of 1-{2-[4-(benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carboxylic acid ethyl ester (EXAMPLE 17; 235 mg, 0.5 mmol) in THF (2.5 mL) was added potassium trimethylsilanoate (282 mg, 2.2 mmol). The reaction mixture was stirred at room temperature for 2 h, then concentrated under reduced pressure. The resultant oil was dissolved in H_2O, and the solution was treated to pH 9 with 1 M HCl. The resulting solution was extracted with 1:3 isopropyl alcohol/chloroform (3 x 25 mL). The combined extracts were concentrated under reduced pressure to yield a tan solid that was triturated with diethyl ether. Filtration of the suspension afforded a tan solid (140 mg, 64% yield). MS (ESI): mass calculated for $C_{21}H_{22}N_2O_4S$.(free acid), 398.13; m/z found, 399.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.01 (d, J = 7.3, 1H), 7.76 (d, J = 7.5, 1H), 7.51 (t, J = 8.4, 1H), 7.45 (d, J = 9.0, 2H), 7.40 (t, J = 7.2, 1H), 7.14 (d, J = 9.0, 2H), 4.18 (t, J = 5.5, 2H), 2.95 (m, 2H), 2.74 (t, J = 5.8, 2H), 2.10 (t, J = 10.5, 2H), 1.81 (m, 2H), 1.59 (m, 2H).

Example 19

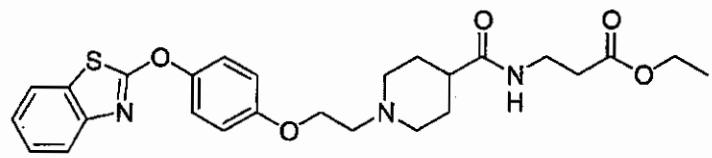


(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-pyrrolidin-1-yl-methanone.

To a suspension of 1-{2-[4-(benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carboxylic acid (EXAMPLE 18; 100 mg, 0.25 mmol) in $CHCl_3$ (2 mL) was added oxalyl chloride (132 µL, 1.5 mmol). The reaction mixture was stirred at room temperature for 2 h, and then concentrated under reduced pressure. The resultant solid was re-suspended in $CHCl_3$ (2 mL), and pyrrolidine was added (100 µL, 1.2 mmol). The solution that formed was stirred for 1 h and then was diluted with CH_2Cl_2 (10 mL) and washed with sat. aq. $NaHCO_3$ (10 mL). The

organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to a yellow oil. The crude oil was purified on SiO_2 (10 g; 0–100% acetone/CH_2Cl_2) to provide the desired product as a colorless oil (71 mg, 63% yield). MS (ESI): mass calculated for $C_{25}H_{29}N_3O_3S$, 451.19; m/z found, 452.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 7.6, 1H), 7.66 (dd, J = 8.0, 0.8, 1H), 7.41-7.37 (m, 1H), 7.29-7.24 (m, 3H), 6.99-6.96 (m, 2H), 4.13 (t, J = 6.0, 2H), 3.50-3.45 (m, 4H), 3.10-3.04 (m, 2H), 2.83 (t, J = 6.0, 2H), 2.38-2.31 (m, 1H), 2.21-2.14 (m, 2H), 1.98-1.84 (m, 6H), 1.74-1.71 (m, 2H).

Example 20

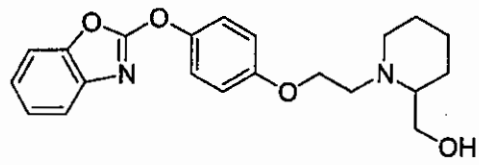


3-[(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carbonyl)-amino]-propionic acid ethyl ester.

1-Hydroxybenzotriazole hydrate (HOBT; 1.0 mL, 0.5 M in DMF, 0.5 mmol), 3-amino-propionic acid ethyl ester (120 mg, 0.785 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI; 150 m, 0.785 mmol) were added in succession at 5 min intervals to a stirred suspension of 1-{2-[4-(benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carboxylic acid (EXAMPLE 18; 210 mg, 0.53 mmol) in CH_2Cl_2 (3 mL). The resulting mixture was stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with sat. aq. $NaHCO_3$ (10 mL) then H_2O (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield an off-white semi-solid. The crude residue was purified on SiO_2 (35 g; 0–5% 2 M NH_3 in CH_3OH/CH_2Cl_2) to provide the desired product as a white solid (186 mg, 48% yield). MS (ESI): mass calculated for $C_{26}H_{31}N_3O_5S$, 497.20; m/z found, 498.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (dd, J = 8.1, 0.6, 1H), 7.66 (dd, J = 8.1, 0.8, 1H), 7.39 (dt, J = 7.4, 1.3, 1H), 7.29-7.24 (m, 3H), 7.01-6.94 (m, 2H), 6.18-6.15 (m, 1H), 4.19-4.11 (m,

4H), 3.53 (q, J = 6.0, 2H), 3.06-3.04 (m, 2H), 2.81 (t, J = 5.9, 2H), 2.53 (t, J = 6.0, 2H), 2.18-2.06 (m, 3H), 1.88-1.72 (m, 4H), 1.28 (t, J = 7.2, 3H).

EXAMPLE 21



(1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidin-2-yl)-methanol.

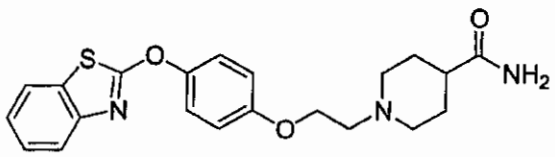
A. {1-[2-(4-Benzyloxy-phenoxy)-ethyl]-piperidin-2-yl}-methanol. To a stirred solution of 2-(4-benzyloxy-phenoxy)-ethyl bromide (EXAMPLE 1; 7.0 g mg, 22.8 mmol) and piperidin-2-yl-methanol (3.3 g, 28.7 mmol) in CH_3CN (100 mL) was added K_2CO_3 (7.1 g, 51.4 mmol). The mixture was heated at reflux for 20 h and then filtered. The filtrate was concentrated under reduced pressure to a clear golden oil, which was purified on SiO_2 (120 g; 0-100% acetone/CH_2Cl_2) to give 6.0 g (77% yield) of a white solid. TLC (SiO_2, acetone): R_f = 0.15. MS (ESI): mass calculated for $C_{21}H_{27}NO_3$, 341.20; m/z found, 342.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.48-7.25 (m, 5H), 6.92 (d, J = 9.1, 2H), 6.85 (d, J = 9.1, 2H), 5.02 (s, 2H), 4.38 (t, J = 5.3, 2H), 3.96 (t, J = 6.2, 2H), 3.55-3.48 (m, 1H), 3.43-3.32 (m, 1H), 3.15-3.00 (m, 1H), 2.88-2.85 (m, 1H), 2.75-2.62 (m, 1H), 2.30-2.22 (m, 2H), 1.61 (d, J = 9.4, 2H), 1.52-1.44 (m, 1H), 1.44-1.31 (m, 1H), 1.30-1.17 (m, 2H).

B. 4-[2-(2-Hydroxymethyl-piperidin-1-yl)-ethoxy]-phenol. To a solution of {1-[2-(4-benzyloxy-phenoxy)-ethyl]-piperidin-2-yl}-methanol (6.0 g, 17.6 mmol) in 1:1 ethanol/ethyl acetate (75 mL) was added Pd on carbon (10 wt %, 614 mg). The mixture was placed on a Parr hydrogenator at 40 psi of H_2 for 20 h. The reaction mixture was filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure to give 4.5 g (100% yield) of the desired product as a clear and colorless oil. TLC (SiO_2, acetone): R_f = 0.29. MS (ESI): mass calculated for $C_{14}H_{21}NO_3$, 251.15; m/z found, 252.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 6.77 (d, J = 6.6, 2H), 6.68 (d, J = 6.6, 2H), 4.06-4.01

(m, 2H), 3.70-3.55 (m, 2H), 3.22-3.10 (m, 1H), 3.05-2.96 (m, 1H), 2.88-2.79 (m, 1H), 2.47-2.36 (m, 2H), 1.76-1.70 (m, 2H), 1.63-1.32 (m, 4H).

C. (1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidin-2-yl)-methanol. A mixture of 4-[2-(2-hydroxymethyl-piperidin-1-yl)-ethoxy]-phenol (197 mg, 0.78 mmol), 2-chloro-benzooxazole (116 μL, 1.02 mmol) and Cs_2CO_3 (700 mg, 2.15 mmol) in acetone (10 mL) was stirred at room temperature for 20 h. The resulting mixture was filtered through diatomaceous earth. The pad was washed with acetone, and the combined filtrates were concentrated under reduced pressure to a golden oil. The oil was purified on SiO_2 (10 g; 0-100% acetone/CH_2Cl_2) to give the desired product as a clear and colorless oil (202 mg, 70%). TLC (SiO_2, acetone): R_f = 0.17. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_3S$, 384.15; m/z found, 369.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.61 (d, J = 7.0, 2H), 7.50 (d, J = 7.0, 2H), 7.41 (d, J = 9.1, 4H), 7.35-7.30 (m, 4H), 7.03 (d, J = 9.1, 4H,), 4.41 (t, J = 5.3, 2H), 4.07 (t, J = 6.2, 4H), 3.60-3.52 (m, 2H), 3.44-3.35 (m, 2H), 3.18-3.08 (m, 2H), 2.90-2.85 (m, 2H), 2.78-2.72 (m, 2H), 2.35-2.28 (m, 4H), 1.62 (d, J = 9.2, 4H), 1.53-1.47 (m, 2H), 1.47-1.34 (m, 2H), 1.32-1.18 (m, 4H).

EXAMPLE 22

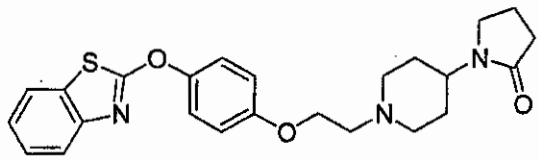


1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carboxylic acid amide.

A suspension of 2-[4-(2-bromo-ethoxy)-phenoxy]-benzothiazole (EXAMPLE 9; 200 mg, 0.57 mmol), isonipecotamide (73 mg, 0.57 mmol) and Silicycle® dimethylamine resin (800 mg, 1.14 mmol) in CH_3CN was heated to 70 °C for 18 h. The reaction mixture was filtered, and the collected resin was rinsed with CH_3CN. The combined filtrates were concentrated under reduced pressure yielding a crude solid, which was purified on SiO_2 (10 g; 0–100% 10% [2 M NH_3 in CH_3OH] in CH_2Cl_2/CH_2Cl_2) to provide 142 mg (63% yield) of a white

solid. MS (ESI): mass calculated for $C_{21}H_{23}N_3O_3S$, 397.15; m/z found, 398.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.85 (dd, J=8.0, 0.3, 1H), 7.75 (dd, J =8.0, 0.6, 1H), 7.42 (dd, J =7.4, 1.1, 1H), 7.32-7.22 (m, 3H), 7.02-6.91 (m, 2H), 5.67 (br d, J =47, 2H), 4.15 (t, J = 5.8, 2H), 3.09 (br d, J =8.8, 2H), 2.85 (t, J =5.7, 2H), 2.28-2.12 (m, 3H), 2.00-1.88 (m, 2H), 1.87-1.72 (m, 2H).

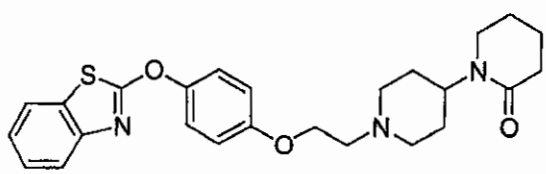
EXAMPLE 23



1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-pyrrolidin-2-one

A suspension of 2-[4-(2-bromo-ethoxy)-phenoxy]-benzothiazole (EXAMPLE 9; 200 mg, 0.57 mmol), 1-piperidin-4-yl-pyrrolidin-2-one hydrochloride (117 mg, 0.57 mmol), and Silicycle® dimethylamine resin (800 mg, 1.14 mmol) in CH_3CN was heated to 70 °C for 18 h. The reaction mixture was filtered, and the collected resin was rinsed with CH_3CN. The combined filtrates were concentrated under reduced pressure yielding a crude solid, which was purified on SiO_2 (10 g; 0–100% 10% [2 M NH_3 in CH_3OH] in CH_2Cl_2/CH_2Cl_2) to provide a tacky off-white solid (142 mg, 63% yield). MS (ESI): mass calculated for $C_{24}H_{27}N_3O_3S$, 337.18; m/z found, 348.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.85 (dd, J = 8.0, 0.5, 1H), 7.75 (dd, J = 8.0, 0.8, 1H), 7.41 (dt, J = 7.3, 1.5, 1H), 7.34-7.22 (m, 3H), 7.02-6.92 (m, 2H), 4.15 (br d, J = 48.8, 2H), 3.80-3.65 (m, 1H), 3.40 (t, J = 7.0, 1H), 3.30-3.10 (br s, 1H), 3.15, (q, J = 7.2, 1H), 2.96 (br s, 1H), 2.42, (t, J = 7.9, 2H), 2.10-1.99 (m, 1H), 1.81-1.70 (m, 1H) 1.68-1.52 (m, 4H), 1.50 (d, J = 6.5, 3H).

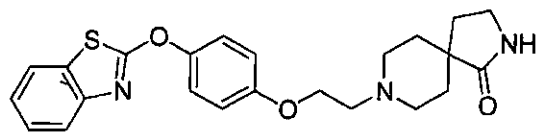
EXAMPLE 24



1'-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-[1,4']bipiperidinyl-2-one.

To a stirred solution of 2-[4-(2-bromo-ethoxy)-phenoxy]-benzothiazole (EXAMPLE 9; 542 mg, 1.55 mmol) and [1,4']bipiperidinyl-2-one hydrochloride (371 mg, 1.69 mmol) in CH_3CN (20 mL) was added K_2CO_3 (517 mg, 3.74 mmol). The mixture was heated at reflux for 20 h and then was filtered. The filtrate was concentrated under reduced pressure to a clear golden oil, which was purified on SiO_2 (10 g; 0-100% acetone/CH_2Cl_2) to give 294 mg (42% yield) of a white solid. TLC (SiO_2, acetone): R_f = 0.15. MS (ESI): mass calculated for $C_{25}H_{29}N_3O_3S$, 451.19; m/z found, 452.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.92 (d, J = 1.1, 2H), 7.90 (d, J = 1.1, 2H), 7.42 (t, J = 7.3, 2H), 7.37 (d, J = 9.0, 2H), 7.31 (t, J = 7.3 2H), 7.06 (d, J = 9.0, 2H), 4.32-4.21 (m, 1H), 4.10 (t, J = 5.7, 2H), 3.15 (t., J = 5.3, 2H), 3.00 (d, J = 11.5, 2H), 2.71 (t, J = 5.7, 2H), 2.21 (t, J = 6.5, 2H), 2.10 (t, J = 11.4, 2H), 1.75-1.58 (m, 6H), 1.43 (d, J = 10.0, 2H).

EXAMPLE 25

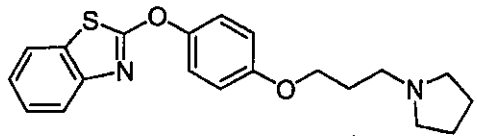


8-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-2,8-diaza-spiro[4.5]decan-1-one.

A suspension of 2-[4-(2-bromo-ethoxy)-phenoxy]-benzothiazole (EXAMPLE 9; 257 mg, 0.73 mmol), 2,8-diaza-spiro[4.5]decan-1-one hydrochloride (153 mg, 0.80 mmol) and Silicycle® dimethylamine resin (1.7 g, 2.4 mmol) in CH_3CN was heated to 80 °C for 18 h. The reaction mixture was filtered, and the collected resin was rinsed with CH_3CN. The combined filtrates were concentrated under reduced pressure to a crude solid, which was purified on SiO_2 (10 g; 0–100% 10% [2 M NH_3 in CH_3OH] in CH_2Cl_2/CH_2Cl_2) to provide an off-white solid (152 mg, 49% yield). MS (ESI): mass calculated for $C_{23}H_{25}N_3O_3S$, 423.16; m/z found, 424.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.78 (dd, J = 8.1, 0.6, 1H), 7.69 (dd, J = 8.0, 0.8, 1H), 7.41 (dt, J = 7.5, 1.3, 1H), 7.32-7.27 (m, 3H), 7.00

(m, 2H), 6.36 (br s, 1H), 4.15 (t, J = 5.9, 2H), 3.36 (t, J = 7.0, 2H), 3.00, (dt, J = 11.9, 3.9, 2H), 2.87 (t, J = 5.8, 2H), 2.32 (dt, J = 11.5, 2.4, 2H), 2.10-1.98 (m, 2H), 2.07 (t, J = 7.0, 2H), 1.50 (br d, J = 13.3, 2H).

EXAMPLE 26



2-[4-(3-Pyrrolidin-1-yl-propoxy)-phenoxy]-benzothiazole.

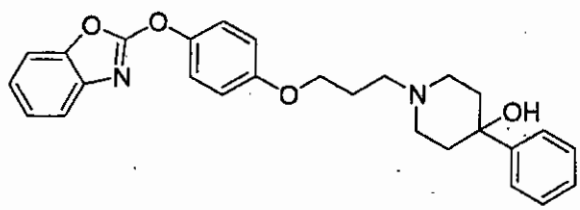
A. 1-[3-(4-Benzyloxy-phenoxy)-propyl]-pyrrolidine. To a mixture of 1-[3-(4-benzyloxy-phenoxy)-propyl]-bromide (EXAMPLE 2; 1.50 g, 4.7 mmol) was added pyrrolidine (2.0 mL, 24.0 mmol) in CH_3CN. The mixture was stirred for 20 h then concentrated under reduced pressure to give a yellow oil, which was purified on SiO_2 (35 g; acetone) to give 1.2 g (80% yield) of the desired product as a white solid. TLC (SiO_2, acetone): R_f = 0.05. MS (ESI): mass calculated for $C_{20}H_{25}NO_2$, 311.19; m/z found, 312.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.50-7.30 (m, 5H), 6.90 (d, J = 9.1, 2H), 6.82 (d, J = 9.1, 2H), 5.02 (s, 2H), 4.00 (t, J = 6.1, 2H), 3.0-2.75 (m, 6H), 2.15 (d, J = 6.2, 2H), 1.94 (br s, 4H).

B. 4-(3-Pyrrolidin-1-yl-propoxy)-phenol. To a solution of 1-[3-(4-benzyloxy-phenoxy)-propyl]-pyrrolidine (1.2 g, 3.9 mmol) in 1:1 ethanol/ethyl acetate (65 mL) was added Pd on carbon (10 wt %, 206 mg). The mixture was placed on a Parr hydrogenator at 40 psi of H_2 for 20 h. The resultant mixture was filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure to give 875 mg (100% yield) of the desired product as a brown solid. MS (ESI): mass calculated for $C_{13}H_{19}NO_2$, 221.14; m/z found, 222.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.90 (s, 1H), 6.74 (d, J = 9.0, 2H), 6.65 (d, J = 9.0, 2H), 3.90 (t, J = 6.3, 2H), 2.72 (br s, 6H), 1.90 (quint, J = 7.4, 2H), 1.76 (s, 4H).

C. 2-[4-(3-Pyrrolidin-1-yl-propoxy)-phenoxy]-benzothiazole. To a stirred solution of 4-(3-pyrrolidin-1-yl-propoxy)-phenol (100 mg, 0.45 mmol) in acetone (5 mL) containing Cs_2CO_3 (213 mg, 0.65 mmol) was added

2-chlorobenzthiazole (65 μL, 0.50 mmol). The mixture was heated at reflux for 24 h and then filtered. The filtrate was concentrated under reduced pressure to give a clear golden oil, which was purified on SiO_2 (10 g; acetone) to give 97 mg (61% yield) of the desired product. TLC (SiO_2, acetone): R_f = 0.02. MS (ESI): mass calculated for $C_{20}H_{22}N_2O_2S$, 354.14; m/z found, 355.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.73 (d, 1H), 6.95 (d, 1H), 7.39 (m, 1H), 7.26 (m, 3H), 6.96 (d, J = 9.1, 2H), 4.06 (t, J = 6.4, 2H), 2.65 (t, J = 7.3, 2H), 2.55 (br s, 4H), 2.04 (quint, J = 6.5, 2H), 1.82 (br s, 4H).

EXAMPLE 27



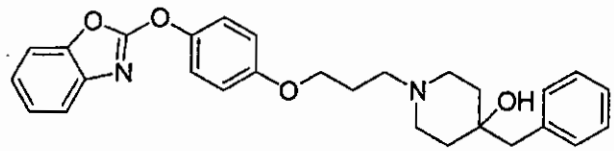
1-{3-[4-(Benzooxazol-2-yloxy)-phenoxy]-propyl}-4-phenyl-piperidin-4-ol.

A. 1-[3-(4-Hydroxy-phenoxy)-propyl]-4-phenyl-piperidin-4-ol hydrogen bromide. 4-(3-Bromo-propoxy)-phenol (EXAMPLE 4; 3 g, 13 mmol) was dissolved in CH_3CN (65 mL). To this solution was added 4-hydroxy-4-phenylpiperidine (6.8 g, 39 mmol), and the mixture was stirred at room temperature overnight, yielding a white precipitate. The suspension was filtered to give the title compound as a white solid (5 g, 11.9 mmol, 91% yield). MS (ESI): mass calculated for $C_{20}H_{25}NO_3$ (free base), 327.18; m/z found, 328.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.49 (d, J = 7.5, 2H), 7.32 (t, J = 7.5, 2H), 7.21 (t, J =7.2, 1H), 6.73 (q, J = 12.3, 4H), 3.96 (t, J = 6.1, 2H), 2.85 (d, J = 11.3, 2H), 2.64-2.54 (m, 4H), 2.13 (dt, J = 9.0, 3.9, 2H), 2.00 (m, 2H), 1.75 (d, J = 12.2, 2H).

B. 1-{3-[4-(Benzooxazol-2-yloxy)-phenoxy]-propyl}-4-phenyl-piperidin-4-ol. To a stirring solution of 1-[3-(4-hydroxy-phenoxy)-propyl]-4-phenyl-piperidin-4-ol hydrogen bromide (500 mg, 1.5 mmol) in acetone (7 mL) was added Cs_2CO_3 (1.03 g, 3.15 mmol). This suspension was cooled to 0 °C, and 2-chloro-benzooxazole (276 mg, 1.8 mmol, 0.2 mL) was added dropwise. The reaction

mixture was allowed to warm to room temperature overnight, then filtered and concentrated under reduced pressure. The resultant oil was dissolved in CH_2Cl_2 and purified on SiO_2 (40 g; 0–100% acetone/CH_2Cl_2) to give 450 mg (1.05 mmol, 70% yield) of a white solid. MS (ESI): mass calculated for $C_{26}H_{26}N_2O_4$, 444.20; m/z found, 445.20 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.47-7.43 (m, 3H), 7.36-7.11 (m, 8H), 6.90 (d, J = 9.1, 2H), 3.99 (t, J = 5.8, 2H), 2.80 (d, J = 9.5, 2H), 2.56 (t, J = 6.8 Hz, 2H), 2.44 (t, J = 10.9, 2H), 2.13 (t, J = 11.0, 2H), 1.98 (m, J = 6.8, 2H), 1.71 (d, J = 6.9, 2H).

EXAMPLE 28



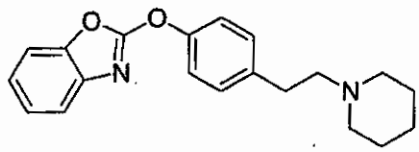
1-{3-[4-(Benzooxazol-2-yloxy)-phenoxy]-propyl}-4-benzyl-piperidin-4-ol.

A. 4-Benzyl-1-[3-(4-hydroxy-phenoxy)-propyl]-piperidin-4-ol. 4-Benzyl-4-hydroxy-piperidine (750 mg, 3.9 mmol) was added to a solution of 4-(3-bromo-propoxy)-phenol (EXAMPLE 4; 300 mg, 1.31 mmol) in CH_3CN (6 mL). The reaction mixture was stirred at room temperature overnight, yielding a white precipitate. The suspension was filtered, and the filtrate was concentrated under reduced pressure. The resultant oil was purified on SiO_2 (10 g; 0–100% acetone/CH_2Cl_2) to give 110 mg (0.32 mmol, 25% yield) of a white solid. MS (ESI): mass calculated for $C_{21}H_{22}NO_3$, 341.20; m/z found, 342.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.36-7.24 (m, 3H), 7.22 (d, J = 6.9, 2H), 6.7 (m, 4H), 4.07 (t, J = 6.5, 2H), 3.41 (d, J = 11.7, 2H), 3.19 (t, J = 7.8, 2H), 3.11 (t, J = 11.8, 4H), 2.84 (br s, 2H), 2.34 (br s, 4H), 2.18 (br s, 1H), 1.72 (d, 14.5, 2H).

B. 1-{3-[4-(Benzooxazol-2-yloxy)-phenoxy]-propyl}-4-benzyl-piperidin-4-ol. To a stirring solution of 4-benzyl-1-[3-(4-hydroxy-phenoxy)-propyl]-piperidin-4-ol (2.5 g, 7.3 mmol) in acetone (37 mL) was added Cs_2CO_3 (4.99 g, 15.3 mmol). This suspension was cooled to 0 °C, and 2-chloro-benzooxazole (1.1 mL, 9.5 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature overnight, was filtered and then was concentrated under

reduced pressure. The resultant oil was dissolved in CH_2Cl_2 and purified on SiO_2 (110 g; 0–100% acetone/CH_2Cl_2) to give 310 mg (0.67 mmol, 9% yield) of a white solid. MS (ESI): mass calculated for $C_{28}H_{30}N_2O_4$, 458.2; m/z found, 459.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.49 (d, J = 7.2, 1H), 7.41 (d, J = 7.2, 1H), 7.35-7.18 (m, 9H), 6.94 (d, J = 9.1, 2H), 4.04 (t, J = 6.5, 2H), 2.93-2.45 (m, 7H), 2.16 (s, 4H), 1.60 (d, J = 13.0, 2H), 1.29 (br s, 1H).

EXAMPLE 29



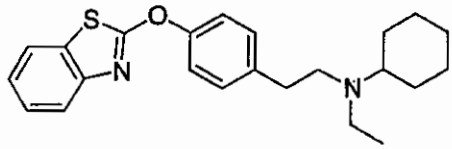
2-[4-(2-Piperidin-1-yl-ethyl)-phenoxy]-benzooxazole.

A. 4-(2-Piperidin-1-yl-ethyl)-phenol. A solution of 4-(2-bromo-ethyl)-phenol (EXAMPLE 5; 4.5 g, 22.4 mmol), piperidine (3.3 mL, 33.5 mmol), and *N,N*-diisopropylethylamine (5.8 mL, 33.5 mmol) in CH_3CN (100 mL) was stirred at 60 °C for 18 h. The resulting solution was cooled to room temperature and concentrated under reduced pressure to yield a pale orange solid. Diethyl ether (100 mL) was added, and the title compound was collected by filtration as an off-white solid (4.6 g, 100% crude yield). TLC (SiO_2, 5% 2 M NH_3 in CH_3OH/CH_2Cl_2): R_f = 0.19. MS (ESI): mass calculated for $C_{13}H_{19}NO_2$, 205.15; m/z found, 206.1 $M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.07-7.04 (m 2H), 6.74-6.71 (m, 2H), 3.32-3.30 (m, 2H), 3.14-3.11 (m, 3H), 2.87-2.80 (m, 1H), 1.82-1.67 (m, 6H), 1.65-1.55 (m, 2H).

B. 2-[4-(2-Piperidin-1-yl-ethyl)-phenoxy]-benzooxazole. A mixture of 4-(2-piperidin-1-yl-ethyl)-phenol (0.5 g, 2.43 mmol), 2-chloro-benzooxazole (304 μL, 2.67 mmol) and Cs_2CO_3 (1.8 g, 5.62 mmol) in acetone (10 mL) was stirred at room temperature for 48 h. The reaction mixture was filtered through diatomaceous earth, and the pad was washed with CH_2Cl_2. The combined filtrates were concentrated under reduced pressure to an orange oil, which was purified on SiO_2 (40 g; 0–100% acetone/CH_2Cl_2) to give the desired product as white solid (325 mg, 42% yield). TLC (SiO_2, 5% 2 M NH_3 in CH_3OH/CH_2Cl_2):

R_f = 0.36. MS (ESI): mass calculated for $C_{20}H_{22}N_2O_2$, 322.17; m/z found, 323.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.53-7.51 (m, 1H), 7.44-7.42 (m, 1H), 7.34-7.20 (m, 6H), 2.87-2.83 (m, 2H), 2.60-2.56 (m, 2H), 2.48 (br s, 2H), 1.66-1.59 (m, 6H), 1.50-1.43 (m, 2H).

EXAMPLE 30



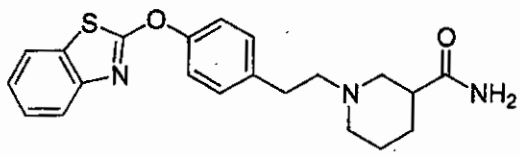
{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclohexyl-ethyl-amine.

A. 4-[2-(Cyclohexyl-ethyl-amino)-ethyl]-phenol. To a stirring solution of 4-(2-bromo-ethyl)-phenol (EXAMPLE 5; 4.48 g, 22.3 mmol) in CH_3CN (100 mL) was added cyclohexyl-ethyl-amine (5.0 mL, 33.4 mmol), followed by *N,N*-diisopropylethylamine (7.76 mL, 44.6 mmol). The resulting solution was stirred at 60 °C for 16 h, yielding a suspension. The suspension was allowed to cool to room temperature and was filtered. The filtered solid was washed with ethyl acetate (2 x 20 mL) and dried to give a white solid (4.8 g, 87% yield). MS (ESI): mass calculated for $C_{16}H_{25}NO$, 247.19; m/z found, 248.2 $[M+H]^+$. ^1H NMR: (400 MHz, $CDCl_3$): 7.01 (d, J = 8.6, 2H), 6.87 (d, J = 8.6, 2H), 3.32-3.17 (m, 2H), 3.15-2.98 (m, 4H), 2.30-2.21 (m, 2H), 1.77-1.59 (m, 2H), 1.57-1.46 (m, 5H), 1.40-1.10 (m, 3H).

B. {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclohexyl-ethyl-amine. To a stirring solution of 1-[2-(4-hydroxy-phenoxy)-ethyl]-piperidin-4-ol (495 mg, 2.0 mmol) in DMF (10 mL), was added Cs_2CO_3 (1.3 g, 4.0 mmol) and 2-chlorobenzothiazole (0.33 mL, 2.5 mmol). The suspension was stirred at 80 °C overnight. The reaction mixture was allowed to cool to room temperature and was then filtered through diatomaceous earth. The filtrate was concentrated under reduced pressure, and the residue was purified on SiO_2 (40 g; 0–100% acetone/CH_2Cl_2) to give 548 mg (72% yield) of a tan solid. MS (ESI): mass calculated for $C_{23}H_{28}N_2OS$, 380.19; m/z found, 381.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.0, 1H), 7.63 (d, J = 8.0, 1H), 7.30 (t, J = 8.0, 1H),

7.29-7.20 (m, 5H), 2.78-2.68 (m, 4H), 2.62 (dd, J = 6.8, 7.4, 2H), 2.56-2.46 (m 1H), 1.83-1.74 (m, 4H), 1.66-1.57 (m, 1H), 1.21 (dd, J = 9.0, 8.6, 4H), 1.15-1.11 (m, 1H), 1.06 (t, J = 7.2, 3H).

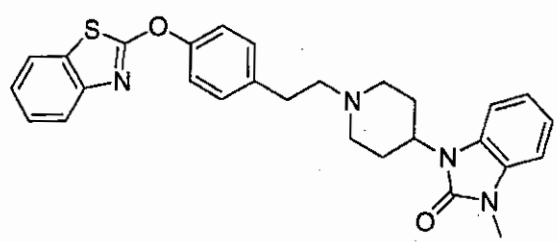
EXAMPLE 31



1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-3-carboxylic acid amide.

A suspension of 2-[4-(2-bromo-ethyl)-phenoxy]-benzothiazole (EXAMPLE 10; 250 mg, 0.75 mmol), nipecotamide (96 mg, 0.75 mmol) and Silicycle® dimethylamine resin (1.1 g, 1.50 mmol) in CH_3CN was heated to 70 °C for 18 h. The reaction mixture was filtered, and the collected resin was washed with CH_3CN. The combined filtrates were concentrated under reduced pressure to a crude solid, which was purified on SiO_2 (10 g; 0–100% 10% [2 M NH_3 in CH_3OH] in CH_2Cl_2/CH_2Cl_2) to provide 135 mg (47% yield) of a white solid. MS (ESI): mass calculated for $C_{21}H_{23}N_3O_2S$, 381.15; m/z found, 382.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.10 (d, J = 8.1, 1H), 7.75 (dd, J = 8.0, 0.8, 1H), 7.42 (dt, J = 7.4, 1.3, 1H), 7.21 (br s, 1H) 6.42 (br s, 1H), 3.05 (br d, J = 10.3, 1H), 2.95-2.80 (m, 3H), 2.80-2.62 (m, 2H), 2.47-2.40 (m, 1H), 2.36 (d, J = 11.5, 1H), 2.08 (t, J = 10.5, 1H), 1.98 (d, J = 11.0, 1H), 1.76-1.63 (m, 1H), 1.63-1.50 (m, 2H).

EXAMPLE 32

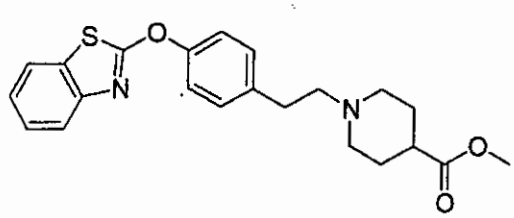


1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one.

A. Toluene-4-sulfonic acid 2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl ester. To a stirring solution of 2-[4-(benzothiazol-2-yloxy)-phenyl]-ethanol (EXAMPLE 10; 12.25 g, 45.2 mmol) in CH_2Cl_2 (225 mL) was added *p*-toluenesulfonyl chloride (17.23 g, 90 mmol) and TEA (31 mL, 225 mmol). The mixture was stirred at room temperature for 72 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (400 mL). The solution was washed with sat. aq. $NaHCO_3$ (3 x 200 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The resultant oil was dissolved in CH_2Cl_2 and purified on SiO_2 (300 g; CH_2Cl_2) to give a tan solid (8.8 g, 45% yield). MS (ESI): mass calculated for $C_{22}H_{19}N_2O_4S_2$, 425.08; m/z found, 426.0 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.70 (q, *J* = 9.7, 4H), 7.39 (t, *J* = 7.8, 1H), 7.32-7.17 (m, 8H), 4.23 (t, *J* = 6.9, 2H), 2.99 (d, *J* = 6.9, 2H), 2.43 (s, 3H).

B. 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one. To a stirring solution of toluene-4-sulfonic acid 2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl ester (400 mg, 0.94 mmol) in CH_3CN (5 mL), was added 1-methyl-3-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (653 mg, 2.82 mmol). The reaction mixture was stirred at room temperature overnight, then concentrated under reduced pressure and purified on SiO_2 (12 g; 50% acetone/CH_2Cl_2) to give a clear oil (16 mg, 3.3% yield). MS (ESI): mass calculated for $C_{28}H_{28}N_4O_2S$, 484.19; m/z found, 485.5 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.75 (d, *J* = 7.9, 1H), 7.65 (d, *J* = 8.1, 1H), 7.41-7.29 (m, 7H), 7.13 (m, 3H), 4.37 (m, 1H), 3.40 (s, 3H), 3.25 (d, *J* = 11.8, 2H), 2.94 (m, 2H), 2.75 (m, 2h), 2.57 (qd, *J* = 12.6, 3.7, 2H), 2.33 (t, *J* = 11.3, 2H), 1.81 (d, *J* = 12.2, 2H).

EXAMPLE 33

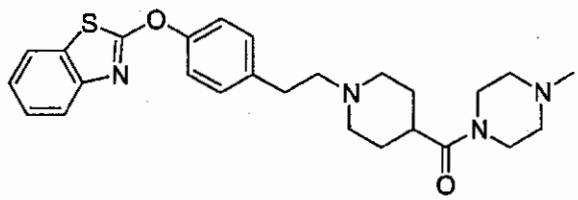


1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid methyl ester.

A. 1-[2-(4-Hydroxy-phenyl)-ethyl]-piperidine-4-carboxylic acid methyl ester. To a stirring solution of 4-(2-bromo-ethyl)-phenol (EXAMPLE 5; 5.05 g, 25 mmol) in CH_3CN (100 mL) was added piperidine-4-carboxylic acid methyl ester (5.07 mL, 37.5 mmol), followed by *N,N*-diisopropylethylamine (8.7 mL, 50 mmol). The reaction mixture was stirred at 60 °C for 16 h, and then allowed to cool to room temperature. CH_2Cl_2 (250 mL) was added, and the resulting solution was washed with H_2O (2 x 30 mL), dried, filtered, and then concentrated under reduced pressure to afford 5.2 g (79%) of a tan solid. MS (ESI): mass calculated for $C_{15}H_{21}NO_3$, 263.15; m/z found, 264.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 6.97 (d, J = 8.2, 2H), 6.70 (d, J = 8.6, 2H), 3.67 (s, 3H), 2.99 (d, J = 11.5, 2H), 2.76-2.68 (m, 2H), 2.60-2.54 (m, 2H), 2.40-2.30 (m, 1H), 2.18 (t, J = 10.8, 2H), 1.99-1.90 (m, 2H), 1.90-1.78 (m, 2H).

B. 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid methyl ester. To a stirring solution of 1-[2-(4-hydroxy-phenyl)-ethyl]-piperidine-4-carboxylic acid methyl ester (790 mg, 3.0 mmol) in DMF (15 mL), was added Cs_2CO_3 (1.95 g, 6.0 mmol) and 2-chlorobenzothiazole (0.47 mL, 3.9 mmol). The suspension was heated to 100 °C and stirred overnight. The reaction mixture was allowed to cool to room temperature and then filtered through diatomaceous earth. The filtrate was concentrated under reduced pressure, and the residue was purified on SiO_2 (40 g; 0–100% acetone/CH_2Cl_2) to give 1.04 g (87% yield) of a tan solid. MS (ESI): mass calculated for $C_{22}H_{24}N_2O_3S$, 396.15; m/z found, 397.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 7.8, 1H), 7.65 (d, J = 7.8, 1H), 7.38 (t, J = 7.6, 1H), 7.28-7.25 (m, 5H), 3.69 (s, 3H), 3.00-2.93 (m, 2H), 2.83 (dd, J = 7.6, 3.0, 2H), 2.61 (dd, J = 7.6, 3.0, 2H), 2.38-2.28 (m 1H), 2.11 (t, J = 10.4, 2H), 1.98-1.89 (m, 2H), 1.87-1.74 (m, 2H).

EXAMPLE 34



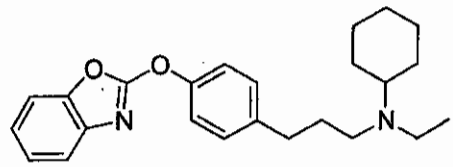
(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-(4-methyl-piperazin-1-yl)-methanone.

A. 1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid trifluoroacetic acid salt. To a solution of 1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid methyl ester (EXAMPLE 33; 4.6 g, 11.7 mmol) in 3:1 THF/CH_3OH (100 mL), was added lithium hydroxide (1.1 g, 46.6 mmol) in H_2O (25 mL). This dark yellow solution was stirred at room temperature for 16 h and then concentrated under reduced pressure. The residue was dissolved in CH_3OH and purified by reversed-phase HPLC to give the title compound as a light yellow solid (3.9 g, 68% yield). MS (ESI): mass calculated for $C_{21}H_{22}N_2O_3S$, 382.14; m/z found, 383.4 $[M+H]^+$.

B. (1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-(4-methyl-piperazin-1-yl)-methanone. To a mixture of 1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid TFA salt (300 mg, 0.6 mmol) in CH_2Cl_2 (15 mL) and a drop of DMF, was added oxalyl chloride (0.11 mL, 1.2 mmol). The mixture was stirred at room temperature for 1 h. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (15 mL), and *N*-methylpiperizine (0.2 mL, 1.8 mmol) was added. This reaction mixture was stirred at room temperature for 1 h, diluted with CH_2Cl_2 (100 mL), washed with H_2O, sat. aq. $NaHCO_3$ then brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified on SiO_2 (40 g; 0–10% 2 M NH_3 in CH_3OH/CH_2Cl_2) to give the title compound (240 mg, 86%). MS (ESI): mass calculated for $C_{26}H_{32}N_2O_3S$, 464.22; m/z found, 465.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.72 (d, J = 7.6, 1H), 7.65 (d, J = 7.6, 1H), 7.37 (t, J = 7.6, 1H), 7.29-7.22 (m, 5H), 3.64 (br s, 2H), 3.51 (br s, 2H), 3.06 (d, J = 11.4, 2H), 2.83 (dd, J =

7.3, 3.5, 2H), 2.60 (dd, *J* = 7.3, 3.5, 2H), 2.51-2.43 (m 1H), 2.42-2.33 (m, 4H), 2.30 (s, 3H), 2.06 (t, *J* = 12.1, 2H), 1.99-1.84 (m, 2H), 1.72 (d, *J* = 13.1, 2H).

EXAMPLE 35



{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-cyclohexyl-ethyl-amine.

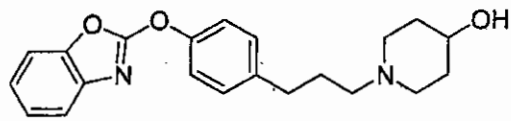
A. [3-(4-Benzyloxy-phenyl)-propyl]-cyclohexyl-ethyl-amine. To a solution of 3-(4-benzyloxy-phenyl)-propyl-1-bromide (504 mg, 1.65 mmol) and *N*-ethylcyclohexylamine (497 μL, 3.30 mmol) in CH_3CN (15 mL) was added K_2CO_3 (510 mg, 3.69 mmol). The reaction mixture was heated at reflux for 20 h. The mixture was filtered and then concentrated under reduced pressure to a golden oil, which was purified on SiO_2 (10 g; 50% acetone/CH_2Cl_2) to give 484 mg (83% yield) of the desired product as a clear and colorless oil. TLC (SiO_2, acetone): R_f = 0.13. MS (ESI): mass calculated for $C_{24}H_{33}NO$, 351.26; m/z found, 352.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.50-7.28 (m, 5H), 7.12 (d, *J* = 8.6, 2H), 6.90 (d, *J* = 8.6, 2H), 5.06 (s, 2H), 2.60-2.45 (m, 7H), 1.78 (br s, 6H), 1.20 (br s, 4H), 1.05 (t, *J* = 7.1, 4H).

B. 4-[3-(Cyclohexyl-ethyl-amino)-propyl]-phenol. To a solution of [3-(4-benzyloxy-phenyl)-propyl]-cyclohexyl-ethyl-amine (420 mg, 1.19 mmol) in 1:1 ethanol/ethyl acetate (16 mL) was added Pd on carbon (10 wt %, 46 mg). The mixture was placed on a Parr hydrogenator at 40 psi of H_2 for 20 h. The resultant mixture was filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure to give 308 mg (99% yield) of the desired product as a golden oil. TLC (SiO_2, acetone): R_f = 0.18. MS (ESI): mass calculated for $C_{17}H_{27}NO$, 261.21; m/z found, 262.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.00 (d, *J* = 8.5, 2H), 6.75 (d, *J* = 8.5, 2H), 2.65 (br s, 5H), 2.54 (t, *J* = 7.6, 2H), 1.82 (br s, 6H), 1.30-1.05 (m, 8H).

C. {3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-cyclohexyl-ethyl-amine. To a mixture of 4-[3-(cyclohexyl-ethyl-amino)-propyl]-phenol (283 mg, 1.08 mmol)

and Cs_2CO_3 (885 mg, 2.72 mmol) in acetone (15 mL) at 5 °C was added 2-chloro-benzooxazole (155 µL, 1.36 mmol). The reaction mixture was allowed to warm slowly to room temperature overnight, then was filtered. The filtrate was concentrated under reduced pressure to give a golden oil, which was purified on SiO_2 (10 g; acetone) to give 333 mg (81% yield) of the desired product as a golden oil. TLC (SiO_2, acetone): R_f = 0.12. MS (ESI): mass calculated for $C_{24}H_{30}N_2O_2$, 378.23; m/z found, 379.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.61 (d, *J* = 7.3, 1H), 7.49 (d, *J* = 7.8, 1H), 7.39 (d, *J* = 8.6, 2H), 7.38-7.25 (m, 4H), 2.62 (t, *J* = 7.5, 2H), 2.65-2.35 (m, 8H), 1.67 (br s, 5H), 1.19-1.10 (m, 4H), 0.95 (t, *J* = 7.1, 3H).

EXAMPLE 36



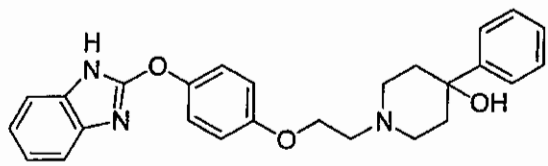
1-{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-piperidin-4-ol.

A. 1-[3-(4-Hydroxy-phenyl)-propyl]-piperidin-4-ol. A solution of 4-(3-bromo-propyl)-phenol (EXAMPLE 6; 1.42 g, 6.6 mmol), 4-hydroxypiperidine hydrochloride (908 mg, 6.6 mmol), and *N,N*-diisopropylethyamine (2.2 mL, 12.3 mmol) in CH_3CN (20 mL) was stirred at 60 °C for 18 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure to yield an off-white solid. This material was dissolved in CH_2Cl_2 (200 mL), and the solution was washed with H_2O (2 x 50 mL), dried (Na_2SO_4), filtered and concentrated under reduce pressure to yield a white solid. Diethyl ether was added, and the title compound was collected by filtration (1.4 g, 90% yield). TLC (SiO_2, 5% 2 M NH_3 in CH_3OH/CH_2Cl_2): R_f = 0.05. MS (ESI): mass calculated for $C_{14}H_{21}NO_2$, 235.16; m/z found, 236.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 6.96-6.94 (m, 2H), 6.64-6.61 (m, 2H), 3.89-3.82 (m, 1H), 3.29-3.20 (m, 4H), 3.02-2.95 (m, 4H), 2.52 (t, *J* = 7.4, 2H), 1.95-1.87 (m, 4H), 1.68-1.60 (m, 2H).

B. 1-{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-piperidin-4-ol. A mixture of 1-[3-(4-hydroxy-phenyl)-propyl]-piperidin-4-ol (0.4 g, 1.69 mmol), 2-chloro-

benzooxazole (176 μL, 1.54 mmol) and Cs_2CO_3 (1.45 g, 4.45 mmol) in acetone (8.0 mL) was stirred at room temperature for 48 h. The resulting mixture was filtered through diatomaceous earth, which was then washed with CH_2Cl_2. The combined filtrates were concentrated under reduced pressure to a yellow oil. The oil was purified on SiO_2 (40 g; 0–100% acetone/CH_2Cl_2) to give a white solid, which was dissolved in CH_2Cl_2. The solution was washed with 1 M NaOH (3 x 5 mL) then H_2O (5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield the title compound as a white solid (98 mg, 16.4% yield). TLC (SiO_2, 5% 2 M NH_3 in CH_3OH/CH_2Cl_2): R_f = 0.14. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_3$, 352.18; m/z found, 363.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.66-7.51 (m, 1H), 7.44-7.42 (m, 1H), 7.34-7.21 (m, 6H), 3.72-3.69 (m, 1H), 2.79-2.76 (m, 2H), 2.67 (t, *J* = 7.8, 2H), 2.38 (t, *J* = 7.6, 2H), 2.15-2.11 (m, 2H), 1.98-1.80 (m, 3H), 1.65-1.55 (m, 3H), 1.42 (m, 1H).

EXAMPLE 37



1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidin-4-ol.

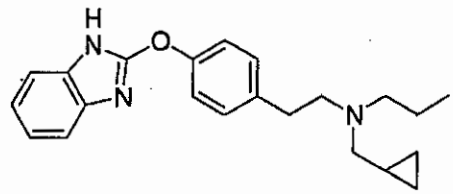
A. 1-[2-(4-Hydroxy-phenoxy)-ethyl]-4-phenyl-piperidin-4-ol. To a solution of 4-(2-bromo-ethoxy)-phenol (EXAMPLE 3; 8.0 g, 36.8 mmol) and 4-hydroxy-4-phenylpiperidine (8.2 g, 46.3 mmol) in CH_3CN (150 mL) was added DIEA (7.0 mL, 40.2 mmol). The mixture was stirred for 20 h at room temperature and for an additional 4 h at 65 °C, then was concentrated under reduced pressure to give a brown solid. The solid was dissolved in ethyl acetate (250 mL), and the solution was washed with H_2O (250 mL, 100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a brown solid. The solid was purified on SiO_2 (120 g; 0-100% acetone/CH_2Cl_2) e to give 8.9 g (77% yield) of the desired product as a tan solid. TLC (SiO_2, acetone): R_f = 0.42. MS (ESI): mass calculated for $C_{19}H_{23}NO_3$, 313.17; m/z found 314.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.52 (d, *J* = 8.6, 2H), 7.37 (t, *J* = 7.3, 2H), 7.27 (m, 1H),

6.75 (s, 4H), 4.08 (t, J = 5.8, 2H), 3.05-2.90 (m, 2H), 2.88 (t, J = 5.8, 2H), 2.80-2.62 (m, 2H), 2.31-2.18 (m, 2H), 1.81 (d, J = 11.8, 2H).

B. 4-Phenyl-1-(2-{4-[1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-benzoimidazol-2-yloxy]-phenoxy}-ethyl)-piperidin-4-ol. To a mixture of 2-chloro-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-benzoimidazole (EXAMPLE 7; 630 mg, 2.2 mmol) and 1-[2-(4-hydroxy-phenoxy)-ethyl]-4-phenyl-piperidin-4-ol (690 mg, 2.2 mmol) in DMF (10 mL) was added Cs_2CO_3 (1.5 g, 4.6 mmol). The reaction mixture was stirred at 100 °C for 18 h, and then partitioned in 1:1 ethyl acetate/H_2O (50 mL) . The organic layer was collected, dried ($MgSO_4$), and concentrated under reduced pressure to give a clear brown oil, which was purified on SiO_2 (35 g; acetone) to give 867 mg (70% yield) of the desired product as a clear golden oil. TLC (SiO_2, acetone): R_f = 0.38. MS (ESI): mass calculated for $C_{32}H_{41}N_3O_4Si$, 559.29; m/z found, 560.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.55 (m, 3H), 7.38 (m, 3H), 7.30-7.20 (m, 5H), 6.99 (d, J = 9.0, 2H), 5.55 (s, 2H), 4.17 (t, J = 5.9, 2H), 6.37 (m, 2H), 2.92 (m, 5H), 2.65 (t, J = 12.4, 2H), 2.21 (t, J = 15.9, 2H), 1.81 (d, J = 12.1, 2H), 0.96 (t, J = 8.1, 2H).

C. 1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidin-4-ol. To a solution of 4-phenyl-1-(2-{4-[1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-benzoimidazol-2-yloxy]-phenoxy}-ethyl)-piperidin-4-ol (816 mg, 1.46 mmol) in THF (5 mL) containing *N*,*N*,*N*,*N*-tetramethylethylenediamine (TMEDA, 2.2 mL, 14.6 mmol), was added a 1 M THF solution of tetrabutylammonium fluoride (TBAF, 15 mL, 15 mmol). The mixture was stirred at 55 °C for 5 h, then was concentrated under reduced pressure. The resulting oil was dissolved in diethyl ether(100 mL), and the solution was washed with H_2O (3 x 75 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a white solid. Diethyl ether was added, and filtration gave the desired product as a white solid (155 mg, 25% yield). TLC (SiO_2, acetone): R_f = 0.16. MS (ESI): mass calculated for $C_{26}H_{27}N_3O_3$, 429.21; m/z found, 430.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.23 (br s, 1H), 7.48 (d, J = 7.3, 2H), 7.35-7.25 (m, 6H), 7.20 (t, J = 7.4, 1H), 7.10-7.04 (m, 2H), 7.00 (d, J = 9.0, 2H), 4.80 (s, 1H), 4.13 (t, J = 5.8, 2H), 2.76 (t, J = 5.8, 2H), 2.58-2.48 (m, 2H), 1.94 (dt, J = 12.7, 4.0, 2H), 1.58 (d, J = 12.1, 2H).

EXAMPLE 38



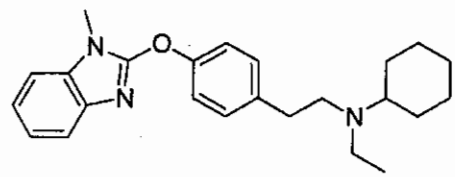
{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-propyl-amine.

A. 4-[2-(Cyclopropylmethyl-propyl-amino)-ethyl]-phenol. To a solution of 4-(2-bromo-ethyl)-phenol (EXAMPLE 5; 5.0 g, 25.0 mmol) in CH_3CN (100 mL) was added cyclopropylmethyl-propyl-amine (5.4 mL, 37.5 mmol), followed by *N,N*-diisopropylethylamine (8.70 mL, 50.0 mmol). The resulting solution was stirred at 60 °C for 16 h, yielding a suspension, which was cooled to room temperature and filtered. The filtered solid was washed with ethyl acetate (2 x 20 mL) and dried to give a white solid (5.7 g, 98% yield). MS (ESI): mass calculated for $C_{15}H_{23}NO$, 233.18; m/z found, 234.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.01 (d, J = 8.6, 2H), 6.87 (d, J = 8.6, 2H), 3.34-3.30 (m, 2H), 3.19-3.04 (m, 2H), 2.94-2.75 (m, 4H), 1.75-1.56 (m, 2H), 1.16-0.99 (m, 1H), 0.95-0.87 (m, 3H), 0.68-0.53 (m, 2H), 0.44-0.32 (m, 2H).

B. {2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-propyl-amine. A mixture of 2-chloro-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-benzoimidazole (EXAMPLE 7; 707 mg, 2.5 mmol), 4-[2-(cyclopropylmethyl-propyl-amino)-ethyl]-phenol (467 mg, 2.0 mmol), and Cs_2CO_3 (1.3 g, 4.0 mmol) in DMF (10 mL) was stirred at 100 °C for 18 h. The reaction mixture was cooled to room temperature, and then partitioned in 1:1 ethyl acetate/H_2O (200 mL). The organic layer was collected, dried ($MgSO_4$), and concentrated under reduced pressure to give a clear brown oil, which was purified on SiO_2 (40 g; 0–100% acetone/CH_2Cl_2), giving 729 mg (76% yield) of a clear golden oil. MS (ESI): mass calculated for $C_{28}H_{41}N_3O_2Si$, 479.30; m/z found, 480.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.63-7.58 (m, 1H), 7.49-7.39 (m, 1H), 7.31 (s, 4H), 7.26-7.22 (m, 2H), 5.58 (s, 2H), 3.69 (t, J = 8.2, 2H), 2.89-2.79 (m, 4H), 22.63-2.58 (m, 2H), 2.48 (d, J = 6.5, 2H), 1.61-1.50 (m, 2H), 1.01-0.91 (m, 6H), 0.59-0.53 (m, 2H), 0.20-0.15 (m, 2H), 0.1 (s, 9H).

C. {2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-propyl-amine. To a solution of cyclopropylmethyl-propyl-(2-{4-[1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-benzoimidazol-2-yloxy]-phenyl}-ethyl)-amine (411 mg, 0.87 mmol) in THF (5 mL), TBAF (1 M in THF, 2.57 mL, 2.57 mmol) was added via syringe, and the mixture was stirred at reflux for 16 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting oil was purified on SiO_2 (40 g; 0–20% CH_3OH/CH_2Cl_2), giving 284 mg (95% yield) of a clear oil. MS (ESI): mass calculated for $C_{22}H_{27}N_3O$, 349.22; m/z found, 350.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.34 (br s, 2H), 7.18-7.05 (m, 6H), 2.82-2.70 (m, 4H), 2.69-2.62 (m, 2H), 2.52 (d, J = 6.8, 2H), 1.61-1.50 (m, 2H), 0.91 (t, J = 6.8, 4H), 0.57-0.51 (m, 2H), 0.16 (dd, J = 5.3, 5.1, 2H).

EXAMPLE 39

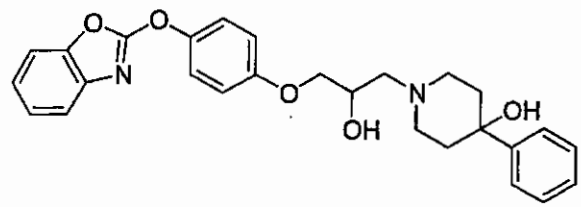


Cyclohexyl-ethyl-{2-[4-(1-methyl-1*H*-benzoimidazol-2-yloxy)-phenyl]-ethyl}-amine.

A mixture of 4-[2-(cyclohexyl-ethyl-amino)-ethyl]-phenol (247 mg, 1.0 mmol), *N*-methyl benzimidazole (EXAMPLE 8; 200 mg, 1.2 mmol), and Cs_2CO_3 (652 mg, 2.0 mmol) in DMF (3 mL) was stirred at 100 °C for 16 h. The reaction mixture was cooled and filtered through diatomaceous earth, which was then washed with ethyl acetate (30 mL). The combined filtrates were washed with H_2O (3 x 10 mL) then brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified on SiO_2 (10 g; 0–100% 10% [2 M NH_3 in CH_3OH] in CH_2Cl_2/CH_2Cl_2) to provide 105 mg (28% yield) of a brown oil. MS (ESI): mass calculated for $C_{24}H_{31}N_3O$, 377.53; m/z found, 378.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.52 (d, J =7.2, 1H), 7.63-7.58 (m, 1H), 7.33-7.18 (m, 7H), 3.75 (s, 3H), 2.81-2.70, m, 4H), 2.68 (q, J = 7.1, 2H), 2.60-

2.50 (m, 1H), 1.90- 1.80 (m, 4H), 1.67 (d, J = 12.3, 1H), 1.35-1.18 (m, 4H), 1.15-1.05 (m, 1H), 1.12 (t, J = 7.1, 3H).

EXAMPLE 40



1-{3-[4-(Benzooxazol-2-yloxy)-phenoxy]-2-hydroxy-propyl}-4-phenyl-piperidin-4-ol.

A. 2-(4-Benzyloxy-phenoxymethyl)-oxirane. To a solution of 4-(benzyloxy)phenol (15.0 g, 74.9 mmol) and epichlorohydrin (30 mL, 384 mmol) in DMF (200 mL) was added Cs_2CO_3 (51.2 g, 157 mmol). The mixture was heated to 75 °C for 3 days. The reaction mixture was cooled to room temperature, and then partitioned in 1:1 ethyl acetate/H_2O (600 mL). The organic layer was collected, washed with H_2O (3 x 250 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give 38 g of a clear, dark brown liquid. The liquid was purified on SiO_2 (300 g; 50-100% CH_2Cl_2/hexanes) to give the desired product as a white solid (13 g, 68% yield). TLC (SiO_2, CH_2Cl_2): R_f = 0.64. ^{1}H NMR (400 MHz, $CDCl_3$): 7.55-7.28 (m, 5H), 6.91 (d, J = 9.3, 2H), 6.86 (d, J = 9.3, 2H), 5.03 (s, 2H), 4.17 (dd, J = 11.0, 3.2, 1H), 3.95-3.88 (m, 1H), 3.36-3.33 (m, 1H), 2.91 (t, J = 4.8, 1H), 2.75 (dd, J = 4.9, 2.6, 1H).

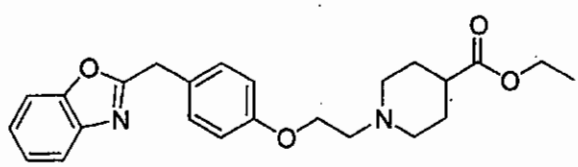
B. 1-[3-(4-Benzyloxy-phenoxy)-2-hydroxy-propyl]-4-phenyl-piperidin-4-ol. To a solution of 2-(4-benzyloxy-phenoxymethyl)-oxirane (1.50 g, 5.85 mmol) and 4-hydroxy-4-phenylpiperidine (1.30 g, 7.33 mmol) in CH_3CN (50 mL) was added K_2CO_3 (1.0 g, 7.23 mmol). The mixture was heated at reflux for 20 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to give a white solid, which was purified on SiO_2 (40 g; acetone) to give 1.4 g (56% yield) of the desired product as a white solid. TLC (SiO_2, acetone): R_f = 0.36. MS (ESI): mass calculated for $C_{27}H_{31}NO_4$, 433.23; m/z found, 434.3 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6): 7.56-7.23 (m, 10 H),

6.93 (d, J = 9.2, 2H), 6.88 (d, J = 9.2, 2H), 5.03 (s, 2H), 4.77 (s, 2H), 3.93 (br d, J = 10.8, 2H), 3.81 (t, J = 7.2, 1H), 2.80-2.60 (m, 2H), 2.50-2.35 (m, 4H), 1.97-1.90 (m, 2H), 1.60-1.50 (d, J = 13.4, 2H).

C. 1-[2-Hydroxy-3-(4-hydroxy-phenoxy)-propyl]-4-phenyl-piperidin-4-ol. To a solution of 1-[3-(4-benzyloxy-phenoxy)-2-hydroxy-propyl]-4-phenyl-piperidin-4-ol (1.3 g, 3.0 mmol) in 1:1 ethanol/ethyl acetate (50 mL) was added Pd on carbon (10 wt %, 165 mg). The mixture was placed on a Parr hydrogenator at 40 psi of H_2 for 20 h. The reaction mixture was filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure to give 1.0 g (100% yield) of desired product as a white solid. TLC (SiO_2, acetone): R_f = 0.27. MS (ESI): mass calculated for $C_{20}H_{25}NO_4$, 343.18; m/z found, 344.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.61 (d, J = 8.1, 2H), 7.42 (t, J = 7.4, 2H), 7.30 (t, J = 7.3, 1H), 6.90 (d, J = 9.0, 2H), 6.81 (d, J = 9.0, 2H), 4.25 (br s, 1H), 4.05-3.95 (m, 2H), 3.10-2.92 (m, 2H), 2.80-2.60 (m, 4H), 2.30-2.20 (m, 2H), 1.81 (d, J = 11.8, 2H).

D. 1-{3-[4-(Benzooxazol-2-yloxy)-phenoxy]-2-hydroxy-propyl}-4-phenyl-piperidin-4-ol. To a mixture of 1-[2-hydroxy-3-(4-hydroxy-phenoxy)-propyl]-4-phenyl-piperidin-4-ol (251 mg, 0.73 mmol) and Cs_2CO_3 (667 mg, 2.05 mmol) in acetone (10 mL) at 5 °C, was added 2-chloro-benzooxazole (108 µL, 0.95 mmol). The reaction mixture, left on ice, warmed to room temperature overnight and was then filtered. The filtrate was concentrated under reduced pressure to give a golden oil, which was purified on SiO_2 (10 g; acetone) to give 127 mg (38% yield) of the desired product as a white solid. TLC (SiO_2, acetone): R_f = 0.27. MS (ESI): mass calculated for $C_{27}H_{28}N_2O_5$, 460.20; m/z found, 461.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.60 (d, J = 6.6, 1H), 7.55-7.35 (m, 5H), 7.32-7.25 (m, 4H), 7.20 (t, J = 7.3, 1H), 7.06 (d, J = 9.1, 2H), 4.78 (s, 1H), 4.10-3.85 (m, 3H), 2.80-2.65 (m, 2H), 2.55-2.35 (m, 4H), 1.95 (t, J = 13.1, 2H), 1.59 (d, J = 13.2, 2H).

EXAMPLE 41



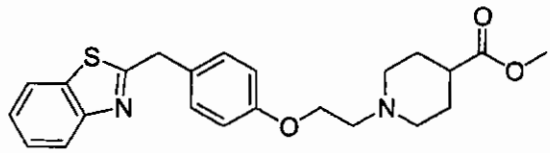
1-[2-(4-Benzooxazol-2-ylmethyl-phenoxy)-ethyl]-piperidine-4-carboxylic acid ethyl ester.

A. 4-Benzooxazol-2-ylmethyl-phenol. A mixture of 4-hydroxyphenylacetic acid (35 g, 230 mmol) and 2-aminophenol (43 g, 400 mmol) was heated at 180°C for 3 h and then cooled to room temperature. The resultant solid was ground and dissolved in THF (200 mL), and carbonyldiimidazole (27 g, 170 mmol) was added. The solution was stirred at 60 °C overnight. The reaction mixture was concentrated under reduced pressure, and partitioned between ethyl acetate (400 mL) and H_2O (300 mL). The organic layer was concentrated under reduced pressure. The resultant oil was dissolved in CH_2Cl_2 and purified on SiO_2 (200 g; 0–50% acetone/CH_2Cl_2) to give a brown solid (31 g, 40% yield). MS (ESI): mass calculated for $C_{14}H_{11}NO_2$, 225.08; m/z found, 226.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.62 (m, 1H), 7.53 (m, 1H), 7.32 (m, 2H), 7.17 (d, J = 8.5, 2H), 6.75 (d, J = 8.5, 2H), 4.18 (s, 2H).

B. 2-[4-(2-Bromo-ethoxy)-benzyl]-benzooxazole. To a stirring solution of 4-benzooxazol-2-ylmethyl-phenol (5 g, 22.2 mmol) in CH_3CN (100 mL) was added Na_2CO_3 (6.4 g, 46.6 mmol) and dibromoethane (7.9 mL, 88.8 mmol). The resulting suspension was heated to 70°C for 72 h and filtered while hot. The filtrate was concentrated under reduced pressure. The resulting solid was suspended in diethyl ether and filtered, and the filtrate was concentrated under reduced pressure. The resultant oil was dissolved in CH_2Cl_2 and purified on SiO_2 (110 g; CH_2Cl_2) to give an off-white solid (1g, 13.7% yield). MS (ESI): mass calculated for $C_{16}H_{14}BrNO_2$, 331.02; m/z found, 332.0 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.62 (m, 1H), 7.53 (m, 1H), 7.34 (m, 2H), 7.29 (d, J = 8.6, 2H), 6.92 (d, J = 8.7, 2H), 4.28 (t, J = 5.9, 2H), 4.23 (s, 2H), 3.67 (t, J = 5.9, 2H).

C. 1-[2-(4-Benzooxazol-2-ylmethyl-phenoxy)-ethyl]-piperidine-4-carboxylic acid ethyl ester. To a stirring solution of 2-[4-(2-bromo-ethoxy)-benzyl]-benzooxazole (0.5 g, 1.5 mmol) in CH_3CN (7.5 mL) was added ethyl isonepicotate (0.7 mL, 4.5 mmol). The mixture was stirred at room temperature for 48 h, then concentrated under reduced pressure. The resultant oil was dissolved in CH_2Cl_2 and purified on SiO_2 (40 g; 0–25% acetone/CH_2Cl_2) to give an off-white solid (275 mg, 45% yield). MS (ESI): mass calculated for $C_{24}H_{28}N_2O_4$, 408.20; m/z found, 409.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.67 (m, 1H), 7.45 (m, 1H), 7.28 (d, J = 9.0, 4H), 6.88 (d, J = 8.7, 2H), 4.20 (s, 2H), 4.12 (q, J = 7.1, 2H), 4.08 (t, J = 5.9, 2H), 2.95 (d, J = 11.5, 2H), 2.77 (t, J = 5.9, 2H), 2.24 (m, 1H), 2.16 (m, 2H), 1.84 (m, 2H), 1.76 (m, 2H). 1.24 (t, J = 7.2, 3H).

EXAMPLE 42



1-[2-(4-Benzothiazol-2-ylmethyl-phenoxy)-ethyl]-piperidine-4-carboxylic acid methyl ester.

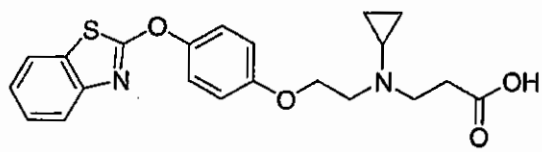
A. 4-Benzothiazol-2-ylmethyl-phenol. A mixture of 4-hydroxyphenylacetic acid (15.2 g, 100 mmol) and 2-amino-benzenethiol (10.7 mL, 100 mmol) was heated at 150°C for 16 h and then cooled to room temperature. The resultant solid was ground and dissolved in CH_2Cl_2 (400 mL). The solution was washed with 1 N HCl (2 x 50 mL) then sat. aq. $NaHCO_3$ (2 x 50 mL), dried, filtered, and concentrated under reduced pressure. The residue was purified on SiO_2 (0–50% ethyl acetate/hexanes) to give a white solid (10.5 g, 44% yield). MS (ESI): mass calculated for $C_{14}H_{11}NOS$, 241.06; m/z found, 342.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.89 (dd, J = 8.6, 4.8, 2H), 7.47 (t, J = 7.8, 1H), 7.31 (t, J = 7.8, 1H), 7.18 (d, J = 8.3, 2H), 6.77 (d, J = 8.6, 2H), 4.89 (s, 1H), 4.33 (s, 2H).

B. 2-[4-(2-Bromo-ethoxy)-benzyl]-benzothiazole. To a stirring solution of 4-benzothiazol-2-ylmethyl-phenol (10.5 g, 43.5 mmol) in CH_3CN (100 mL) was

added Cs_2CO_3 (28.3 g, 87 mmol) and dibromoethane (18.7 mL, 21.8 mmol). The resulting suspension was heated to 70 °C for 16 h, cooled to room temperature, and then dissolved in CH_2Cl_2 (400 mL). The solution was washed with H_2O (2 x 50 mL), dried, and concentrated. The resultant oil was dissolved in CH_2Cl_2 and purified on SiO_2 (0–50% ethyl acetate/hexanes) to give a white solid (7.5 g, 49.5% yield). MS (ESI): mass calculated for $C_{16}H_{14}BrNOS$, 347.00; m/z found, 348.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.99 (d, J = 8.1, 1H), 7.79 (d, J = 8.1, 1H), 7.45 (t, J = 7.6, 1H), 7.36-7.25 (m, 3H), 6.89 (d, J = 8.8, 2H), 4.38 (s, 2H), 4.28 (t, J = 6.3, 2H), 3.63 (t, J = 6.3, 2H).

C. 1-[2-(4-Benzothiazol-2-ylmethyl-phenoxy)-ethyl]-piperidine-4-carboxylic acid methyl ester. To a stirring solution of 2-[4-(2-bromo-ethoxy)-benzyl]-benzothiazole (1.0 g, 2.9 mmol) in CH_3CN (20 mL) was added methyl isonepicotate (0.7 mL, 55.7 mmol) and *N,N*-diisopropylethylamine (1.5 mL, 8.6 mmol). The mixture was heated to 60 °C for 16 h, cooled to room temperature, and then dissolved in CH_2Cl_2 (100 mL). The solution was washed with H_2O (2 x 20 mL), dried, and concentrated. The resultant oil was dissolved in CH_2Cl_2 and purified on SiO_2 (0–15% CH_3OH/CH_2Cl_2) to give a white solid (1.1 g, 92% yield). MS (ESI): mass calculated for $C_{23}H_{26}N_2O_3S$, 410.17; m/z found, 411.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.98 (d, J = 8.3, 1H), 7.76 (d, J = 8.3, 1H), 7.42 (t, J = 7.8, 1H), 7.33-7.24 (m, 3H), 6.88 (d, J = 8.8, 2H), 4.36 (s, 2H), 4.07 (t, J = 6.1, 2H), 3.66 (s, 3H), 2.97-2.90 (m, 2H), 2.76 (t, J = 6.1, 2H), 2.33-2.24 (m 1H), 2.15 (t, J = 11.4, 2H), 1.93-1.86 (m, 2H), 1.83-1.72 (m, 2H).

Example 43



3-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropyl-amino)-propionic acid trifluoroacetic acid salt.

A. 3-[2-(4-Hydroxy-phenoxy)-ethylamino]-propionic acid ethyl ester. To a stirring solution of 4-(2-bromo-ethoxy)-phenol (EXAMPLE 3; 2.4 g, 11 mmol) in

CH_3CN (50 mL) was added 3-amino-propionic acid ethyl ester hydrochloride (3.4 g, 22 mmol) followed by *N,N*-diisopropylethylamine (7.7 mL, 44 mmol). The mixture was stirred at 60 °C for 16 h, allowed to cool to room temperature, and then dissolved in CH_2Cl_2 (100 mL). The resulting solution was washed with H_2O (2 x 15 mL), dried, filtered, and then concentrated under reduced pressure to afford a brown oil, which was used in the next step.

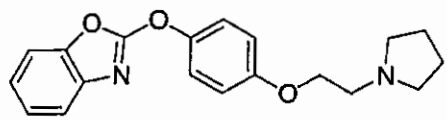
B. 3-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethylamino}-propionic acid ethyl ester. To a stirring solution of 3-[2-(4-hydroxy-phenoxy)-ethylamino]-propionic acid ethyl ester (11 mmol) in DMF (30 mL), was added Cs_2CO_3 (10.8 g, 33 mmol) and 2-chlorobenzothiazole (2.72 mL, 22 mmol). The suspension was stirred at 100 °C overnight. The reaction mixture was allowed to cool to room temperature and then filtered through diatomaceous earth. The filtrate was concentrated under reduced pressure, and purified on SiO_2 (100 g; 0–100% CH_3OH/CH_2Cl_2), giving 1.9 g (45% yield) of a light brown oil. MS (ESI): mass calculated for $C_{22}H_{22}N_2O_4S$, 386.13; m/z found, 387.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.66 (d, *J* = 8.1, 1H), 7.58 (d, *J* = 8.3, 1H), 7.30 (d, *J* = 7.8, 1H), 7.22-7.15 (m, 3H), 6.86 (d, *J* = 9.1, 2H), 4.09 (dd, *J* = 7.1, 7.1, 2H), 4.01 (t, *J* = 5.3, 2H), 2.98 (t, *J* = 5.3, 2H), 2.92 (t, *J* = 6.6, 2H), 2.49 (t, *J* = 6.6, 2H), 2.20 (br s, 1H), 1.20 (t, *J* = 7.1, 3H).

C. 3-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropyl-amino)-propionic acid ethyl ester. To a solution of 3-{2-[4-(benzothiazol-2-yloxy)-phenoxy]-ethylamino}-propionic acid ethyl ester (500 mg, 1.29 mmol) in CH_3OH (15 mL) was added acetic acid (0.73 mL, 12.9 mmol), 3 Å molecular sieves and [(1-ethoxycyclopropyl)oxy]trimethylsilane (1.55 mL, 7.7 mmol). Sodium cyanoborohydride (365 mg, 5.8 mmol) was added, and the mixture was heated at reflux overnight. The mixture was cooled, filtered and concentrated. The residue was dissolved in CH_2Cl_2, and the resulting solution was washed with sat. aq. $NaHCO_3$ then brine, dried, and concentrated. This residue was purified on SiO_2 (40 g; 10–50% ethyl acetate/hexanes), giving 374 mg (68% yield) of a colorless oil. MS (ESI): mass calculated for $C_{23}H_{26}N_2O_4S$, 426.16; m/z found, 427.1.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, *J* = 8.3, 1H), 7.64 (d, *J* = 8.1, 1H), 7.38 (d, *J* = 7.8, 1H), 7.29-7.22 (m, 3H), 6.94 (d, *J* = 9.1, 2H), 4.14 (dd, *J* = 7.1, 7.1, 2H), 4.10 (t, *J* = 6.1, 2H), 3.07 (t, *J* = 7.1, 2H), 3.05

(t, J = 6.1, 2H), 2.58 (t, J = 7.3, 2H), 1.92-1.86 (m, 1H), 1.26 (t, J = 7.1, 3H), 0.54-0.43 (m, 4H).

D. 3-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropyl-amino)-propionic acid trifluoroacetic acid salt. To a solution of 3-({2-[4-(benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropyl-amino)-propionic acid ethyl ester (355 mg, 11.7 mmol) in THF (15 mL) and CH_3OH (5 mL), was added lithium hydroxide (80 mg, 3.3 mmol) in H_2O (10 mL). The mixture was stirred at room temperature for 16 h, and then concentrated under reduced pressure. The residue was dissolved in CH_3OH and was purified by reversed-phase HPLC to give the title compound (391 mg, 92% yield). MS (ESI): mass calculated for $C_{21}H_{22}N_2O_4S$, 398.13; m/z found, 399.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.73 (d, J = 8.3, 1H), 7.64 (d, J = 8.1, 1H), 7.48 (d, J = 7.8, 1H), 7.35-7.25 (m, 3H), 7.11 (d, J = 9.1, 2H), 5.17 (br s, 1H), 4.48 (t, J = 4.6, 2H), 3.81 (t, J = 4.6, 2H), 3.76 (t, J = 7.1, 2H), 3.04-2.93 (m, 3H), 1.17-1.10 (m, 2H), 1.05-0.97 (m, 2H).

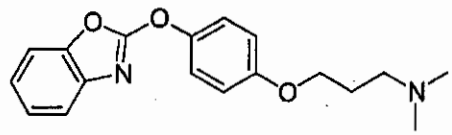
EXAMPLE 44



2-[4-(2-Pyrrolidin-1-yl-ethoxy)-phenoxy]-benzooxazole.

The title compound was prepared according to the procedure for EXAMPLE 11 using 1-(2-chloro-ethyl)-pyrrolidine. MS (ESI): mass calculated for $C_{19}H_{20}N_2O_3$, 324.15; m/z found, 325.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.75 (d, J = 8.1,1H), 7.66 (d, J = 8.0, 1H), 7.40 (dt, J = 7.4, 1.3, 1H), 7.31-7.23 (m, 3H), 6.98 (d, J = 6.8, 2H), 4.08 (t, J = 6.3, 2H), 2.91 (t, J = 6.3, 2H), 2.67 (q, J = 7.2, 4H), 1.10 (t, J = 7.2, 6H).

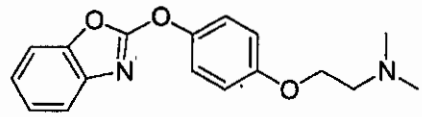
EXAMPLE 45



{3-[4-(Benzooxazol-2-yloxy)-phenoxy]-propyl}-dimethyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 11 using (2-chloro-propyl)-dimethyl-amine hydrochloride. MS (ESI): mass calculated for $C_{18}H_{20}N_2O_3$, 312.15; m/z found, 313.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.48-7.45 (m, 1H), 7.40-7.38 (m, 1H), 7.30 (d, J = 7.9, 2H), 7.23-7.18 (m, 2H), 6.91 (d, J = 8.3, 2H), 4.09 (br s, 2H), 3.23 (br s, 2H), 2.85 (br s, 6H), 2.42 (br s, 2H).

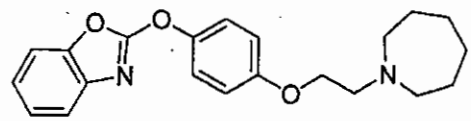
EXAMPLE 46



{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-dimethyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 11 using (2-chloro-ethyl)-dimethyl-amine hydrochloride. MS (ESI): mass calculated for $C_{17}H_{18}N_2O_3$, 298.13; m/z found, 299.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.49-7.47 (m, 1H), 7.41-7.38 (m, 1H), 7.32-7.27 (m, 2H), 7.26-7.18 (m, 2H), 6.98-6.95 (m, 2H), 4.05 (t, J = 5.7, 2H), 2.72 (t, J = 5.7, 2H), 2.32 (s, 6H).

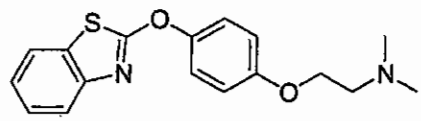
EXAMPLE 47



2-[4-(2-Azepan-1-yl-ethoxy)-phenoxy]-benzooxazole.

The title compound was prepared according to the procedure for EXAMPLE 11 using 1-(2-chloro-ethyl)-azepane hydrochloride. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_3$, 352.18; m/z found, 353.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.49-7.47 (m, 1H), 7.41-7.38 (m, 1H), 7.31-7.27 (m, 2H), 7.26-7.18 (m, 2H), 6.97-6.93 (m, 2H), 4.06 (t, J = 6.2, 2H), 2.94 (t, J = 6.2, 2H), 2.77-2.75 (m, 4H), 1.65-1.58 (m, 8H).

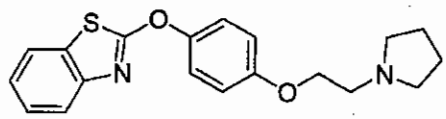
EXAMPLE 48



{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-dimethyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 12 using (2-chloro-ethyl)-dimethyl-amine hydrochloride and 2-chlorobenzothiazole. MS (ESI): mass calculated for $C_{17}H_{18}N_2O_2S$, 314.11; m/z found, 315.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.79-7.77 (m, 1H), 7.65-7.63 (m, 1H), 7.45-7.29 (m, 4H), 7.18-7.14 (m, 2H), .4.41 (t, J = 4.9, 2H), 3.63 (t, J = 4.9, 2H), 3.04 (s, 6H).

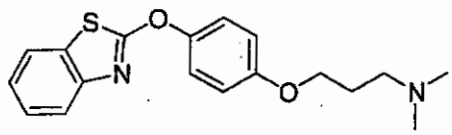
EXAMPLE 49



2-[4-(2-Pyrrolidin-1-yl-ethoxy)-phenoxy]-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 12 using 1-(2-chloro-ethyl)-pyrrolidine and 2-chlorobenzothiazole. MS (ESI): mass calculated for $C_{19}H_{20}N_2O_2S$, 340.12; m/z found, 341.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (d, J = 7.6, 1H), 7.66 (d, J = 8.6, 1H), 7.41 (t, J = 7.4, 1H), 7.32-7.25 (m, 3H), 7.00 (d, J = 9.0, 2H), 4.16 (t, J = 6.0, 2H), 2.96 (t, J = 6.0, 2H), 2.67 (t, J = 6.6, 4H), 1.86 (quint, J = 3.5, 4H).

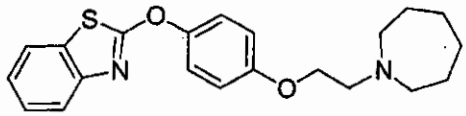
EXAMPLE 50



{3-[4-(Benzothiazol-2-yloxy)-phenoxy]-propyl}-dimethyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 12 using (2-chloro-propyl)-dimethyl-amine hydrochloride and 2-chlorobenzothiazole. MS (ESI): mass calculated for $C_{18}H_{20}N_2O_2S$, 328.12; m/z found, 329.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.64 (d, J = 7.9, 1H), 7.37 (t, J = 7.5, 1H), 7.31-7.20 (m, 3H), 6.92 (d, J = 7.9, 2H), 4.11 (s, 2H), 3.25 (s, 2H), 2.85 (s, 6H), 2.43 (s, 2H).

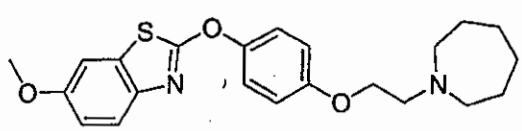
EXAMPLE 51



2-[4-(2-Azepan-1-yl-ethoxy)-phenoxy]-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 12 using 1-(2-chloro-ethyl)-azepane hydrochloride and 2-chlorobenzothiazole. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_2S$, 368.16; m/z found, 369.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.70 (d, J = 7.5, 1H), 7.65 (d, J = 7.9, 1H), 7.38-7.34 (m, 1H), 7.29-7.23 (m, 3H), 6.97 (br d, 2H), 4.59 (br s, 2H), 3.64 (br s, 2H), 3.46 (br s, 2H), 3.13 (br s, 3H), 2.19 (br s, 2H), 1.87 (br s, 2H), 1.72-1.58 (m, 2H).

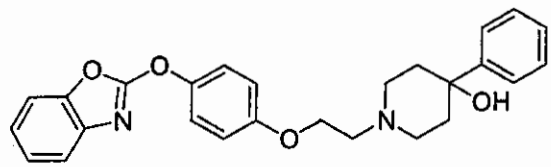
EXAMPLE 52



2-[4-(2-Azepan-1-yl-ethoxy)-phenoxy]-6-methoxy-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 12 using 1-(2-chloro-ethyl)-azepane hydrochloride and 2-chloro-6-methoxy-benzothiazole. MS (ESI): mass calculated for $C_{22}H_{26}N_2O_3S$, 398.17; m/z found, 399.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.75 (d, J = 8.9, 1H), 7.37-7.35 (m, 2H), 7.26 (br d, 2H), 7.09-7.05 (m, 3H), 4.19 (t, J = 6.1, 2H), 3.95 (s, 3H), 3.08 (t, J = 6.1, 2H), 2.91-2.88 (m, 4H), 1.76 (br d, 8H).

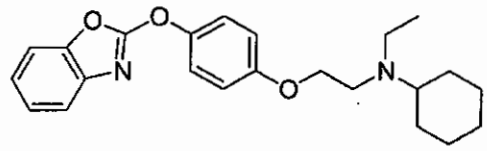
EXAMPLE 53



1-{2-[4-(Benzoœxazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 13 using 4-phenyl-piperidin-4-ol. MS (ESI): mass calculated for $C_{26}H_{26}N_2O_4$, 430.19; m/z found, 431.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.60-7.45 (m, 3H), 7.40-7.18 (m, 8H), 7.00 (d, J = 9.1, 2H), 4.18 (t, J = 5.9, 2H), 2.92 (t, J = 5.9, 2H), 2.66 (dt, J = 12.1, 2.4, 2H), 2.22 (dt, J = 13.4, 4.5, 2H), 1.80 (dd, J = 14.1, 2.4, 2H).

EXAMPLE 54

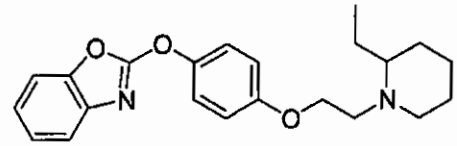


{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-cyclohexyl-ethyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 13 using cyclohexyl-ethyl-amine. MS (ESI): mass calculated for $C_{23}H_{28}N_2O_3$, 380.21; m/z found, 381.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.51 (d, J = 8.4, 1H), 7.42 (d, J = 7.5, 1H), 7.35-7.18 (m, 4H), 6.97 (d, J = 9.1, 2H), 3.98 (t, J =

6.9, 2H), 2.88 (t, *J* = 6.9, 2H), 2.67 (q, *J* = 7.1, 2H), 2.55-2.50 (m, 1H), 1.82 (t, *J* = 7.4, 4H), 1.64 (d, *J* = 12.4, 1H), 1.21 (t, *J* = 7.9, 4H), 1.08 (t, *J* = 7.1, 4H).

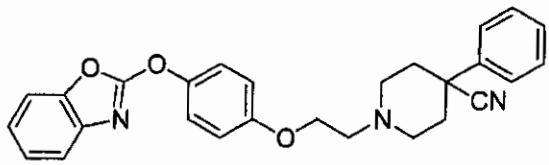
EXAMPLE 55



2-{4-[2-(2-Ethyl-piperidin-1-yl)-ethoxy]-phenoxy}-benzooxazole.

The title compound was prepared according to the procedure for EXAMPLE 13 using 2-ethyl-piperidine. MS (ESI): mass calculated for $C_{22}H_{26}N_2O_3$, 366.19; m/z found, 367.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.51 (d, *J* = 7.4, 1H), 7.42 (d, *J* = 7.4, 1H), 7.31 (d, *J* = 9.1, 2H), 7.30-7.20 (m, 2H), 6.97 (d, *J* = 9.1, 2H), 4.09 (t, *J* = 6.4, 2H), 3.15-3.05 (m, 1H), 3.00-2.92 (m, 1H), 2.88-2.80 (m, 1H), 2.48-2.37 (m, 1H), 2.30-2.25 (m, 1H), 1.75-1.65 (m, 4H), 1.60-1.54 (m, 2H), 1.52-1.42 (m, 1H), 1.38-1.24 (m, 2H), 0.92 (t, *J* = 7.4, 3H).

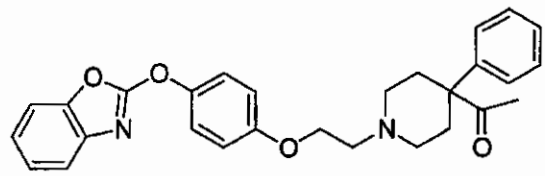
EXAMPLE 56



1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidine-4-carbonitrile.

The title compound was prepared according to the procedure for EXAMPLE 13 using 4-phenyl-piperidine-4-carbonitrile. MS (ESI): mass calculated for $C_{27}H_{25}N_3O_5$, 439.19; m/z found, 440.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.61-7.49 (m, 3H), 7.43-7.38 (m, 3H), 7.36-7.29 (m, 3H), 7.28-7.20 (m, 3H), 7.03-6.96 (m, 2H), 4.15 (t, *J* = 5.6, 2H), 3.18 (br d, 2H), 2.93 (t, *J* = 5.6, 2H), 2.71-2.61 (m, 2H), 2.22-2.10 (m, 8H).

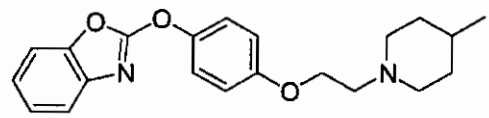
EXAMPLE 57



1-(1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidin-4-yl)-ethanone.

The title compound was prepared according to the procedure for EXAMPLE 13 using 1-(4-phenyl-piperidin-4-yl)-ethanone. MS (ESI): mass calculated for $C_{28}H_{28}N_2O_4$, 456.20; m/z found, 457.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.52-7.49 (m, 1H), 7.43-7.40 (m, 1H), 7.37-7.16 (m, 9H), 6.99-6.92 (m, 2H), 4.10 (t, J = 5.8, 2H), 2.87-2.82 (m, 2H), 2.78 (t, J = 5.8, 2H), 2.51-2.47 (m, 2H), 2.39 (br t, 2H), 2.17-2.05 (m, 2H), 1.92 (s, 3H).

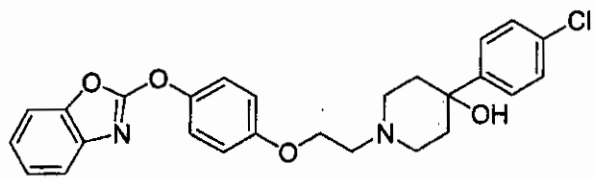
EXAMPLE 58



2-{4-[2-(4-Methyl-piperidin-1-yl)-ethoxy]-phenoxy}-benzooxazole.

The title compound was prepared according to the procedure for EXAMPLE 13 using 4-methyl-piperidine. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_3$, 352.18; m/z found, 353.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.50 (d, J = 6.8, 1H), 7.42 (d, J = 6.8, 1H), 7.31 (d, J = 9.0, 2H), 7.30-7.20 (m, 2H), 6.97 (d, J = 9.0, 2H), 4.13 (t, J = 6.0, 2H), 2.97 (d, J = 11.7, 2H), 2.80 (t, J = 6.0, 2H), 2.11 (dt, J = 11.7, J = 2.2, 2H), 1.67 (s, 2H), 1.34 (br s, 1H), 1.28 (dt, J = 12.2, J = 3.4, 2H), 0.94 (d, J = 6.2, 3H).

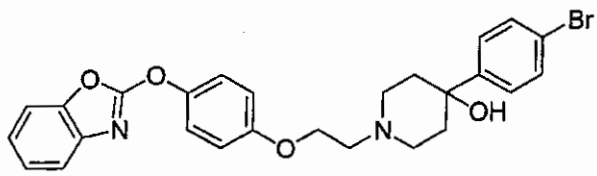
EXAMPLE 59



1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-(4-chloro-phenyl)-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 13 using 4-(4-chloro-phenyl)-piperidin-4-ol. MS (ESI): mass calculated for $C_{26}H_{25}ClN_2O_4$, 464.15; m/z found, 465.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.54-7.42 (m, 4H), 7.37-7.31 (m, 4H), 7.29-7.21 (m, 2H), 7.03-6.98 (m, 2H), 4.16 (t, J = 5.8, 2H), 2.93-2.89 (m, 4H), 2.62 (dt, J = 12.2, 2.4, 2H), 2.21-2.14 (m, 2H), 1.78-1.74 (m, 2H), 1.56 (br s, 1H).

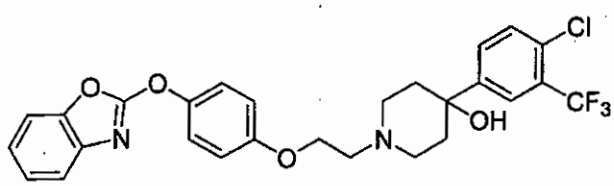
EXAMPLE 60



1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-(4-bromo-phenyl)-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 13 using 4-(4-bromo-phenyl)-piperidin-4-ol. MS (ESI): mass calculated for $C_{26}H_{25}BrN_2O_4$, 508.10; m/z found, 509.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.55-7.47 (m, 3H), 7.44-7.39 (m, 3H), 7.37-7.31 (m, 2H), 7.30-7.19 (m, 2H), 7.02-6.98 (m, 2H), 4.17 (t, J = 5.7, 2H), 2.94-2.89 (m, 4H), 2.62 (dt, J = 12.2, 2.4, 2H), 2.21-2.13 (m, 2H), 1.78-1.74 (m, 2H), 1.56 (br s, 1H).

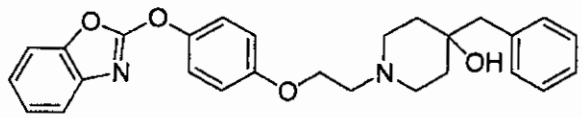
EXAMPLE 61



1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-(4-chloro-3-trifluoromethyl-phenyl)-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 13 using 4-(4-chloro-3-trifluoromethyl-phenyl)-piperidin-4-ol. MS (ESI): mass calculated for $C_{27}H_{24}ClF_3N_2O_4$, 532.14; m/z found, 533.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.89 (d, J = 2.1, 1H), 7.62 (dd, J = 8.4, 2.1, 1H), 7.51-7.41 (m, 3H), 7.33-7.21 (m, 4H), 6.99-6.95 (m, 2H), 4.14 (t, J = 5.7, 2H), 2.94-2.89 (m, 4H), 2.65-2.59 (m, 2H), 2.21-2.13 (m, 4H), 1.74 (br s, 1H).

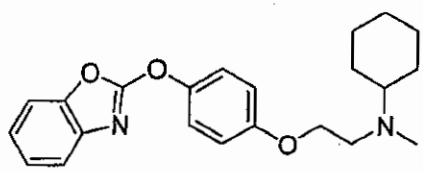
EXAMPLE 62



1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-benzyl-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 13 using 4-benzyl-piperidin-4-ol. MS (ESI): mass calculated for $C_{27}H_{28}N_2O_4$, 444.20; m/z found, 445.1 $[M+H]^+$. ^1H NMR: (400 MHz, $CDCl_3$) 7.53-7.50 (m, 1H), 7.43-7.40 (m, 1H), 7.53-7.21 (m, 10H), 7.01-6.95 (m, 2H), 4.12 (t, J = 5.9, 2H), 2.84 (t, J = 5.8, 2H), 2.78-2.76 (m, 4H), 2.47 (dt, J = 11.6, 2.4, 2H), 1.83-1.75 (m, 2H), 1.59-1.53 (m, 2H).

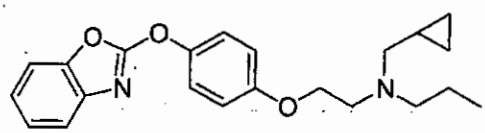
EXAMPLE 63



{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-cyclohexyl-methyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 13 using cyclohexyl-methyl-amine. MS (ESI): mass calculated for $C_{22}H_{26}N_2O_3$, 366.19; m/z found, 367.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.62 (dd, J = 6.2, J = 2.0, 1H), 7.50 (dd, J = 6.1, 2.1, 1H), 7.42 (d, J = 9.1, 2H), 7.35-7.25 (m, 2H), 7.03 (d, J = 9.1, 2H), 4.04 (t, J = 6.1, 2H), 2.79 (t, J = 6.1, 2H), 2.45-2.32 (m, 1H), 1.73 (d, J = 7.9, 4H), 1.57 (d, J = 12.2, 2H), 1.30-1.12 (m, 4H), 1.10-1.00 (m, 1H).

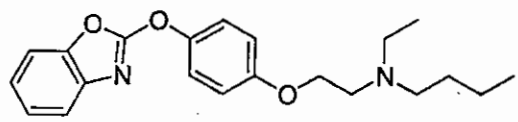
EXAMPLE 64



{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-cyclopropylmethyl-propyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 13 using cyclopropylmethyl-propyl-amine. MS (ESI): mass calculated for $C_{22}H_{26}N_2O_3$, 366.19; m/z found, 367.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.52-7.50 (m, 1H), 7.44-7.41 (m, 1H), 7.33-7.21 (m, 4H), 6.99-6.95 (m, 2H), 4.09 (t, J = 6.2, 2H), 3.01 (t, J = 6.2, 2H), 2.64-2.59 (m, 2H), 2.49 (d, J = 6.3, 2H), 1.60-1.50 (m, 2H), 0.92 (t, J = 7.3, 4H), 0.55-0.52 (m, 2H), 0.16-0.13 (m, 2H).

EXAMPLE 65

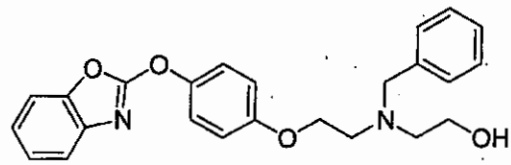


{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-butyl-ethyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 13 using butyl-ethyl-amine. MS (ESI): mass calculated for $C_{21}H_{26}N_2O_3$, 354.19;

m/z found, 355.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.41(d, J = 7.2, 1H), 7.32 (dd, J = 7.3, 1.6, 1H), 7.22 (d, J = 9.1, 1H), 7.18-7.10 (m, 2H), 6.87 (d, J = 9.1, 2H), 4.02 (br s, 2H), 2.85 (br s, 2H), 2.61 (br s, 2H), 2.49 (br s, 2H), 1.42 (br s, 2H), 1.31-1.19 (m, 2H), 1.05 (br s, 3H), 0.83 (t, J = 7.3, 3H).

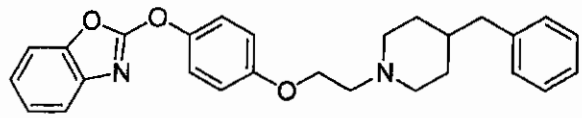
EXAMPLE 66



2-({2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-benzyl-amino)-ethanol.

The title compound was prepared according to the procedure for EXAMPLE 13 using benzylamino-ethanol. MS (ESI): mass calculated for $C_{24}H_{24}N_2O_4$, 404.17; m/z found, 405.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.46-7.37(m, 3H), 7.33 (d, J = 16.9, 2H), 7.29-7.00 (m, 6H), 6.95 (d, J = 6.9, 2H), 4.06 (t, J = 5.8, 2H), 3.76 (s, 2H), 3.64 (t, J = 6.2, 2H), 2.95 (d, J = 5.8, 2H), 2.76 (t, J = 6.1, 2H).

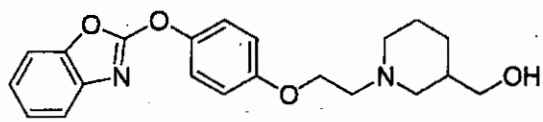
EXAMPLE 67



2-{4-[2-(4-Benzyl-piperidin-1-yl)-ethoxy]-phenoxy}-benzooxazole.

The title compound was prepared according to the procedure for EXAMPLE 13 using 4-benzyl-piperidine. MS (ESI): mass calculated for $C_{27}H_{28}N_2O_3$, 428.21; m/z found, 429.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.53-7.50 (m, 1H), 7.44-7.41 (m, 1H), 7.33-7.15 (m, 9H), 6.98-6.95 (m, 2H), 4.11 (t, J = 6.0, 2H), 3.01-2.96 (m, 2H), 2.79 (t, J = 6.0, 2H), 2.55 (d, J = 7.0, 2H), 2.09-2.02 (m, 2H), 1.67-1.64 (m, 2H), 1.59-1.51 (m, 1H) 1.40-1.29 (m, 2H).

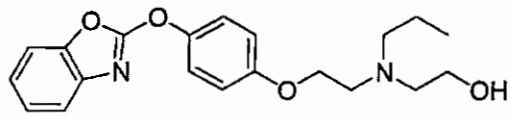
EXAMPLE 68



(1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidin-3-yl)-methanol.

The title compound was prepared according to the procedure for EXAMPLE 13 using piperidin-3-yl-methanol. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_4$, 368.17; m/z found, 369.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.55-7.52 (m, 1H), 7.48-7.44 (m, 1H), 7.38-7.23 (m, 4H), 7.05-6.99 (m, 2H), 4.23 (t, J = 5.6, 2H), 3.71 (dd, J = 10.7, 5.1, 1H), 3.59 (dd, J = 10.6, 6.4, 1H), 3.09 (br d, J = 9.7, 1H), 2.94 (t, J = 5.6, 2H), 2.42 (t, J = 9.1, 1H), 2.29 (t, J = 9.3, 1H), 2.24-1.98 (m, 2H), 2.00-1.90 (m, 1H), 1.90-1.80 (m, 1H), 1.80-1.71 (m, 2H), 1.20-1.10 (m, 1H).

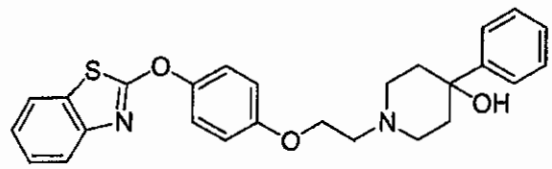
EXAMPLE 69



2-({2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-propyl-amino)-ethanol.

The title compound was prepared according to the procedure for EXAMPLE 13 using 2-propylamino-ethanol. MS (ESI): mass calculated for $C_{20}H_{24}N_2O_4$, 356.17; m/z found, 357.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.62 (dd, J = 6.2, 2.0, 1H), 7.50 (dd, J = 6.1, 2.1, 1H), 7.42 (d, J = 9.1, 2H), 7.35-7.25 (m, 2H), 7.03 (d, J = 9.1, 2H), 4.31 (t, J = 5.4, 1H), 4.04 (t, J = 6.0, 2H), 3.46 (q, J = 6.4, 2H), 2.85 (t, J = 6.0, 2H), 2.59 (t, J = 6.5, 2H), 2.51-2.48 (m, 2H), 1.41 (q, J = 7.4, 2H), 0.84 (t, J = 7.3, 3H).

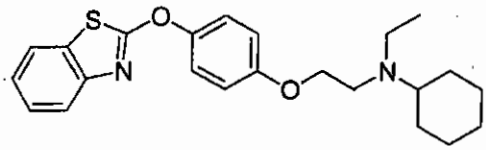
EXAMPLE 70



1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 17 using 4-phenyl-piperidin-4-ol. MS (ESI): mass calculated for $C_{26}H_{26}N_2O_3S$, 446.17; m/z found, 447.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.1, 1H), 7.66 (d, J = 7.4, 1H), 7.54 (d, J = 7.6, 2H), 7.42-7.35 (m, 3H), 7.33-7.22 (m, 4H), 6.99 (d, J = 9.0, 2H), 4.19 (t, J = 5.8, 2H), 2.98-2.86 (m, 4H), 2.65 (dt, J = 13.8, 2.1, 2H), 2.24 (dt, J = 13.4, 4.5, 2H), 1.80 (dd, J = 14.1, 2.2, 2H).

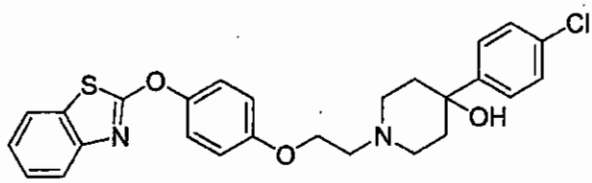
EXAMPLE 71



{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclohexyl-ethyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 17 using cyclohexyl-ethyl-amine. MS (ESI): mass calculated for $C_{23}H_{28}N_2O_2S$, 396.19; m/z found, 397.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.1, 1H), 7.65 (d, J = 7.9, 1H), 7.39 (t, J = 7.9, 4H), 7.30-7.20 (m, 4H), 6.96 (d, J = 8.9, 2H), 3.98 (t, J = 6.8, 2H), 2.89 (t, J = 6.8, 2H), 2.66 (q, J = 7.1, 2H), 2.55-2.50 (m, 1H), 1.82 (t, J = 7.7, 4H), 1.65 (d, J = 11.9, 1H), 1.30-1.18 (m, 4H), 1.09 (t, J = 7.2, 4H).

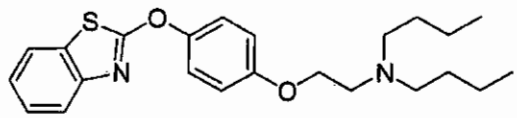
EXAMPLE 72



1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-(4-chloro-phenyl)-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 17 using 4-(4-chloro-phenyl)-piperidin-4-ol. MS (ESI): mass calculated for $C_{26}H_{25}ClN_3O_3S$, 480.13; m/z found, 481.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 7.6, 1H), 7.66 (dd, J = 7.9, 0.8, 1H), 7.49-7.45 (m, 2H), 7.41-7.22 (m, 6H), 7.01-6.97 (m, 2H), 4.18 (t, J = 5.8, 2H), 2.96-2.89 (m, 4H), 2.63 (dt, J = 12.1, 2.4, 2H), 2.21-2.14 (m, 2H), 1.79-1.74 (m, 2H), 1.56 (br s, 1H).

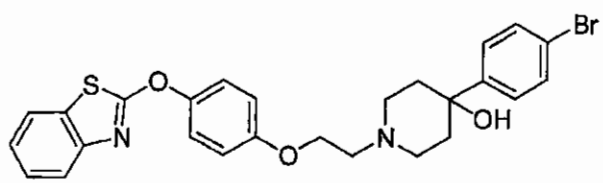
EXAMPLE 73



{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-dibutyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 17 using dibutyl-amine. MS (ESI): mass calculated for $C_{23}H_{30}N_2O_2S$, 398.20; m/z found, 399.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.63 (d, J = 8.1, 1H), 7.55 (d, J = 7.9, 1H), 7.28 (tt, J = 7.7, 1.3, 1H), 7.20-7.13 (m, 3H), 6.85 (d, J = 12.8, 2H), 3.96 (t, J = 5.6, 2H), 2.80 (m, 2H), 2.43 (m, 4H), 1.38 (m, 4H), 1.22 (m, 4H), 0.83 (t, J = 7.3 Hz, 6H).

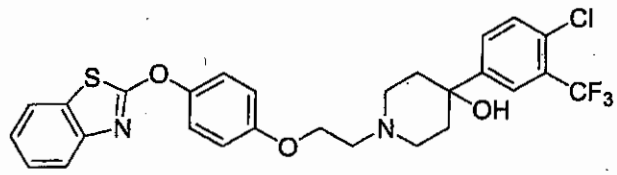
EXAMPLE 74



1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-(4-bromo-phenyl)-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 17 using 4-(4-bromo-phenyl)-piperidin-4-ol. MS (ESI): mass calculated for $C_{26}H_{25}BrN_2O_3S$, 524.08; m/z found, 525.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (dd, J = 8.0, 0.6, 1H), 7.67 (dd, J = 8.0, 0.8, 1H), 7.53-7.47 (m, 2H), 7.43-7.37 (m, 3H), 7.30-7.22 (m, 3H), 7.01-6.98 (m, 2H), 4.17 (t, J = 5.8, 2H), 2.94-2.89 (m, 4H), 2.63 (dt, J = 12.1, 2.5, 2H), 2.21-2.14 (m, 2H), 1.76 (dd, J = 14.22.6, 2H), 1.56 (br s, 1H).

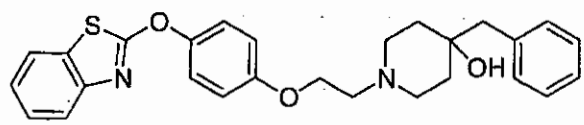
EXAMPLE 75



1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-(4-chloro-3-trifluoromethyl-phenyl)-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 17 using 4-(4-chloro-3-trifluoromethyl-phenyl)-piperidin-4-ol. MS (ESI): mass calculated for $C_{27}H_{24}ClF_3N_2O_3S$, 548.11; m/z found, 549.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.89 (d, J = 2.1, 1H), 7.62-7.48 (m, 4H), 7.41-7.37 (m, 1H), 7.30-7.24 (m, 3H), 7.01-6.97 (m, 2H), 4.17 (t, J = 5.8, 2H), 2.94-2.91 (m, 6H), 2.66-2.59 (m, 2H), 2.22-2.15 (m, 2H), 1.83 (br s, 1H).

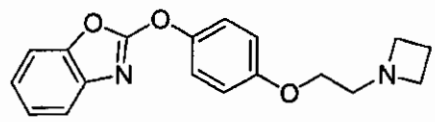
EXAMPLE 76



1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-benzyl-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 17 using 4-benzyl-piperidin-4-ol. MS (ESI): mass calculated for $C_{27}H_{28}N_2O_3S$, 460.18; m/z found, 461.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.0, 1H), 7.66 (d, J = 7.7, 1H), 7.41-7.23 (m, 9H), 6.99-6.94 (m, 2H), 4.13 (t, J = 5.9, 2H), 4.84 (t, J = 5.9, 2H), 2.78 (m, 4H), 2.50-2.45 (m, 2H), 1.83-1.76 (m, 2H), 1.59-1.52 (m, 2H), 1.23 (br s, 1H).

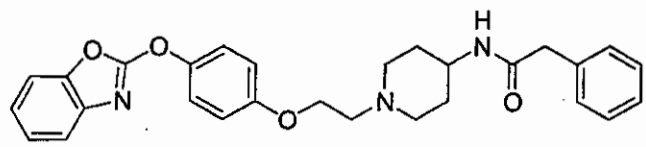
EXAMPLE 77



2-[4-(2-Azetidin-1-yl-ethoxy)-phenoxy]-benzooxazole.

The title compound was prepared according to the procedure for EXAMPLE 21 using azetidine. MS (ESI): mass calculated for $C_{18}H_{18}N_2O_3$, 310.13; m/z found, 311.2 [M+H]+. ^1H NMR (400 MHz, DMSO-d_6): 7.61 (d, J = 7.0, 2H), 7.48 (d, J = 7.0, 2H), 7.41 (d, J = 9.1, 2H), 7.32-7.24 (m, 2H), 7.00 (d, J = 6.9, 2H), 3.93 (t, J = 5.6, 2H), 3.18 (t, J = 6.9, 4H), 2.70 (t, J = 5.6, 2H), 1.97 (t, J = 6.9, 2H).

EXAMPLE 78

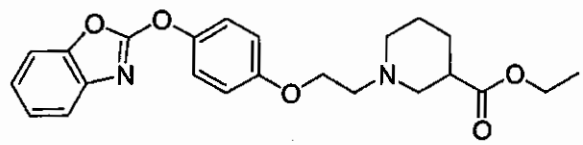


N-(1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-2-phenyl-acetamide.

The title compound was prepared according to the procedure for EXAMPLE 22 using 2-phenyl-N-piperidin-4-yl-acetamide and 2-chloro-benzooxazole. MS (ESI): mass calculated for $C_{28}H_{29}N_3O_4$, 471.22; m/z found, 472.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.55-7.51 (m, 1H), 7.47-7.43 (m, 1H), 7.41-7.23 (m, 9H), 7.00-6.95 (m, 2H), 5.28 (br d, J = 7.8, 1H), 4.10 (t, J = 5.7, 2H), 3.90-3.80

(m, 1H), 3.60 (s, 2H), 2.89 (br d, J = 11.5, 2H), 2.81 (t, J = 5.8, 2H), 2.28 (dt, J = 11.6, 2.2, 2H), 1.92 (br dd, J = 12.6, 2.3, 2H), 1.46-1.37 (m, 2H).

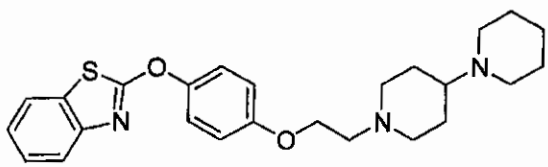
EXAMPLE 79



1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidine-3-carboxylic acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 22 using piperidine-3-carboxylic acid ethyl ester and 2-chloro-benzooxazole. MS (ESI): mass calculated for $C_{23}H_{26}N_2O_5$, 410.18; m/z found, 411.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.56-7.52 (m, 1H), 7.47-7.43 (m, 1H), 7.37-7.32 (m, 2H), 7.32-7.23 (m, 2H), 7.02-6.98 (m, 2H), 4.18 (q, J = 7.1, 2H), 4.15 (t, J = 5.9, 2H), 3.14 (br d, J = 8.2, 1H), 2.96-2.82 (m, 3H), 2.65 (tt, J = 10.6, 3.7, 1H), 2.37 (t, J = 10.7, 1H), 2.20 (dt, J = 10.9, 2.7, 1H), 2.03-1.97 (m, 1H), 1.82-1.75 (m, 1H), 1.73-1.60 (m, 1H), 1.54-1.45 (m, 1H) 1.30 (t, J = 7.2, 3H).

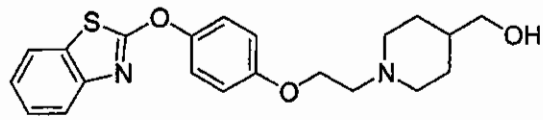
EXAMPLE 80



1'-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-[1,4']bipiperidine.

The title compound was prepared according to the procedure for EXAMPLE 22 using 4-piperidinyl-piperidine. MS (ESI): mass calculated for $C_{25}H_{31}N_3O_2S$, 437.21; m/z found, 438.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (d, J = 8.0, 1H), 7.69 (d, J = 7.0, 1H), 7.42 (dt, J = 7.1, 1.1, 1H), 7.35-7.26 (m, 3H), 7.04-6.97 (m, 2H), 4.15 (t, J = 5.9, 2H), 3.11 (br d, J = 11.7, 2H), 2.84 (t, J = 6.0, 2H), 2.57 (br s, 2H), 2.40-2.30 (m, 1H), 2.16 (dt, J = 11.7, 1.6, 1H), 1.85 (br d, J = 12.1, 2H), 1.75-1.59 (m, 8H), 1.52-1.40 (m, 2H).

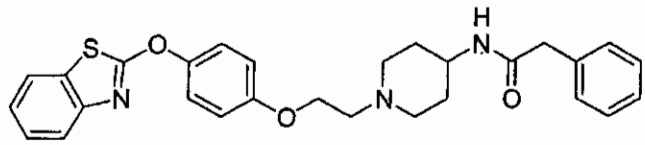
EXAMPLE 81



(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-methanol.

The title compound was prepared according to the procedure for EXAMPLE 17 using piperidin-4-yl-methanol. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_3S$, 384.15; m/z found, 385.1 $[M+H]^+$. ^1H NMR (500 MHz, $CDCl_3$): 7.75-7.73 (m, 1H), 7.67-7.65 (m, 1H), 7.41-7.37 (m, 1H), 7.31-7.36 (m, 3H), 6.98-6.95 (m, 2H), 4.13 (t, J = 5.9, 2H), 3.52 (t, J = 5.4, 2H), 3.10-3.03 (m, 2H), 2.83 (t, J = 5.9, 2H), 2.14 (dt, J = 11.8, 2.4, 2H), 1.78-1.75 (m, 2H), 1.58-1.52 (m, 2H), 1.37-1.30 (m, 2H).

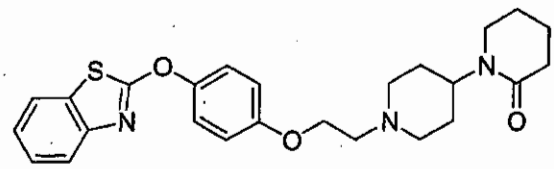
EXAMPLE 82



N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-2-phenyl-acetamide.

The title compound was prepared according to the procedure for EXAMPLE 22 using 2-phenyl-*N*-piperidin-4-yl-acetamide. MS (ESI): mass calculated for $C_{28}H_{29}N_3O_3S$, 487.19; m/z found, 488.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.78 (dd, J = 8.0, 0.6, 1H), 7.69 (dd, J = 7.9, 0.7, 1H), 7.45-7.24 (m, 9H), 7.00-6.88 (m, 2H), 5.33 (d, J = 7.9, 1H), 4.10 (t, J = 5.8, 2H), 3.90-3.79 (m, 1H), 3.60 (s, 2H), 2.88 (d, J = 11.7, 2H), 2.80 (t, J = 5.7, 2H), 2.27 (dt, J = 11.6, 2.2, 2H), 1.92 (dd, J = 12.7, 3.6, 2H), 1.39 (dq, J = 11.1, 3.8, 2H).

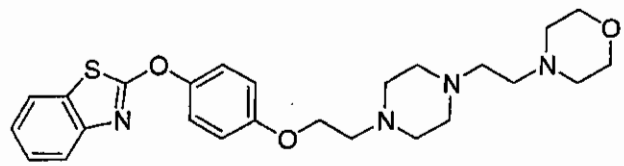
EXAMPLE 83



1'-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-[1,4']bipiperidinyl-2-one.

The title compound was prepared according to the procedure for EXAMPLE 22 using [1,4']bipiperidinyl-2-one. MS (ESI): mass calculated for $C_{25}H_{29}N_3O_3S$, 451.59; m/z found, 452.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.91 (d, J = 7.4, 1H), 7.67 (d, J = 7.4, 1H), 7.45-7.32 (m, 4H), 7.06 (d, J = 9.0, 2H), 4.35-4.15 (m, 1H), 4.10 (t, J = 5.7, 2H), 3.15 (t, J = 5.3, 2H), 3.00 (d, J = 11.5, 2H), 2.71 (t, J = 5.7, 2H), 2.21 (t, J = 6.5, 2H), 2.10 (t, J = 11.5, 2H), 1.75-1.60 (m, 6H), 1.43 (d, J = 10.0, 2H).

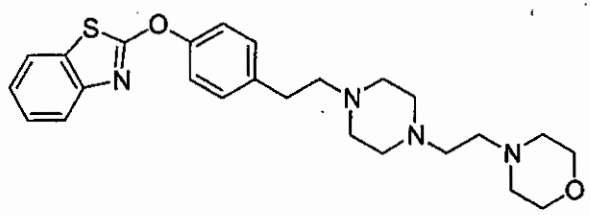
EXAMPLE 84



2-(4-{2-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-yl]-ethoxy}-phenoxy)-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 22 using 4-(2-piperazin-1-yl-ethyl)-morpholine. MS (ESI): mass calculated for $C_{25}H_{32}N_4O_3S$, 468.22; m/z found, 469.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.91 (d, J = 7.9, 1H), 7.67 (d, J = 7.9, 1H), 7.45-7.32 (m, 4H), 7.06 (d, J = 9.1, 2H), 4.09 (t, J = 5.8, 2H), 3.54 (t, J = 4.6, 2H), 2.68 (t, J = 5.7, 2H), 2.50-2.20 (br s, 16H).

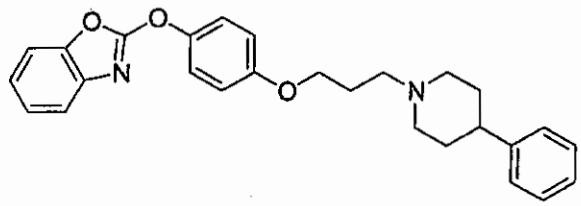
EXAMPLE 85



2-(4-{2-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-yl]-ethyl}-phenoxy)-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 32 using 4-(2-piperazin-1-yl-ethyl)-morpholine. MS (ESI): mass calculated for $C_{25}H_{32}N_4O_2S$, 452.22; m/z found, 453.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.92 (d, J = 8.0, 1H), 7.68 (d, J = 8.0, 1H), 7.45-7.30 (m, 6H), 3.54 (t, J = 4.5, 4H), 2.75 (t, J = 8.3, 4H), 2.50-2.20 (br s, 16H).

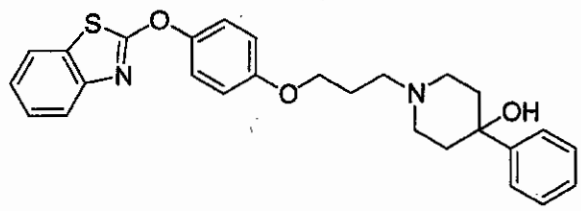
EXAMPLE 86



2-{4-[3-(4-Phenyl-piperidin-1-yl)-propoxy]-phenoxy}-benzooxazole.

The title compound was prepared according to the procedure for EXAMPLE 27 using 4-phenyl-piperidine. MS (ESI): mass calculated for $C_{27}H_{28}N_2O_3$, 428.21; m/z found, 429.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.40-7.38 (m, 1H), 7.34-7.32 (m, 1H), 7.24 (d, J = 9.1, 2H), 7.22-7.12 (m, 4H), 7.07 (t, J = 7.0, 1H), 6.94 (d, J = 9.1, 2H), 3.99 (t, J = 6.1, 2H), 3.06 (d, J = 11.7, 2H), 2.57 (t, J = 7.6, 2H), 2.49 (m, 1H), 2.13 (t, J = 11.6, 2H), 1.97 (m, 2H), 1.73 (m, 4H).

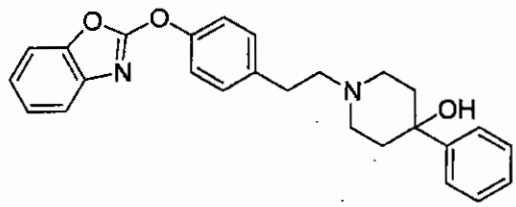
EXAMPLE 87



1-{3-[4-(Benzothiazol-2-yloxy)-phenoxy]-propyl}-4-phenyl-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 27 using 2-chlorobenzothiazole. MS (ESI): mass calculated for $C_{27}H_{28}N_2O_3S$, 460.18; m/z found, 461.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.1, 1H), 7.65 (d, J = 7.8, 1H), 7.53 (d, J = 8.2, 2H), 7.39-7.35 (m, 3H), 7.29-7.23 (m, 5H), 6.96 (d, J = 9.1, 2H), 4.08 (t, J = 6.2, 2H), 2.92 (m, 2H), 2.72-2.49 (m, 4H), 2.34-2.02 (m, 4H), 1.81 (d, J = 12.3, 2H).

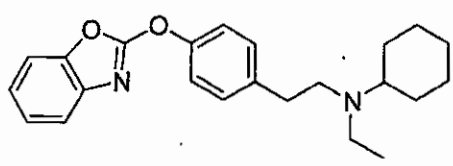
EXAMPLE 88



1-{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-4-phenyl-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 29 using 4-phenyl-piperidin-4-ol. MS (ESI): mass calculated for $C_{26}H_{26}N_2O_3$, 414.51; m/z found, 415.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.56-7.51 (m, 3H), 7.45-7.32 (m, 6H), 7.30-7.22 (m, 4H), 2.96-2.89 (m, 2H), 2.74-2.69 (m, 2H), 2.61-2.54 (m, 2H), 2.26-2.18 (m, 2H), 1.84-1.79 (m, 2H), 1.62 (br s, 1H).

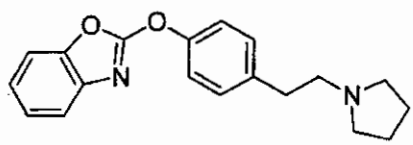
EXAMPLE 89



{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-cyclohexyl-ethyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 29 using cyclohexyl-ethyl-amine. MS (ESI): mass calculated for $C_{23}H_{28}N_2O_2$, 364.22; m/z found, 365.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.51 (d, J = 7.8, 1H), 7.41 (d, J = 7.6, 1H), 7.33-7.18 (m, 6H), 2.80-2.68 (m, 4H), 2.64 (dd, J = 6.8, 7.04, 2H), 2.58-2.50 (m 1H), 1.80 (t, J = 8.8, 4H), 1.63 (d, J = 12.3, 1H), 1.22 (dd, J = 9.8, 8.4, 4H), 1.08 (t, J = 7.0, 4H).

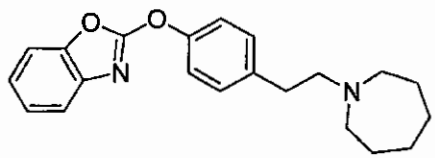
EXAMPLE 90



2-[4-(2-Pyrrolidin-1-yl-ethyl)-phenoxy]-benzooxazole.

The title compound was prepared according to the procedure for EXAMPLE 29 using pyrrolidine. MS (ESI): mass calculated for $C_{19}H_{20}N_2O_2$, 308.15; m/z found, 309.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.51 (d, J = 7.6, 1H), 7.42 (d, J = 7.2, 1H), 7.35-7.20 (m, 6H), 2.90-2.84 (m, 2H), 2.75-2.68 (m 2H), 2.62-2.55 (m, 4H), 1.85-1.79 (m, 4H).

EXAMPLE 91

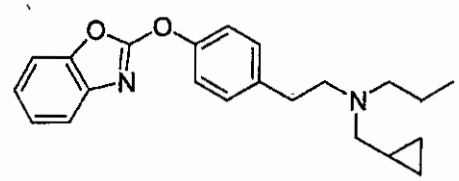


2-[4-(2-Azepan-1-yl-ethyl)-phenoxy]-benzooxazole.

The title compound was prepared according to the procedure for EXAMPLE 29 using azepane. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_2$, 336.18; m/z found, 337.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.50 (d, J = 7.6, 1H), 7.39

(d, J = 7.8, 1H), 7.33-7.17 (m, 6H), 2.84-2.73 (m, 4H), 2.71 (t, J = 5.3, 4H), 1.71-1.57 (m, 8H).

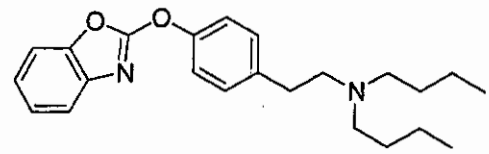
EXAMPLE 92



{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-propyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 29 using cyclopropylmethyl-propyl-amine. MS (ESI): mass calculated for $C_{22}H_{26}N_2O_2$, 350.20; m/z found, 351.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.50 (d, J = 7.6, 1H), 7.39 (d, J = 7.8, 1H), 7.33-7.17 (m, 6H), 2.85-2.74 (m, 4H), 2.56 (t, J = 7.6, 2H), 2.43 (d, J = 6.5, 2H), 1.56-1.44 (m, 2H), 0.90 (t, J = 7.2, 4H), 0.51 (dd, J = 7.8, 5.5, 2H), 0.13 (dd, J = 7.8, 5.5, 2H).

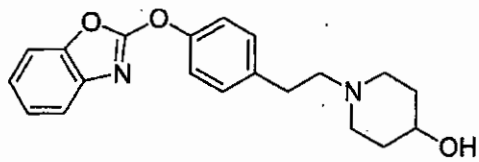
EXAMPLE 93



{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-dibutyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 29 using dibutyl-amine. MS (ESI): mass calculated for $C_{23}H_{30}N_2O_2$, 366.23; m/z found, 367.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.51 (d, J = 7.4, 1H), 7.39 (d, J = 7.6, 1H), 7.33-7.17 (m, 6H), 2.80-2.66 (m, 4H), 2.49 (t, J = 7.3, 4H), 1.50-1.40 (m, 4H), 1.37-1.26 (m, 4H), 0.93 (t, J = 7.2, 6H).

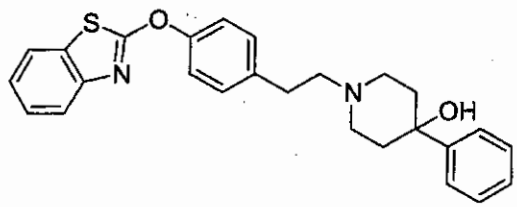
EXAMPLE 94



1-{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 29 using 4-hydroxypiperidine. MS (ESI): mass calculated for $C_{20}H_{22}N_2O_3$, 338.16; m/z found, 339.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.50 (d, J = 7.6, 1H), 7.39 (d, J = 7.6, 1H), 7.34-7.16 (m, 6H), 3.72-3.63 (m, 1H), 3.29 (br s, 1H), 2.91-2.78 (m, 4H), 2.63-2.56 (m, 2H), 2.21 (t, J = 10.0, 2H), 1.96-1.86 (m, 2H), 1.70-1.57 (m, 2H).

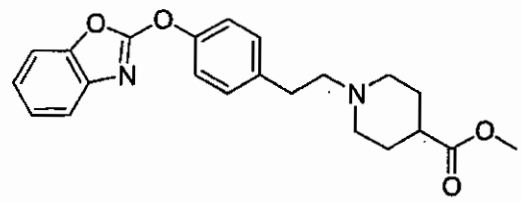
EXAMPLE 95



1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-4-phenyl-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 30 using 4-phenyl-piperidin-4-ol. MS (ESI): mass calculated for $C_{26}H_{26}N_2O_3S$, 430.57; m/z found, 431.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.76-7.74 (m, 1H), 7.67 (dd, J = 8.0, 0.7, 1H), 7.56-7.53 (m, 2H), 7.42-7.36 (m, 3H), 7.33-7.26 (m, 6H), 2.96-2.86 (m, 4H), 2.75-7.71 (m, 2H), 2.64-2.56 (m, 2H) 2.27-2.18 (m, 2H), 1.86-1.80 (m, 2H), 1.67-1.66 (br m, 2H).

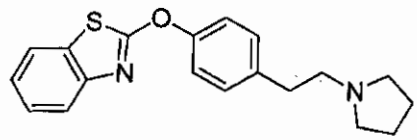
EXAMPLE 96



1-{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid methyl ester.

The title compound was prepared according to the procedure for EXAMPLE 29 using piperidine-4-carboxylic acid methyl ester. MS (ESI): mass calculated for $C_{22}H_{24}N_2O_4$, 380.17; m/z found, 381.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.50 (d, J = 8.1, 1H), 7.39 (d, J = 8.1, 1H), 7.34-7.16 (m, 6H), 3.67 (s, 3H), 2.97-2.90 (m, 2H), 2.84-2.78 (m, 2H), 2.60-2.55 (m, 2H), 2.35-2.25 (m, 1H), 2.10 (t, J = 11.4, 2H), 1.96-1.88 (m, 2H), 1.84-1.73 (m, 2H).

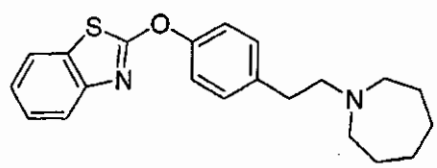
EXAMPLE 97



2-[4-(2-Pyrrolidin-1-yl-ethyl)-phenoxy]-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 30 using pyrrolidine. MS (ESI): mass calculated for $C_{19}H_{20}N_2OS$, 324.13; m/z found, 325.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.0, 1H), 7.65 (d, J = 8.0, 1H), 7.38 (t, J = 7.2, 1H), 7.31-7.22 (m, 5H), 2.91-2.83 (m, 2H), 2.77-2.69 (m 2H), 2.64-2.55 (m, 4H), 1.87-1.77 (m, 4H).

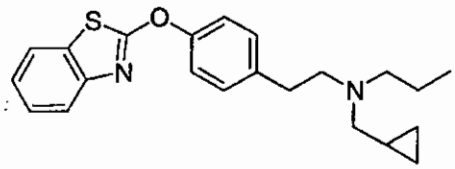
EXAMPLE 98



2-[4-(2-Azepan-1-yl-ethyl)-phenoxy]-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 30 using azepane. MS (ESI): mass calculated for $C_{21}H_{24}N_2OS$, 352.16; m/z found, 353.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.0, 1H), 7.65 (d, J = 8.0, 1H), 7.37 (t, J = 7.4, 1H), 7.30-7.22 (m, 5H), 2.87-2.70 (m, 8H), 1.73-1.57 (m, 8H).

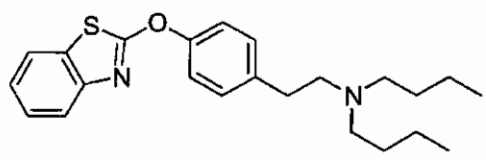
EXAMPLE 99



{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-propyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 30 using cyclopropylmethyl-propyl-amine. MS (ESI): mass calculated for $C_{22}H_{26}N_2OS$, 366.18; m/z found, 367.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.6, 1H), 7.65 (d, J = 8.2, 1H), 7.38 (t, J = 8.6, 1H), 7.30-7.22 (m, 5H), 2.87-2.76 (m, 4H), 2.57 (t, J = 7.6, 2H), 2.44 (d, J = 6.5, 2H), 1.56-1.45 (m, 2H), 0.90 (t, J = 7.4, 4H), 0.52 (dd, J = 7.8, 5.5, 2H), 0.14 (dd, J = 5.7, 5.1, 2H).

EXAMPLE 100

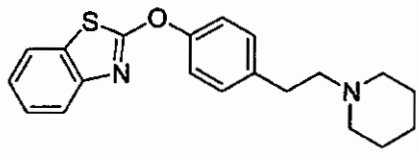


{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-dibutyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 30 using dibutyl-amine. MS (ESI): mass calculated for $C_{23}H_{30}N_2OS$, 382.21; m/z found, 383.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.2, 1H), 7.65

(d, J = 8.2, 1H), 7.38 (t, J = 8.2, 1H), 7.30-7.22 (m, 5H), 2.82-2.67 (m, 4H), 2.51 (t, J = 7.2, 4H), 1.50-1.40 (m, 4H), 1.37-1.25 (m, 4H), 0.93 (t, J = 7.2, 6H).

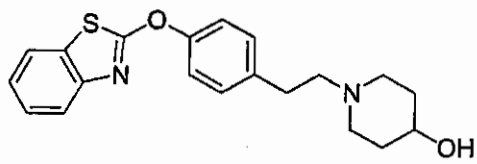
EXAMPLE 101



2-[4-(2-Piperidin-1-yl-ethyl)-phenoxy]-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 30 using piperidine. MS (ESI): mass calculated for $C_{20}H_{22}N_2OS$, 338.48; m/z found, 339.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.76-7.73 (m, 1H), 7.64-7.61 (m, 1H), 7.42-7.25 (m, 6H), 2.88-2.83 (m, 2H), 2.60-2.52 (m, 6H), 1.66-1.61 (m, 4H), 1.53-1.45 (m, 2H).

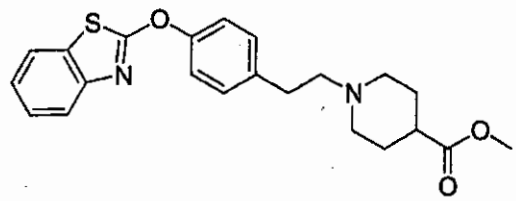
EXAMPLE 102



1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 30 using 4-hydroxypiperidine. MS (ESI): mass calculated for $C_{20}H_{22}N_2O_2S$, 354.14; m/z found, 355.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.2, 1H), 7.64 (d, J = 8.0, 1H), 7.37 (t, J = 8.2, 1H), 7.29-7.20 (m, 5H), 3.75-3.65 (m, 1H), 2.92-2.79 (m, 4H), 2.76 (br s, 1H), 2.65-2.55 (m, 2H), 2.21 (t, J = 10.0, 2H), 1.98-1.87 (m, 2H), 1.70-1.57 (m, 2H).

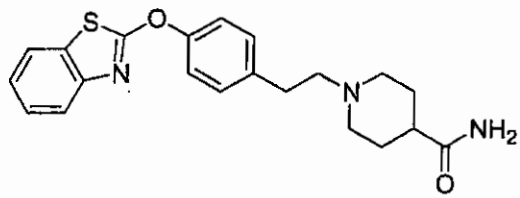
EXAMPLE 103



1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid methyl ester.

The title compound was prepared according to the procedure for EXAMPLE 30 using piperidine-4-carboxylic acid methyl ester. MS (ESI): mass calculated for $C_{22}H_{24}N_2O_3S$, 396.15; m/z found, 397.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.3, 1H), 7.66 (d, J = 8.3, 1H), 7.38 (t, J = 8.3, 1H), 7.29-7.23 (m, 5H), 3.69 (s, 3H), 3.00-2.93 (m, 2H), 2.87-2.80 (m, 2H), 2.63-2.56 (m, 2H), 2.38-2.28 (m, 1H), 2.11 (t, J = 11.1, 2H), 1.98-1.91 (m, 2H), 1.86-1.74 (m, 2H).

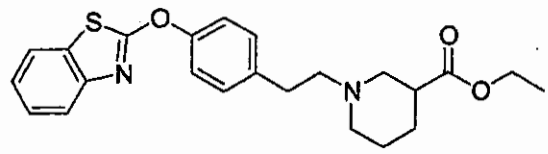
EXAMPLE 104



1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid amide.

The title compound was prepared according to the procedure for EXAMPLE 31 using piperidine-4-carboxylic acid amide. MS (ESI): mass calculated for $C_{21}H_{23}N_3O2S$, 381.15; m/z found, 382.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.78 (dd, J = 8.1, 0.4, 1H), 7.71 (dd, J = 7.9, 0.7, 1H), 7.43 (dt, J = 7.5, 2.3, 1H), 7.35-7.25 (m, 5H), 5.51 (br d, J = 26.0, 1H), 3.09 (br d, J = 11.7, 2H), 2.87, (dd, J = 8.3, 7.6, 2H), 2.65 (dd, J = 8.5, 5.4, 2H), 2.29-2.18 (m, 1H), 2.13 (t, J = 11.4, 2H), 1.98 (br d, J = 11.2, 2H), 1.87-1.77 (m, 2H).

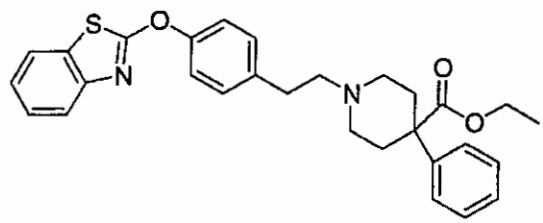
EXAMPLE 105



1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-3-carboxylic acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 31 using piperidine-3-carboxylic acid ethyl ester. MS (ESI): mass calculated for $C_{23}H_{26}N_2O_3S$, 410.17; m/z found, 411.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (d, J = 8.0, 1H), 7.70 (dd, J = 7.9, 0.5, 1H), 7.42 (dt, J = 7.5, 1.3, 1H), 7.34-7.27 (m, 5H), 4.18 (q, J = 7.1, 2H), 3.13 (br d, J = 8.8, 1H), 2.92-2.85 (m, 2H), 2.70-2.59 (m, 2H), 2.30 (t, J = 10.7, 1H), 2.13 (dt, J = 10.9, 2.7, 1H), 2.04-1.97 (m, 1H), 1.84-1.76 (m, 1H), 1.71-1.59 (m, 1H), 1.57-1.45 (m, 1H) 1.30 (t, J = 7.2, 3H).

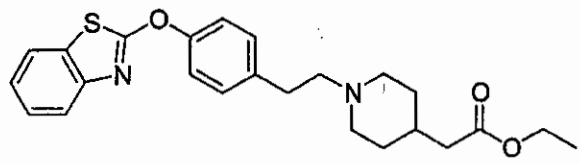
EXAMPLE 106



1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-4-phenyl-piperidine-4-carboxylic acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 31 using 4-phenyl-piperidine-4-carboxylic acid ethyl ester. MS (ESI): mass calculated for $C_{29}H_{30}N_2O_3S$, 486.20; m/z found, 487.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.78 (dd, J = 8.1, 0.5, 1H), 7.70 (dd, J = 7.9, 0.7, 1H), 7.46-7.24 (m, 11H), 4.19 (q, J = 7.1, 2H), 3.06 (br d, J = 10.1, 2H), 2.96-2.90 (m, 2H), 2.75-2.64 (m, 4H), 2.35 (t, J = 11.0, 2H), 2.14, (t, J = 11.3, 2H), 1.24, (t, J = 7.3, 3H).

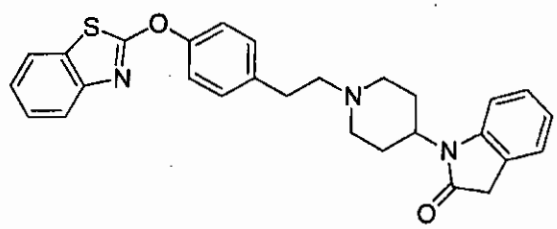
EXAMPLE 107



(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-acetic acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 31 using piperidin-4-yl-acetic acid ethyl ester. MS (ESI): mass calculated for $C_{24}H_{28}N_2O_3S$, 424.18; m/z found, 425.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.76 (d, J = 7.8, 1H), 7.70 (dd, J = 7.9, 0.6, 1H), 7.41 (dt, J = 7.2, 1.2, 1H), 7.36-7.27 (m, 5H), 4.18 (q, J = 5.3, 2H), 3.21 (d, J = 11.3, 2H), 3.03-2.99, (m, 2H), 2.83-2.78 (m, 2H), 2.33-2.25 (m, 4H), 2.00-1.87 (m, 1H), 1.86 (d, J = 14.3, 2H), 1.67-1.55 (m, 2H), 1.29 (t, J = 7.1, 3H).

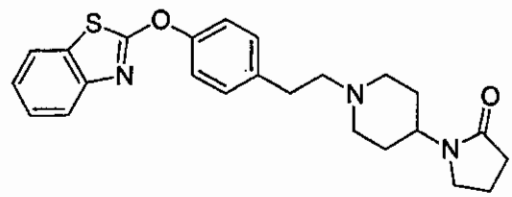
EXAMPLE 108



1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one.

The title compound was prepared according to the procedure for EXAMPLE 31 using 1-piperidin-4-yl-1,3-dihydro-indol-2-one. MS (ESI): mass calculated for $C_{28}H_{27}N_3O_2S$, 469.18; m/z found, 470.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.75 (dd, J = 8.1, 0.4, 1H), 7.68 (dd, J = 7.9, 0.6, 1H), 7.40 (dt, J = 7.5, 1.2, 1H), 7.36-7.23 (m, 8H), 7.04 (dt, J = 7.3, 1.7, 1H), 4.57-4.45 (m, 1H), 3.54 (s, 2H), 3.36 (br d, J = 10.9, 2H), 3.00 (dd, J = 11.4, 6.3, 1H), 2.88 (dd, J = 8.8, 4.5, 2H), 2.75-2.62 (m, 2H), 2.45 (t, J = 11.5, 2H), 1.80 (dd, J = 12.3, 2.1, 2H).

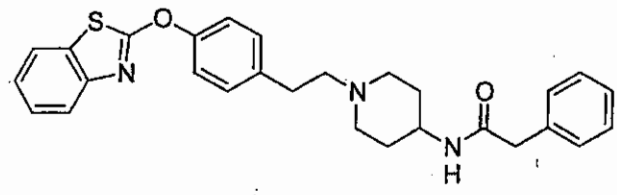
EXAMPLE 109



1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-pyrrolidin-2-one.

The title compound was prepared according to the procedure for EXAMPLE 31 using 1-piperidin-4-yl-pyrrolidin-2-one. MS (ESI): mass calculated for $C_{24}H_{27}N_3O_2S$, 421.18; m/z found, 422.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.76 (d, J = 8.0, 1H), 7.69 (dd, J = 8.0, 0.9, 1H), 7.41 (dt, J = 7.5, 1.2, 1H), 7.32-7.27 (m, 5H), 4.05 (dt, J = 11.9, 4.5, 1H), 3.40 (t, J = 7.0, 2H), 3.10 (br d, J = 11.7, 2H), 2.86 (dd, J = 11.0, 7.7, 2H), 2.66 (dd, J = 8.8, 5.3, 2H), 2.43 (t, J = 8.1, 2H), 2.19 (dt, J = 11.6, 2.8, 2H), 2.09-2.00 (m, 2H), 1.85-1.69 (m, 4H).

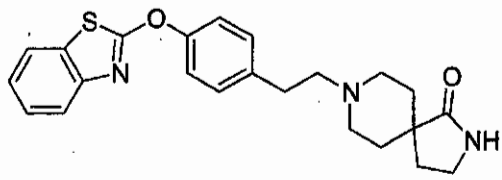
EXAMPLE 110



N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-2-phenyl-acetamide.

The title compound was prepared according to the procedure for EXAMPLE 31 using 2-phenyl-*N*-piperidin-4-yl-acetamide. MS (ESI): mass calculated for $C_{28}H_{29}N_3O_2S$, 471.20; m/z found, 472.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (dd J = 8.1, 0.5, 1H), 7.70 (dd, J = 7.8, 0.7, 1H), 7.45-7.37 (m, 3H), 7.36-7.26 (m, 8H), 5.39 (br d, J = 7.9, 1H), 3.93-3.82 (m, 1H), 3.60 (s, 2H), 2.93 (br d, J = 11.1, 2H), 2.86 (dd, J = 10.9, 7.6, 2H), 2.65 (dd, J = 8.5, 5.2, 2H), 2.25 (t, J = 11.2, 2H), 1.95 (dd, J = 12.8, 3.3, 2H), 1.47 (m, 2H).

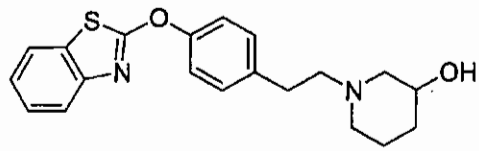
EXAMPLE 111



8-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-2,8-diaza-spiro[4.5]decan-1-one.

The title compound was prepared according to the procedure for EXAMPLE 31 using 2,8-diaza-spiro[4.5]decan-1-one. MS (ESI): mass calculated for $C_{23}H_{25}N_3O_2S$, 407.17; m/z found, 408.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.78 (d, J = 8.1, 1H), 7.70 (dd, J = 7.8, 0.6, 1H), 7.42 (dt, J = 7.6, 1.3, 1H), 7.35-7.25 (m, 5H), 6.40 (br s, 1H), 3.40 (t, J = 6.9, 2H), 3.00 (dt, J = 11.6, 3.6, 2H), 2.88 (dd, J = 10.3, 7.4, 2H), 2.67 (dd, J = 8.5, 5.7, 2H), 2.23 (t, J = 10.7, 2H), 2.10-2.00 (m, 4H), 1.52 (br d, J = 13.1, 2H).

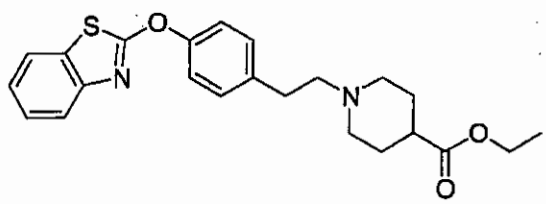
EXAMPLE 112



1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-3-ol.

The title compound was prepared according to the procedure for EXAMPLE 31 using 3-hydroxypiperidine. MS (ESI): mass calculated for $C_{20}H_{22}N_2O_2S$, 354.14; m/z found, 355.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (d, J = 7.6, 1H), 7.70 (dd, J = 8.0, 0.8, 1H), 7.42 (dt, J = 7.5, 1.2, 1H), 7.35-7.28 (m, 5H), 3.89 (m, 1H), 2.89 (dd, J = 10.1, 7.3, 2H), 2.71-2.65 (m, 2H), 2.64-2.54 (m, 2H), 2.53-2.36 (m, 3H), 1.92-1.80 (m, 1H), 1.74-1.55 (m, 3H).

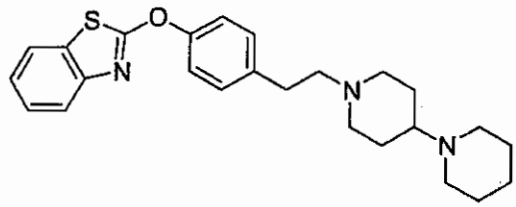
EXAMPLE 113



1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 31 using piperidine-3-carboxylic acid ethyl ester. MS (ESI): mass calculated for $C_{23}H_{26}N_2O_3S$, 410.17; m/z found, 411.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (d, J = 8.0, 1H), 7.69 (dd, J = 7.9, 0.7, 1H), 7.41 (dt, J = 7.5, 1.2, 1H), 7.32-7.27 (m, 5H), 4.18 (q, J = 7.1, 2H), 3.00 (br d, J = 11.5, 2H), 2.88 (dd, J = 10.9, 7.7, 2H), 2.64 (dd, J = 8.5, 5.3, 2H), 2.35 (tt, J = 10.9, 4.3, 1H), 2.14, (t, J = 10.9, 2H), 2.02-1.94 (m, 2H), 1.90-1.78 (m, 2H), 1.30 (t, J = 7.3, 3H).

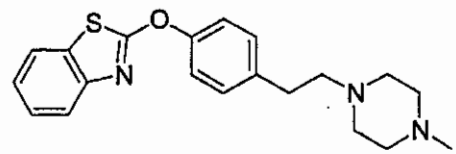
EXAMPLE 114



1'-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-[1,4']bipiperidine.

The title compound was prepared according to the procedure for EXAMPLE 31 using 4-piperidinyl-piperidine. MS (ESI): mass calculated for $C_{25}H_{31}N_3OS$, 421.22; m/z found, 422.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.75 (d, J = 7.8, 1H), 7.69 (dd, J = 7.8, 0.6, 1H), 7.41 (dt, J = 7.6, 1.2, 1H), 7.33-7.25 (m, 5H), 3.15 (br d, J = 11.6, 2H), 2.90-2.70 (m, 7H) 2.65 (dd, J = 8.5, 5.3, 2H), 2.18-2.06 (m, 4H), 1.99-1.87 (m, 4H), 1.85-1.75 (m, 2H), 1.64-1.56 (m, 2H).

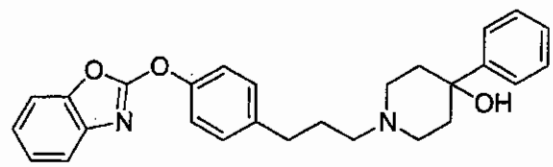
EXAMPLE 115



2-{4-[2-(4-Methyl-piperazin-1-yl)-ethyl]-phenoxy}-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 32 using 1-methyl-piperazine. MS (ESI): mass calculated for $C_{20}H_{23}N_3OS$, 353.16; m/z found, 354.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.77 (d, J = 8.01, 1H), 7.64 (d, J = 8.1, 1H), 7.41 (t, J = 8.2, 1H), 7.37 (d, J = 8.6, 2H), 7.32-7.28 (m, 3H), 2.81-2.35 (m, 8H), 2.87 (m, 2H), 2.65 (m, 2H), 2.30 (s, 3H).

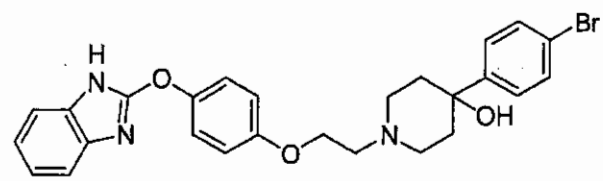
EXAMPLE 116



1-{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-4-phenyl-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 35 using 4-phenyl-piperidin-4-ol. MS (ESI): mass calculated for $C_{27}H_{28}N_2O_3$, 428.21; m/z found, 429.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.48 (d, J = 8.4, 1H), 7.45 (m, 11H), 7.19 (t, J = 8.3, 1H), 4.76 (s, 1H), 2.66 (t, J = 7.6, 4H), 2.45 (m, 4H), 1.92 (t, J = 7.1, 2H), 1.78 (t, J = 7.1, 2H), 1.58 (d, J = 12.3, 2H).

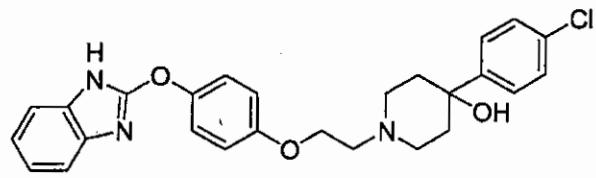
EXAMPLE 117



1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-4-(4-bromo-phenyl)-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 37 using 4-(4-bromo-phenyl)-piperidin-4-ol. MS (ESI): mass calculated for $C_{26}H_{26}BrN_3O_3$, 507.12; m/z found, 508.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.43-7.07 (m, 10H), 6.94-6.89 (m, 2H), 4.11 (t, J = 5.8, 2H), 2.87-2.83 (m, 4H), 2.65-2.58 (m, 2H), 2.13-2.05 (m, 2H), 1.75-1.68 (m, 2H).

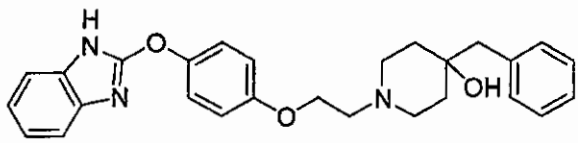
EXAMPLE 118



1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-4-(4-chloro-phenyl)-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 37 using 4-(4-chloro-phenyl)-piperidin-4-ol. MS (ESI): mass calculated for $C_{26}H_{26}ClN_3O_3$, 463.17; m/z found, 464.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.38-7.22 (m, 6H), 7.17-7.12 (m, 2H), 7.09-7.04 (m, 2H), 6.91-6.81 (m, 2H), 4.08 (t, J = 5.6, 2H), 2.84-2.80 (m, 4H), 2.62 (t, J = 11.8, 2H), 2.09-2.02 (m, 2H), 1.70-1.65 (m, 2H).

EXAMPLE 119

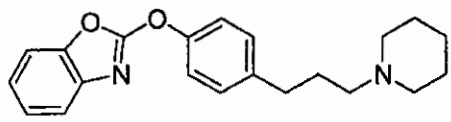


1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-4-benzyl-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 37 using 4-benzyl-piperidin-4-ol. MS (ESI): mass calculated for $C_{27}H_{29}N_3O_3$, 443.22; m/z found, 444.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.53 (br s, 1H),

7.34-7.24 (m, 4H), 7.26-7.16 (m, 7H), 6.91-6.85 (m, 2H), 4.08 (t, J = 5.8, 2H), 2.85-2.77 (m, 6H), 2.48 (dt, J = 2.5, 11.7, 2H), 1.84-1.76 (m, 2H), 1.56 (m, 2H).

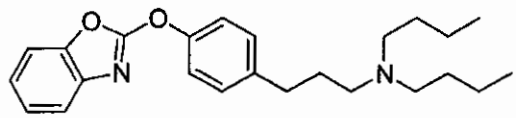
EXAMPLE 120



2-[4-(3-Piperidin-1-yl-propyl)-phenoxy]-benzooxazole.

The title compound was prepared according to the procedure for EXAMPLE 35 using piperidine. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_2$, 336.18; m/z found, 337.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.62 (dd, J = 5.7, 2.1, 1H), 7.50 (dd, J = 6.1, 2.1, 1H), 7.45-7.35 (m, 2H), 7.35-7.25 (m, 4H), 2.62 (t, J = 7.6, 2H), 2.30 (s, 4H), 2.25 (t, J = 7.4, 2H), 1.80-1.70 (m, 2H), 1.55-1.45 (m, 4H), 1.42-1.35 (m, 2H).

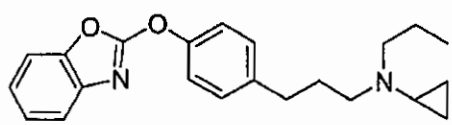
EXAMPLE 121



{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-dibutyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 35 using dibutyl-amine. MS (ESI): mass calculated for $C_{24}H_{32}N_2O_2$, 380.25; m/z found, 381.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.63 (dd, J = 6.1, 2.1, 1H), 7.50 (dd, J = 6.1, 2.1, 1H), 7.40 (d, J = 8.6, 2H), 2.63 (t, J = 7.7, 2H), 2.50-2.30 (m, 6H), 1.70 (quint, J = 7.2, 2H), 1.40-1.20 (m, 8H), 0.88 (t, J = 7.1, 6H).

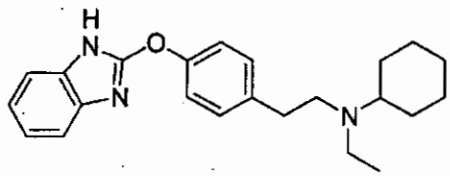
EXAMPLE 122



{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-cyclopropylmethyl-propyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 35 using cyclopropylmethyl-propyl-amine. MS (ESI): mass calculated for $C_{23}H_{28}N_2O_2$, 364.22; m/z found, 365.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.63 (d, J = 8.6, 1H), 7.40 (d, J = 8.6, 1H), 7.32 (d, J = 8.5, 2H), 7.30-7.25 (m, 4H), 2.63 (t, J = 7.6, 2H), 2.41 (t, J = 7.2, 2H), 2.28 (d, J = 6.3, 2H), 1.71 (quint, J = 7.2, 2H), 1.38 (q, J = 7.2, 2H), 0.85 (t, J = 7.3, 2H), 0.88-0.77 (m, 2H), 0.42 (d, J = 4.2, 2H), 0.05 (d, J = 4.8, 2H).

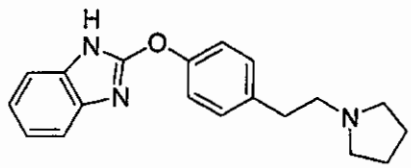
EXAMPLE 123



{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-cyclohexyl-ethyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 38 using cyclohexyl-ethyl-amine. MS (ESI): mass calculated for $C_{23}H_{29}N_3O$, 363.23; m/z found, 364.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 11.44 (br s, 1H), 7.43-7.33 (m, 2H), 7.13-7.05 (m, 6H), 3.17 (t, J = 11.7, 1H), 3.10 (dd, J = 7.0, 7.0, 2H), 2.99-2.83 (m, 4H), 2.06 (d, J =9.8, 2H), 1.89 (d, J = 12.5, 2H), 1.69 (d, J = 12.5, 1H), 1.49-1.22 (m, 7H), 1.19-1.05 (m, 1H).

EXAMPLE 124

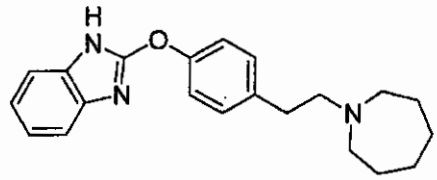


2-[4-(2-Pyrrolidin-1-yl-ethyl)-phenoxy]-1*H*-benzoimidazole.

The title compound was prepared according to the procedure for EXAMPLE 38 using pyrrolidine. MS (ESI): mass calculated for $C_{19}H_{21}N_3O$, 307.17; m/z

found, 308.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.35-7.22 (m, 2H), 7.14-7.04 (m, 6H), 2.79-2.72 (m, 2H), 2.67-2.57 (m, 6H), 1.87-1.77 (m, 4H).

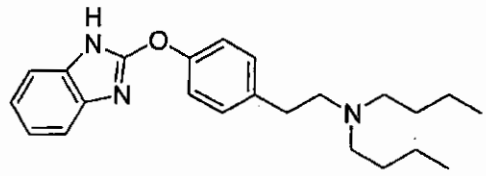
EXAMPLE 125



2-[4-(2-Azepan-1-yl-ethyl)-phenoxy]-1*H*-benzoimidazole.

The title compound was prepared according to the procedure for EXAMPLE 38 using azepane. MS (ESI): mass calculated for $C_{21}H_{25}N_3O$, 335.20; m/z found, 336.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.38 (dd, *J* = 3.1, 2.7, 2H), 7.11 (dd, *J* = 3.1, 2.9, 2H), 7.10-7.00 (m, 4H), 3.25-3.15 (m, 4H), 3.06 (dd, *J* = 6.3, 5.3, 2H), 2.93 (dd, *J* = 6.1, 4.3, 2H), 2.00-1.91 (m, 4H), 1.75-1.67 (m, 4H).

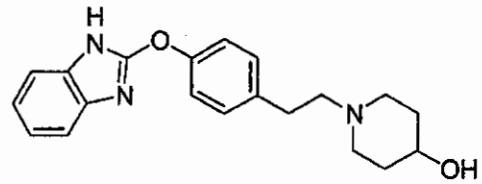
EXAMPLE 126



{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-dibutyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 38 using dibutyl-amine. MS (ESI): mass calculated for $C_{23}H_{31}N_3O$, 365.25; m/z found, 366.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.40-7.29 (m, 2H), 7.17-7.06 (m, 6H), 2.83-2.60 (m, 8H), 1.59-1.47 (m, 4H), 1.38-1.26 (m, 4H), 0.93 (t, *J* = 7.2, 6H).

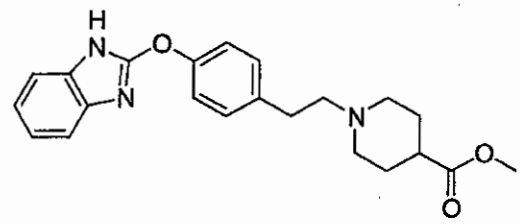
EXAMPLE 127



1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 38 using 4-hydroxypiperidine. MS (ESI): mass calculated for $C_{20}H_{23}N_3O_2$, 337.18; m/z found, 338.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 11.70 (br s, 1H), 7.50-7.44 (m, 1H), 7.33-7.27 (m, 1H), 7.24 (br s, 4H), 7.14-7.07 (m, 2H), 3.93 (br s, 1H), 3.68-3.58 (m, 1H), 2.97-2.75 (m, 4H), 2.63-2.52 (m, 2H), 2.19 (t, J = 9.8, 2H), 1.94-1.84 (m, 2H), 1.65-1.54 (m, 2H).

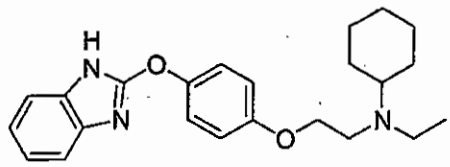
EXAMPLE 128



1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid methyl ester.

The title compound was prepared according to the procedure for EXAMPLE 38 using piperidine-4-carboxylic acid methyl ester. MS (ESI): mass calculated for $C_{22}H_{25}N_3O_3$, 379.19; m/z found, 380.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 11.76 (br s, 1H), 7.50-7.44 (m, 1H), 7.24-7.06 (m, 7H), 3.68 (s, 3H), 3.00-2.92 (m, 2H), 2.77-2.70 (m, 2H), 2.53-2.46 (m, 2H), 2.38-2.28 (m, 1H), 2.10 (t, J = 11.1, 2H), 1.98-1.90 (m, 2H), 1.86-1.74 (m, 2H).

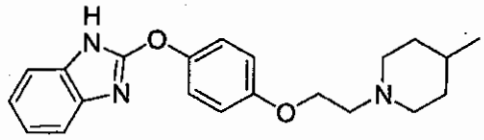
EXAMPLE 129



{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-cyclohexyl-ethyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 37 using cyclohexyl-ethyl-amine. MS (ESI): mass calculated for $C_{23}H_{29}N_3O_2$, 379.23; m/z found, 380.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.23 (s, 1H), 7.34-7.25 (m, 4H), 7.07 (d, J = 3.5, 2H), 6.98 (d, J = 9.0, 2H), 3.94 (t, J = 6.4, 2H), 2.80 (t, J = 6.4, 2H), 2.57 (d, J = 7.1, 2H), 2.50 (s, 2H), 1.72 (d, J = 7.8, 2H), 1.55 (s, 1H), 1.20 (t, J = 9.0, 4H), 0.99 (t J = 7.1, 3H).

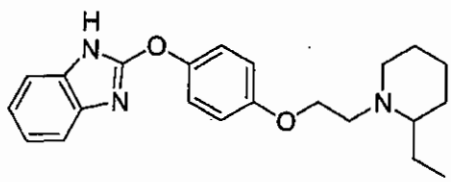
EXAMPLE 130



2-{4-[2-(4-Methyl-piperidin-1-yl)-ethoxy]-phenoxy}-1*H*-benzoimidazole.

The title compound was prepared according to the procedure for EXAMPLE 35 using 4-methyl-piperidine. MS (ESI): mass calculated for $C_{21}H_{25}N_3O_2$, 351.19; m/z found, 352.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.30 (s, 1H), 7.34-7.25 (m, 4H), 7.08 (d, J = 3.8, 2H), 6.99 (d, J = 9.0, 2H), 4.08 (t, J = 5.8, 2H), 2.89 (d, J = 11.4, 2H), 2.67 (t, J = 5.8, 2H), 2.00 (t, J = 11.4, 2H), 1.56 (d, J = 11.5, 2H), 1.36-1.25 (m, 1H), 1.21- 1.08 (m, 2H), 0.88 (d, J = 6.4, 3H).

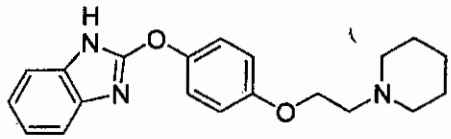
EXAMPLE 131



2-{4-[2-(2-Ethyl-piperidin-1-yl)-ethoxy]-phenoxy}-1*H*-benzoimidazole.

The title compound was prepared according to the procedure for EXAMPLE 37 using 2-ethyl-piperidine. MS (ESI): mass calculated for $C_{22}H_{27}N_3O_2$, 365.21; m/z found, 366.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.28 (s, 1H), 7.32-7.25 (m, 4H), 7.08 (d, J = 3.8, 2H), 6.99 (d, J = 8.4, 2H), 4.05 (t, J = 6.1, 2H), 3.00-2.92 (m, 1H), 2.91-2.85 (m, 1H), 2.72-2.64 (m, 1H), 2.38-2.20 (m, 2H), 1.67-1.36 (m, 6H), 1.35-1.19 (m, 2H), 0.84 (t, J = 7.5, 3H).

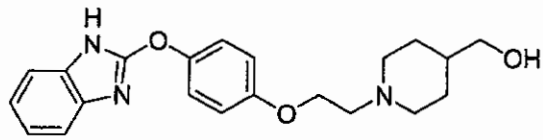
EXAMPLE 132



2-[4-(2-Piperidin-1-yl-ethoxy)-phenoxy]-1*H*-benzoimidazole.

The title compound was prepared according to the procedure for EXAMPLE 37 using piperidine. MS (ESI): mass calculated for $C_{20}H_{23}N_3O_2$, 337.18; m/z found, 338.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.25 (br s, 1H), 7.35-7.25 (m, 4H), 7.10-7.00 (m, 2H), 6.99 (d, J = 9.0, 2H), 4.07 (t, J = 5.9, 2H), 2.79 (t, J = 5.9, 2H), 2.43 (s, 4H), 1.55-1.45 (m, 4H), 1.38 (s, 2H).

EXAMPLE 133

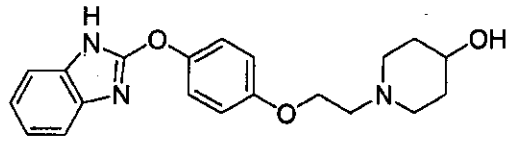


(1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-methanol.

The title compound was prepared according to the procedure for EXAMPLE 35 using piperidin-4-yl-methanol. MS (ESI): mass calculated for $C_{21}H_{25}N_3O_3$, 367.19; m/z found, 368.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.24 (s, 1H), 7.35-7.25 (m, 4H), 7.01 (s, 2H), 6.99 (d, J = 7.1, 2H), 4.40 (s, 1H), 4.10 (t,

J = 5.7, 2H), 3.25 (t, *J* = 5.4, 2H), 2.93 (d, *J* = 11.1, 2H), 2.67 (t, *J* = 5.6, 2H), 1.98 (t, *J* = 11.6, 2H), 1.63 (d, *J* = 11.6, 2H), 1.28 (s, 1H), 1.12 (d, *J* = 9.1, 2H).

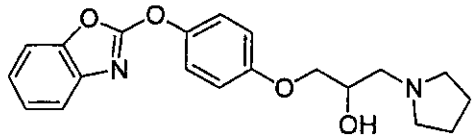
EXAMPLE 134



1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 37 using 4-hydroxypiperidine. MS (ESI): mass calculated for $C_{20}H_{23}N_3O_3$, 353.17; m/z found, 354.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.24 (s, 1H), 7.35-7.25 (m, 4H), 7.07 (d, *J* = 9.0, 2H), 6.99 (d, *J* = 9.0, 2H), 4.40 (s, 1H), 4.08 (t, *J* = 5.8, 2H), 2.53 (s, 1H), 2.78 (d, *J* = 11.2, 2H), 2.66 (t, *J* = 5.8, 2H), 2.12 (t, *J* = 10.3, 2H), 1.70 (d, *J* = 9.1, 2H), 1.38 (d, *J* = 9.9, 2H).

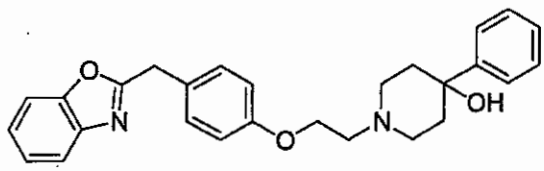
EXAMPLE 135



1-[4-(Benzooxazol-2-yloxy)-phenoxy]-3-pyrrolidin-1-yl-propan-2-ol.

The title compound was prepared according to the procedure for EXAMPLE 40 using pyrrolidine. MS (ESI): mass calculated for $C_{20}H_{22}N_2O_4$, 354.16; m/z found, 355.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.62 (dd, *J* = 6.2, 2.0, 1H), 7.50 (dd, *J* = 6.1, 2.1, 1H), 7.42 (d, *J* = 9.1, 2H), 7.35-7.25 (m, 2H), 7.03 (d, *J* = 9.1, 2H), 4.91 (d, *J* = 4.5, 1H), 4.05-4.00 (m, 1H), 4.00-3.85 (m, 2H), 2.70 (m, 1H), 2.50-2.40 (m, 5H), 1.68 (s, 4H).

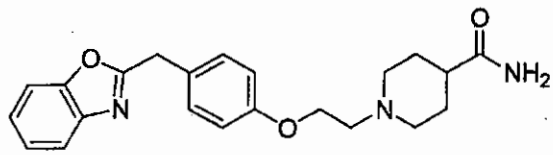
EXAMPLE 136



1-[2-(4-Benzooxazol-2-ylmethyl-phenoxy)-ethyl]-4-phenyl-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 41 using 4-phenyl-piperidin-4-ol. MS (ESI): mass calculated for $C_{27}H_{28}N_2O_3$, 428.21; m/z found, 429.2 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.62-7.58 (m, 1H), 7.54-7.45 (m, 3H), 7.33-7.25 (m, 6H), 7.20-7.15 (m, 1H), 6.91 (d, J = 8.6, 2H), 4.20 (s, 2H), 4.13 (t, J = 5.5, 2H), 2.87 (m, 4H), 2.66 (t, J = 11.4, 2H), 2.13 (dt, J = 12.8, 3.6, 2H), 1.72 (d, J = 12.6, 2H).

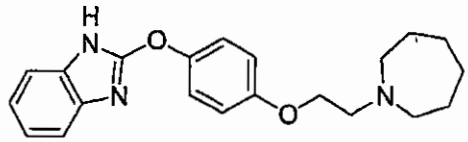
EXAMPLE 137



1-[2-(4-Benzooxazol-2-ylmethyl-phenoxy)-ethyl]-piperidine-4-carboxylic acid amide.

The title compound was prepared according to the procedure for EXAMPLE 41 using piperidine-4-carboxylic acid amide. MS (ESI): mass calculated for $C_{22}H_{25}N_3O_3$, 379.19; m/z found, 380.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.64-7.60 (m, 1H), 7.56-7.52 (m, 1H), 7.36-7.31 (m, 2H), 7.28 (d, J = 8.7, 2H), 6.92 (d, J = 8.7, 2H), 4.22 (s, 2H), 4.11 (t, J = 5.6, 2H), 3.07 (d, J = 12.0, 2H), 2.79 (t, J = 5.6, 2H), 2.18-2.15 (m, 3H), 1.80-1.70 (m, 4H).

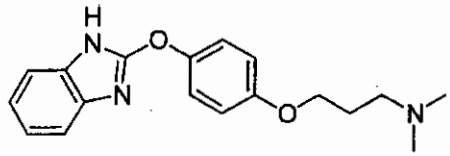
EXAMPLE 138



2-[4-(2-Azepan-1-yl-ethoxy)-phenoxy]-1*H*-benzoimidazole amide.

The title compound was prepared according to the procedure for EXAMPLE 11 steps A and B and EXAMPLE 37 steps B and C using 1-(2-chloro-ethyl)-azepane hydrochloride. MS (ESI): mass calculated for $C_{21}H_{25}N_3O_2$, 351.19; m/z found, 352.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.28 (s, 1H), 7.35-7.25 (m, 4H), 7.07 (d, J = 9.1, 2H), 7.00 (d, J = 9.1, 2H), 4.05 (t, J = 6.0, 2H), 2.86 (t, J = 6.0, 2H), 2.70 (t, J = 5.1, 4H), 1.65-1.50 (m, 8H).

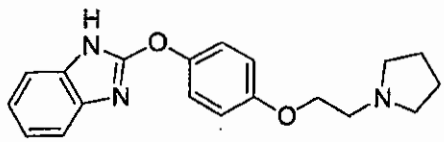
EXAMPLE 139



{3-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-propyl}-dimethyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 11 steps A and B and EXAMPLE 37 steps B and C using (2-chloro-propyl)-dimethyl-amine hydrochloride. MS (ESI): mass calculated for $C_{18}H_{21}N_3O_2$, 311.16; m/z found, 312.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.32-7.23 (m, 2H), 7.21-7.14 (m, 4H), 6.89-6.83 (m, 2H), 3.99-3.91 (m, 2H), 2.51 (t, J = 7.2, 2H), 2.31 (s, 6H) 2.02-1.95 (m, 2H).

EXAMPLE 140

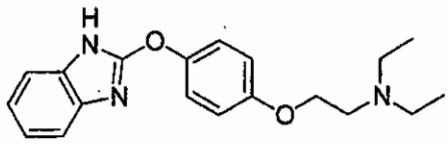


2-[4-(2-Pyrrolidin-1-yl-ethoxy)-phenoxy]-1*H*-benzoimidazole.

The title compound was prepared according to the procedure for EXAMPLE 21 steps A and B and EXAMPLE 35 steps B and C using pyrrolidine. MS (ESI): mass calculated for $C_{19}H_{21}N_3O_2$, 323.16; m/z found, 324.2 $[M+H]^+$. ^1H NMR

(400 MHz, $CDCl_3$): 7.27 (br s, 2H), 7.15 (d, J = 9.1, 4H), 6.81 (d, J = 6.8, 2H), 4.16 (t, J = 5.5, 2H), 3.05 (t, J = 5.5, 2H), 2.86 (br s, 4H), 1.92 (br s, 4H).

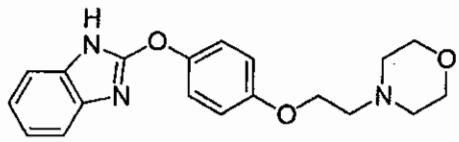
EXAMPLE 141



{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-diethyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 21 steps A and B and EXAMPLE 35 steps B and C using diethylamine. MS (ESI): mass calculated for $C_{19}H_{23}N_3O_2$, 325.18; m/z found, 326.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.29 (br s, 2H), 7.18 (d, J = 9.0, 2H), 7.10-7.05 (m, 2H), 6.98 (d, J = 9.0, 2H), 4.03 (t, J = 6.2, 2H), 2.78 (t, J = 6.1, 2H), 2.55 (q, J = 7.1, 4H), 0.98 (t, J = 7.1, 6H).

EXAMPLE 142



2-[4-(2-Morpholin-4-yl-ethoxy)-phenoxy]-1*H*-benzoimidazole.

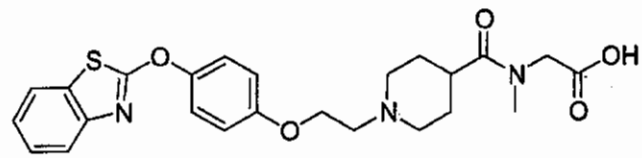
The title compound was prepared according to the procedure for EXAMPLE 21 steps A and B and EXAMPLE 37 steps B and C using morpholine. MS (ESI): mass calculated for $C_{19}H_{21}N_3O_3$, 339.16; m/z found, 340.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.40-7.25 (m, 4H), 7.12-7.08 (m, 2H), 7.00 (d, J = 9.0, 2H), 4.10 (t, J = 5.7, 2H), 3.58 (t, J = 4.5, 4H), 2.70 (t, J = 5.7, 2H), 2.52-2.46 (m, 4H).

EXAMPLES 143-202 and 204-229

Compounds of this invention that are referred to herein for which no explicit preparation description is provided can be prepared according to procedures

analogous to those described herein in light of the knowledge of one of ordinary skill in the art and the teachings provided herein. For example, benzothiazole derivatives listed herein with reference numerals 143-202 and 204-229 can be prepared according to procedures analogous to those described herein for related compounds.

EXAMPLE 203



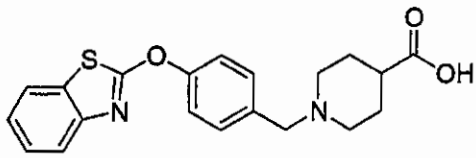
[(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carbonyl)-methyl-amino]-acetic acid

The title compound was prepared according to the procedures for EXAMPLE 20 and EXAMPLE 18 using sarcosine ethyl ester hydrochloride. MS (ESI): mass calculated for $C_{24}H_{27}N_3O_5S$, 469.56; m/z found, 470.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, J = 8.02, 1H), 7.65 (d, J = 8.02, 1H), 7.34-7.40 (m, 1H), 7.23-7.30 (m, 3H), 6.92-6.98 (m, 2H), 4.34-4.44 (m, 2H), 3.92 (br s, 2H), 3.45-3.54 (m, 3H), 3.35 (br s, 1H), 3.25 (br s, 1H), 3.12 (s, 2H), 2.96 (s, 1H), 2.76 (br s, 2H), 1.92-2.08 (m, 4H).

EXAMPLES 230-231 and 485

As indicated in the context of this written description, compounds of this invention that are referred to herein for which no explicit preparation description is provided can be prepared according to procedures analogous to those described herein in light of the knowledge of one of ordinary skill in the art and the teachings provided herein. For example, benzoimidazole derivatives listed herein with reference numerals 230-231 and 485 can be prepared according to procedures analogous to those described herein for related compounds.

EXAMPLE 250



1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidine-4-carboxylic acid.

A. 1-(4-Benzyloxy-benzyl)-piperidine-4-carboxylic acid ethyl ester. A mixture of 4-benzyloxybenzyl chloride (15.2 g, 65.3 mmol), isonipecotic acid ethyl ester (15 mL, 97 mmol), and K_2CO_3 (13.5 g, 97.6 mmol) in CH_3CN (300 mL) was stirred at reflux for 20 h. The reaction mixture was cooled to room temperature and filtered. The solvent was removed under reduced pressure to yield a clear golden oil. This material was diluted with *i*PrOH (100 mL), and the mixture was filtered. The solid was air dried to yield a white solid (19.7 g, 85% yield). TLC (SiO_2, 15% acetone/CH_2Cl_2): R_f = 0.32. MS (ESI): mass calculated for $C_{22}H_{27}NO_3$, 353.2; m/z found, 354.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.44 (d, *J* = 7.1, 2H), 7.39 (t, *J* = 7.1, 2H), 7.33 (d, *J* = 7.2, 1H), 7.18 (d, *J* = 8.2, 2H), 6.94 (2H, *J* = 8.6, 2H), 5.08 (s, 2H), 4.04 (q, *J* = 7.09, 2H), 2.72 (d, *J* = 11.5, 2H), 2.32-2.18 (m, 1H), 1.94 (t, *J* = 11.6, 2H), 1.76 (d, *J* = 10.2, 2H), 1.59-1.48 (m, 2H), 1.17 (t, *J* = 7.1, 3H).

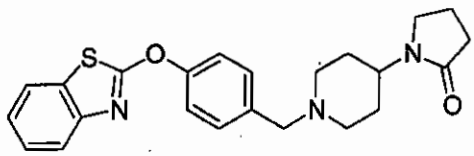
B. 1-(4-Hydroxy-benzyl)-piperidine-4-carboxylic acid ethyl ester. 1-(4-Benzyloxy-benzyl)-piperidine-4-carboxylic acid ethyl ester (10.0 g, 28.3 mmol) was dissolved in 1:1 ethanol/ethyl acetate (150 mL). To this solution was added Pd on carbon (10 wt %, 503 mg) as a suspension in ethanol (5.0 mL). The resulting suspension was placed on a Parr hydrogenator at 40 psi of H_2 and shaken overnight. The reaction mixture was filtered through a pad of diatomaceous earth, and the filtrate was concentrated under reduced pressure to give a clear golden oil. The oil was purified on SiO_2 (90 g; 50% acetone/CH_2Cl_2) to give a white solid (2.0 g, 27% yield). TLC (SiO_2, 50% acetone/CH_2Cl_2): R_f = 0.32. MS (ESI): mass calculated for $C_{15}H_{21}NO_3$, 263.2; m/z found, 264.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 9.25 (s, 1H), 7.05 (d, *J* = 8.4, 2H), 6.68 (d, *J* = 8.4, 2H), 4.04 (q, *J* = 7.1, 2H), 3.34 (s, 2H), 2.71 (d, *J*

= 11.5, 2H), 2.32-2.18 (m, 1H), 1.92 (t, *J* = 11.6, 2H), 1.76 (d, *J* = 10.2, 2H), 1.59- 1.48 (m, 2H), 1.17 (t, *J* = 7.1, 3H).

C. 1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidine-4-carboxylic acid ethyl ester. To a stirring solution of 1-(4-hydroxy-benzyl)-piperidine-4-carboxylic acid ethyl ester (508 mg, 1.93 mmol) in CH_3CN (15 mL), was added K_2CO_3 (564 mg, 4.1 mmol) and 2-chlorobenzothiazole (0.50 mL, 4.0 mmol). The suspension was heated to 80 °C and stirred overnight. The reaction mixture was allowed to cool to room temperature and then filtered through diatomaceous earth. The filtrate was concentrated under reduced pressure, and the residue was purified on SiO_2 (12 g; 0–15% acetone/CH_2Cl_2) to give a clear and colorless tacky oil (717 mg, 94% yield). TLC (SiO_2, 15% acetone/CH_2Cl_2): R_f = 0.5. MS (ESI): mass calculated for $C_{22}H_{24}N_2O_3S$, 396.2; m/z found, 397.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.92 (d, *J* = 8.0, 1H), 7.68 (d, *J* = 8.0, 1H), 7.48-7.33 (m, 5H), 7.33 (t, *J* = 7.1, 1H), 4.06 (q, *J* = 7.1, 2H), 3.49 (s, 2H), 2.76 (d, *J* = 11.5, 2H), 2.34-2.22 (m, 1H), 2.02 (t, *J* = 11.6, 2H), 1.80 (d, *J* = 10.2, 2H), 1.64- 1.54 (m, 2H), 1.18 (t, *J* = 7.1, 3H).

D. 1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidine-4-carboxylic acid. To a stirring solution of 1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidine-4-carboxylic acid ethyl ester (663 mg, 1.7 mmol) in 25% *i*PrOH/H_2O (20 mL) was added potassium hydroxide (206 mg, 3.1 mmol). The reaction mixture was stirred at room temperature for 20 h, and the solution was treated to pH 5.5 with 1 M HCl. The resulting solution was extracted with 10% *i*PrOH/$CHCl_3$ (3 x 50 mL). The combined extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a white solid (561 mg, 91% yield). MS (ESI): mass calculated for $C_{20}H_{20}N_2O_3S$, 368.1; m/z found, 369.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.92 (d, *J* = 7.6, 1H), 7.69 (d, *J* = 7.6, 1H), 7.48-7.34 (m, 5H), 7.33 (t, *J* = 7.1, 1H), 3.49 (s, 2H), 2.76 (d, *J* = 11.4, 2H), 2.22-2.11 (m, 1H), 2.02 (t, *J* = 11.2, 2H), 1.80 (d, *J* = 13.2, 2H), 1.62- 1.48 (m, 2H), 1.18 (t, *J* = 7.1, 3H).

EXAMPLE 251

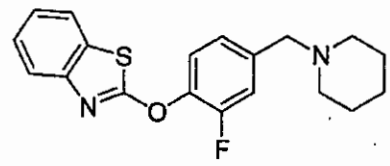


1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-pyrrolidin-2-one.

A. 4-(Benzothiazol-2-yloxy)-benzaldehyde. To a mixture of 4-hydroxybenzaldehyde (1 g, 8.2 mmol) and 2-chlorobenzothiazole (2.03 mL, 16.4 mmol) in CH_3CN (100 mL) was added Cs_2CO_3 (5.5 g, 17.2 mmol). The reaction mixture was stirred at 60 °C for 24 h. The resulting mixture was cooled to room temperature, filtered through diatomaceous earth and concentrated under reduced pressure to yield the crude product as an orange oil. The oil was triturated with hexanes/CH_2Cl_2 (100 mL) and the solvent layer decanted and concentrated under reduced pressure to yield an orange oil which was further purified on SiO_2 (120 g; 0-50% ethyl acetate/hexanes) to give a white solid (853 mg, 41% yield). ^1H NMR (400 MHz, $CDCl_3$): 10.1 (s, 1H), 7.97-7.78 (m, 2H), 7.78-7.70 (m, 2H), 7.60-7.50 (m, 2H), 7.48-7.38 (m, 1H), 7.36-7.30 (m, 1H).

B. 1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-pyrrolidin-2-one. A mixture of 4-(benzothiazol-2-yloxy)-benzaldehyde (500 mg, 1.9 mmol), 1-piperidin-4-yl-pyrrolidin-2-one hydrochloride (440 mg, 2.2 mmol), Et_3N (300 µL, 2.2 mmol) and molecular sieves (500 mg, crushed, 4Å) in $ClCH_2CH_2Cl$ (10 mL) was stirred at room temperature for 1 h. To the resulting mixture was added $NaBH(OAc)_3$ (830 mg, 3.92 mmol). The mixture was stirred at room temperature for 24 h, filtered through diatomaceous earth, rinsed with CH_2Cl_2 (50 mL) and concentrated under reduced pressure to yield the crude product as a yellow oil. The crude product was purified on SiO_2 (40 g; 0-100% acetone/CH_2Cl_2) to give a clear oil which crystallized on standing (287 mg, 36% yield). MS (ESI): mass calculated for $C_{23}H_{25}N_3O_2S$, 407.5; m/z found, 408.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.76 (d, J = 8.0, 1H), 7.69 (d, J = 8.0, 1H), 7.41-7.30 (m, 3H), 7.35-7.27 (m, 3H), 4.46-3.98 (m, 1H), 3.71 (s, 2H), 3.36 (t, J = 6.9, 2H), 2.97 (d, J = 11.7, 2H), 2.40 (t, J = 8.1, 2H), 2.17-1.97 (m, 4H), 1.81-1.62 (m, 4H).

EXAMPLE 252



2-(2-Fluoro-4-piperidin-1-ylmethyl-phenoxy)-benzothiazole.

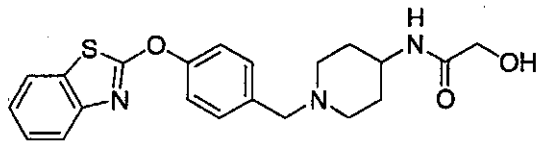
A. (3-Fluoro-4-hydroxy-phenyl)-piperidin-1-yl-methanone. A solution of 3-fluoro-4-hydroxybenzoic acid (5.0 g, 32 mmol), piperidine (5 mL, 51 mmol), and EDCI (9.3 g, 49 mmol) in CH_2Cl_2 (100 mL) was stirred at room temperature for 20 h. The reaction mixture was added to CH_2Cl_2 (200 mL) and was washed with 1 M HCl (2 x 100 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure to yield a clear golden oil. The oil was purified on SiO_2 (120 g; 0–10% acetone/CH_2Cl_2) to give a white solid (2.4 g, 34% yield). TLC (SiO_2, 15% acetone/CH_2Cl_2): R_f = 0.35. MS (ESI): mass calculated for $C_{12}H_{14}FNO_2$, 223.1; m/z found, 224.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 10.26 (s, 1H), 7.18 (d, J = 11.6, 1H), 7.00 (d, J = 8.3, 1H), 6.98 (t, J = 8.5, 1H), 3.42 (br s, 4H), 1.65-1.45 (m, 6H).

B. 2-Fluoro-4-piperidin-1-ylmethyl-phenol. A solution of lithium aluminum hydride (1.9 g, 50 mmol) in THF (40 mL) was stirred at 5 °C. To the mixture was added (3-fluoro-4-hydroxy-phenyl)-piperidin-1-yl-methanone (2.3 g, 10.4 mmol) in THF (10 mL) over 15 min and then the mixture was heated to 60 °C. After 20 h the mixture was cooled to 5 °C and saturated NH_4Cl (200 mL) was added followed by CH_2Cl_2 (200 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure to yield a white solid (812 mg, 37% yield). TLC (SiO_2, acetone): R_f = 0.22. MS (ESI): mass calculated for $C_{12}H_{16}FNO$, 209.1; m/z found, 210.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 6.58 (d, J = 13.4, 1H), 6.48 (d, J = 8.2, 1H), 6.40 (t, J = 9.9, 1H), 3.14 (s, 2H), 2.24 (br s, 4H), 1.54-1.30 (m, 6H).

C. 2-(2-Fluoro-4-piperidin-1-ylmethyl-phenoxy)-benzothiazole. To a stirring solution of 2-fluoro-4-piperidin-1-ylmethyl-phenol (152 mg, 0.73 mmol) in CH_3CN (10 mL), was added K_2CO_3 (201 mg, 1.5 mmol) and 2-chlorobenzothiazole (0.14 mL, 1.1 mmol). The suspension was heated to 80 °C and stirred overnight. The reaction mixture was allowed to cool to room

temperature and then filtered through diatomaceous earth. The filtrate was concentrated under reduced pressure, and the residue was purified on SiO_2 (12 g; 0–50% acetone/CH_2Cl_2) to give a clear golden oil (142 mg, 57% yield). TLC (SiO_2, 50% acetone/CH_2Cl_2): R_f = 0.44. MS (ESI): mass calculated for $C_{19}H_{19}FN_2OS$, 342.1; m/z found, 343.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.95 (d, J = 7.9, 1H), 7.69 (d, J = 7.5, 1H), 7.56 (t, J = 8.2, 1H), 7.47-7.32 (m, 3H), 7.44 (d, J = 15.4, 1H), 3.48 (s, 2H), 2.36 (s, 4H), 1.63-1.37 (m, 6H).

EXAMPLE 253



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-2-hydroxy-acetamide.

A. {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-carbamic acid tert-butyl ester. A mixture of 4-(benzothiazol-2-yloxy)-benzaldehyde (EXAMPLE 251, step A, 500 mg, 1.9 mmol), piperidin-4-yl-carbamic acid tert-butyl ester (785 mg, 3.9 mmol) and molecular sieves (500 mg, crushed, 4Å) in $ClCH_2CH_2Cl$ (10 mL) was stirred at room temperature for 40 min. To the resulting reaction mixture was added $NaBH(OAc)_3$ portion wise over 1.5 h (4 x 207 mg, 3.9 mmol). The resulting mixture was stirred at room temperature for 24 h, filtered through diatomaceous earth and rinsed with CH_2Cl_2 (50 mL). The filtrate was washed with sat. aq. $NaHCO_3$ (1 x 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as a light yellow oil. The crude product was purified on SiO_2 (40 g; 0-5% 2 M NH_3 in CH_3OH/CH_2Cl_2) to give a white foam (504 mg, 59% yield). MS (ESI): mass calculated for $C_{24}H_{29}N_3O_3S$, 439.6; m/z found, 440.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.0, 1H), 7.67 (d, J = 8.0, 1H), 7.42-7.36 (m, 3H), 7.32-7.24 (m, 3H), 4.44 (br s, 1H), 3.50 (s, 2H), 2.82-2.76 (m, 2H), 2.16-2.06 (m, 2H), 1.96-1.88 (m, 2H), 1.45 (s, 9H), 1.48-1.38 (m, 2H).

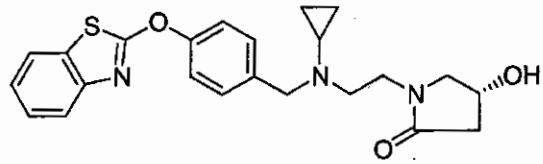
B. 1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylamine. To a solution of {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-carbamic acid tert-butyl ester (200 mg, 0.45 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added 4 N HCl in dioxane (1.8 mL, 7.2 mmol) dropwise. The resulting reaction mixture was stirred at room temperature for 2 h. The desired product was isolated by filtration and was rinsed with Et_2O (50 mL) to yield a white powder (187 mg, 100% yield). MS (ESI): mass calculated for $C_{19}H_{21}N_3OS$, 339.5; m/z found, 340.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.68-7.64 (m, 1H), 7.58-7.52 (m, 2H), 7.48-7.44 (m, 1H), 7.40-7.35 (m, 2H), 7.30-7.24 (m, 1H), 7.20-7.14 (m, 1H), 4.25 (s, 2H), 3.52-3.46 (m, 2H), 3.36-3.28 (m, 1H), 3.08-2.99 (m, 2H), 2.16-2.08 (m, 2H), 1.92-1.80 (m, 2H).

C. Acetic acid {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylcarbamoyl}-methyl ester. To a solution of {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylamine dihydrochloride (413 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) at room temperature was added TEA (0.70 mL, 5.0 mmol), followed by acetoxyacetyl chloride (0.16 mL, 1.5 mmol). The resulting mixture was stirred at room temperature overnight. The reaction mixture was dissolved in CH_2Cl_2 (100 mL), washed with sat. aq. $NaHCO_3$ (1 x 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as an off-white solid. The crude product was purified on SiO_2 (40 g; 0-10% CH_3OH/CH_2Cl_2) to give a white solid (410 mg, 93% yield). MS (ESI): mass calculated for $C_{23}H_{25}N_3O_4S$, 439.2; m/z found, 440.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 7.8, 1H), 7.65 (d, J = 8.1, 1H), 7.40-7.35 (m, 3H), 7.32-7.23 (m, 3H), 6.11 (d, J = 8.3, 1H), 4.53, (s, 2H), 3.93-3.82 (m, 1H), 3.50 (s, 2H), 2.83 (d, J = 11.9, 2H), 2.15 (s, 3H), 2.14 (t, J = 11.9, 2H), 1.93 (d, J = 12.1, 2H), 1.56-1.45 (m, 2H).

D. N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-2-hydroxy-acetamide. To a solution of acetic acid {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylcarbamoyl}-methyl ester (368 mg, 0.84 mmol) in THF (30 mL), CH_3OH (10 mL) and H_2O (10 mL) was added lithium hydroxide (80.2 mg, 3.34 mmol). The resulting mixture was stirred at room temperature overnight. The mixture was extracted with CH_2Cl_2 (30 mL x 3). The combined organic phases were concentrated under reduced pressure to yield the crude product as an off-white

solid. The crude product was purified on SiO_2 (40 g; 0-10% CH_3OH/CH_2Cl_2) to give a white solid (297 mg, 82% yield). MS (ESI): mass calculated for $C_{21}H_{23}N_3O_3S$, 397.2; m/z found, 398.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 7.8, 1H), 7.65 (d, J = 8.1, 1H), 7.40-7.35 (m, 3H), 7.31-7.23 (m, 3H), 6.83 (d, J = 8.1, 1H), 5.33 (br s, 1H), 3.99 (s, 2H), 3.87-3.75 (m, 1H), 3.50 (s, 2H), 2.85 (d, J = 11.4, 2H), 2.14 (t, J = 10.9, 2H), 1.92 (d, J = 12.6, 2H), 1.56-1.43 (m, 2H).

EXAMPLE 254



1-(2-{[4-(Benzothiazol-2-yloxy)-benzyl]-cyclopropyl-amino}-ethyl)-4-hydroxy-pyrrolidin-2-one.

A. [4-(Benzothiazol-2-yloxy)-benzyl]-cyclopropyl-amine. A mixture of 4-(benzothiazol-2-yloxy)-benzaldehyde (5.0 g, 19.6 mmol), cyclopropylamine (3.35 g, 58.7 mmol) in $ClCH_2CH_2Cl$ (80 mL) was stirred at room temperature for 40 min. To the resulting reaction mixture was added $NaBH(OAc)_3$ portion wise over 1.5 h (4 x 2.1 g, 39.2 mmol). The resulting mixture was stirred at room temperature for 24 h, filtered through diatomaceous earth and rinsed with CH_2Cl_2 (500 mL). The filtrate was washed with sat. aq. $NaHCO_3$ (1 x 250 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as a pale yellow oil. The crude product was purified on SiO_2 (330 g; 0-5% CH_3OH/CH_2Cl_2) to give a white solid (3.95 g, 68% yield). MS (ESI): mass calculated for $C_{17}H_{16}N_2OS$, 296.1; m/z found, 297.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.63 (d, J = 8.1, 1H), 7.40-7.33 (m, 3H), 7.32-7.27 (m, 2H), 7.24 (t, J = 8.1, 1H), 3.85 (s, 2H), 2.19-2.12 (m, 1H), 1.86 (br s, 1H), 0.48-0.35 (m, 4H).

B. (2-{[4-(Benzothiazol-2-yloxy)-benzyl]-cyclopropyl-amino}-ethyl)-carbamic acid tert-butyl ester. To a solution of [4-(benzothiazol-2-yloxy)-benzyl]-cyclopropyl-amine (2.96 g, 10 mmol) in CH_3CN (40 mL) at room temperature

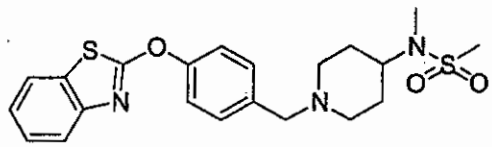
was added *N,N*-diisopropylethylamine (3.48 mL, 20 mmol), followed by (2-bromo-ethyl)-carbamic acid tert-butyl ester (3.36 g, 15 mmol). The resulting mixture was heated at 60 °C overnight. The mixture was cooled and dissolved in CH_2Cl_2 (200 mL), washed with sat. aq. $NaHCO_3$ (1 x 25 mL) and H_2O (2 x 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as a pale yellow solid. The crude product was purified on SiO_2 (120 g; 0-50% ethyl acetate/hexanes) to give a white solid (3.44 g, 78% yield). MS (ESI): mass calculated for $C_{24}H_{29}N_3O_3S$, 439.2; m/z found, 440.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.1, 1H), 7.64 (d, J = 8.1, 1H), 7.39-7.22 (m, 6H), 4.75 (br s, 1H), 3.74 (s, 2H), 3.25 (dd, J = 5.8, 6.1, 2H), 2.65 (t, J = 6.3, 2H), 1.82-1.75 (m, 1H), 1.43 (s, 9H), 0.54-0.48 (m, 2H), 0.43-0.37 (m, 2H).

C. N1-[4-(Benzothiazol-2-yloxy)-benzyl]-N1-cyclopropyl-ethane-1,2-diamine. To a solution of (2-{[4-(benzothiazol-2-yloxy)-benzyl]-cyclopropyl-amino}-ethyl)-carbamic acid tert-butyl ester in CH_2Cl_2 (16 mL) at 0 °C was added trifluoroacetic acid in dioxane (4 mL) dropwise. The resulting reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure to yield the crude product as a pale yellow oil. The oil was dissolved in CH_2Cl_2 (100 mL), washed with sat. aq. $NaHCO_3$ (1 x 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the product as a clear oil. MS (ESI): mass calculated for $C_{19}H_{21}N_3OS$, 339.1; m/z found, 340.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, J = 8.1, 1H), 7.61 (d, J = 8.1, 1H), 7.37-7.18 (m, 6H), 3.75 (s, 2H), 2.76 (t, J = 6.3, 2H), 2.60 (t, J = 6.3, 2H), 1.98 (s, 2H), 1.79-1.73 (m, 1H), 0.51-0.45 (m, 2H), 0.42-0.37 (m, 2H).

D. 1-(2-{[4-(Benzothiazol-2-yloxy)-benzyl]-cyclopropyl-amino}-ethyl)-4-hydroxy-pyrrolidin-2-one. To a solution of N1-[4-(benzothiazol-2-yloxy)-benzyl]-N1-cyclopropyl-ethane-1,2-diamine (1.5 g, 4.4 mmol) in CH_3CN (18 mL) at room temperature was added *N,N*-diisopropylethylamine (1.15 mL, 6.63 mmol), followed by 4-(R)-bromo-3-hydroxy-butyric acid ethyl ester (1.11 g, 5.3 mmol). The resulting mixture was heated at 60 °C overnight. The mixture was cooled and dissolved in CH_2Cl_2 (100 mL), washed with sat. aq. $NaHCO_3$ (1 x 10 mL) and H_2O (2 x 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as a light brown oil. The crude product was

purified on reverse phase HPLC (0-99%, 0.05 % TFA in H_2O/CH_3CN) to give a clear oil (435 mg, 18.3% yield). MS (ESI): mass calculated for $C_{23}H_{25}N_3O_3S$, 423.2; m/z found, 424.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.64 (d, J = 8.1, 1H), 7.58-7.54 (m, 2H), 7.49 (d, J = 8.1, 1H), 7.37-7.33 (m, 2H), 7.26 (t, J = 7.6, 1H), 7.16 (t, J = 7.6, 1H), 4.48 (dd, J = 8.8, 12.9, 2H), 4.32 (t, J = 5.8, 1H), 3.84-3.75 (m, 1H), 3.64-3.56 (m, 2H), 3.38 (t, J = 6.3, 2H), 3.24 (t, J = 10.9, 1H), 2.73-2.66 (m, 1H), 2.59 (dd, J = 6.3, 11.1, 1H), 2.15 (d, J = 17.2, 1H), 0.79 (d, J = 6.6, 4H).

EXAMPLE 255



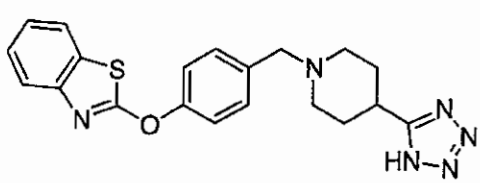
N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-N-methyl-methanesulfonamide.

A. <u>{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-methyl-carbamic acid tert-butyl ester.</u> A mixture of 4-(benzothiazol-2-yloxy)-benzaldehyde (4.4 g, 17.2 mmol), methyl-piperidin-4-yl-carbamic acid tert-butyl ester (4.06 g, 18.9 mmol) in $ClCH_2CH_2Cl$ (172 mL) was stirred at room temperature for 40 min. To the resulting reaction mixture was added $NaBH(OAc)_3$ portion wise over 1.5 h (4 x 1.82 g, 34.4 mmol). The resulting mixture was stirred at room temperature for 24 h, filtered through diatomaceous earth and rinsed with CH_2Cl_2 (300 mL). The filtrate was washed with sat. aq. $NaHCO_3$ (1 x 50 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as a pale yellow oil. The crude product was purified on SiO_2 (330 g; 0-100% ethyl acetate/hexanes) to give a light yellow foam (3.75 g, 48% yield). MS (ESI): mass calculated for $C_{25}H_{31}N_3O_3S$, 453.2; m/z found, 454.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.1, 1H), 7.66 (d, J = 8.1, 1H), 7.41-7.35 (m, 3H), 7.33-7.23 (m, 3H), 4.13-3.94 (m, 1H), 3.53 (s, 2H), 2.93 (d, J = 11.6, 2H), 2.74 (s, 3H), 2.08 (t, J = 11.6, 2H), 1.81-1.69 (m, 2H), 1.65-1.57 (m, 2H), 1.46 (s, 9H).

B. {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-methyl-amine. To a solution of {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-methyl-carbamic acid tert-butyl ester (3.7 g, 8.2 mmol) in CH_2Cl_2 (41 mL) at 0 °C was added 4 N HCl in dioxane (8.2 mL, 32.6 mmol) dropwise. The resulting mixture was stirred at room temperature for 2 h. The desired product was isolated by filtration and was washed with Et_2O (150 mL) to yield a white powder (3.38 g, 97% yield). MS (ESI): mass calculated for $C_{20}H_{23}N_3OS$, 353.2; m/z found, 354.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.92 (br s, 1H), 7.72 (d, J = 8.1, 1H), 7.63 (d, J = 8.1, 1H), 7.39-7.33 (m, 3H), 7.30-7.21 (m, 3H), 3.49 (s, 2H), 2.98-2.86 (m, 3H), 2.63 (s, 3H), 2.08-1.98 (m, 4H), 1.84-1.71 (m, 2H).

C. N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-N-methyl-methanesulfonamide. To a solution of {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-methyl-amine dihydrochloride (354 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) at room temperature was added TEA (0.70 mL, 5.0 mmol), followed by methanesulfonyl chloride (0.12 mL, 1.5 mmol). The resulting mixture was stirred at room temperature overnight. The mixture was dissolved in CH_2Cl_2 (100 mL), washed with sat. aq. $NaHCO_3$ (1 x 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as a pale yellow solid. The crude product was purified on SiO_2 (40 g; 0-10% CH_3OH/CH_2Cl_2) to give a white solid (378 mg, 88% yield). MS (ESI): mass calculated for $C_{21}H_{25}N_3O_3S_2$, 431.1; m/z found, 432.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.1, 1H), 7.66 (d, J = 8.1, 1H), 7.41-7.35 (m, 3H), 7.33-7.23 (m, 3H), 3.80-3.70 (m, 1H), 3.50 (s, 2H), 2.96 (d, J = 11.6, 2H), 2.82 (s, 3H), 2.80 (s, 3H), 2.08 (t, J = 11.6, 2H), 1.89-1.77 (m, 2H), 1.70-1.60 (m, 2H).

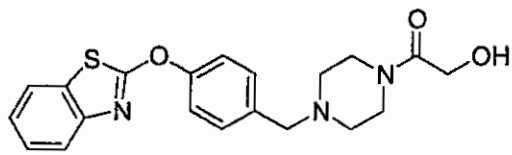
EXAMPLE 256



2-{4-[4-(1H-Tetrazol-5-yl)-piperidin-1-ylmethyl]-phenoxy}-benzothiazole.

A solution of 4-(benzothiazol-2-yloxy)-benzaldehyde (EXAMPLE 251 step A, 620 mg, 2.4 mmol), 4-(1*H*-tetrazol-5-yl)-piperidine hydrochloride (565 mg, 3.0 mmol), and Et_3N (0.43 mL, 3.1 mmol) in 30% THF/CH_2Cl_2 (35 mL) was stirred at room temperature for 30 min. To the stirring mixture was added $Na(AcO)_3BH$ (787 mg, 3.7 mmol). After 20 h the reaction mixture was added to 10% *i*PrOH/H_2O (50 mL) and the organic layer was separated and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield a clear yellow tacky oil. This material was diluted with ethanol (10 mL), heated to 80 °C, and filtered while hot. To the filtrate was added Et_2O (10 mL) and the flask was cooled on ice. A solid formed and was filtered to yield a white solid (48 mg, 5% yield). MS (ESI): mass calculated for $C_{20}H_{20}N_6OS$, 392.1; m/z found, 393.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.95 (d, J = 7.9, 1H), 7.70 (d, J = 7.9, 1H), 7.53-7.35 (m, 5H), 7.33 (t, J = 7.9, 1H), 3.59 (s, 2H), 3.09-3.00 (m, 1H), 2.91 (d, J = 10.8, 2H), 2.22 (t, J = 9.8, 2H), 1.85-1.72 (m, 2H).

EXAMPLE 257



1-{4-[4-(Benzothiazol-2-yloxy)-benzyl]-piperazin-1-yl}-2-hydroxy-ethanone.

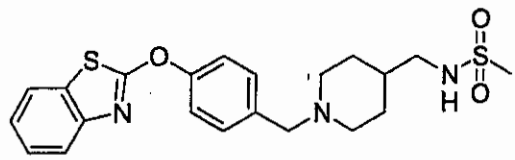
A. 4-[4-(Benzothiazol-2-yloxy)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester. A mixture of 4-(benzothiazol-2-yloxy)-benzaldehyde (2.5 g, 9.8 mmol), piperazine-1-carboxylic acid tert-butyl ester-2-one (3.7 g, 19.6 mmol) and molecular sieves (2.5 g, crushed, 4Å) in $ClCH_2CH_2Cl$ (25 mL) was stirred at room temperature for 40 min. To the resulting reaction mixture was added $NaBH(OAc)_3$ portion wise over 1.5 h (4 x 504 mg, 19.6 mmol). The resulting mixture was stirred at room temperature for 24 h, filtered through diatomaceous earth and rinsed with CH_2Cl_2 (200 mL). The filtrate was washed with sat. aq. $NaHCO_3$ (1 x 50 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as a yellow semi-solid. The crude

product was purified on SiO_2 (120 g; 0-100% acetone/CH_2Cl_2) to give an off-white solid (1.72 g, 42% yield). MS (ESI): mass calculated for $C_{23}H_{27}N_3O_3S$, 425.5; m/z found, 426.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.2, 1H), 7.67 (d, J = 8.2, 1H), 7.42-7.37 (m, 3H), 7.4-7.25 (m, 3H), 3.53 (s, 2H), 3.45 (br t, J = 4.9, 4H), 2.41 (br t, J = 4.5, 4H), 1.46 (s, 9H).

B. 2-(4-Piperazin-1-ylmethyl-phenoxy)-benzothiazole. To a solution of 4-[4-(benzothiazol-2-yloxy)-benzyl]-piperazine-1-carboxylic acid tert-butyl ester (1.7 g, 4.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added 4 N HCl in dioxane (5 mL, 20 mmol) dropwise. The resulting mixture was stirred at room temperature for 2 h and concentrated under reduced pressure to yield the crude product as a white solid. The crude product was triturated with Et_2O (50 mL) and isolated by filtration to yield the desired product as a white powder (1.37 g, 87% yield). MS (ESI): mass calculated for $C_{18}H_{19}N_3OS$, 325.4; m/z found, 326.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.81 (d, J = 8.0, 1H), 7.77-7.72 (m, 2H), 7.62 (d, J = 8.2, 1H), 7.57-7.53 (m, 2H), 7.45-7.40 (m, 1H), 7.35-7.31 (m, 1H), 4.45 (s, 2H), 3.62 (br s, 8H).

C. 1-{4-[4-(Benzothiazol-2-yloxy)-benzyl]-piperazin-1-yl}-2-hydroxy-ethanone. To a mixture of glycolic acid (47 mg, 0.62 mmol) and HOBT (1.25 mL, 0.62 mmol, 0.5 M in DMF) in CH_2Cl_2 (25 mL) was added 2-(4-piperazin-1-ylmethyl-phenoxy)-benzothiazole (150 mg, 0.42 mmol) followed by EDCI (150 mg, 0.79 mmol). The resulting mixture was stirred at room temperature for 24 h, diluted with CH_2Cl_2 (50 mL) and washed with sat. aq. $NaHCO_3$ (1 x 20 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as apale yellow oil. The crude product was purified on SiO_2 (40 g; 0-3% 2 M NH_3 in CH_3OH/CH_2Cl_2) to give a white foam (93 mg, 59% yield). MS (ESI): mass calculated for $C_{20}H_{21}N_3O_3S$, 383.5; m/z found, 384.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.0, 1H), 7.68 (d, J = 8.0, 1H), 7.45-7.25 (m, 6H), 4.16 (d, J = 4.1, 2H), 3.71-3.68 (m, 2H), 3.64-3.61 (m, 1H), 3.55 (s, 2H), 3.32-3.25 (m, 2H), 2.53-2.44 (m, 4H).

EXAMPLE 258



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-methanesulfonamide.

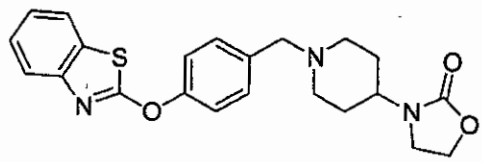
A. {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-carbamic acid tert-butyl ester. A mixture of 4-(benzothiazol-2-yloxy)-benzaldehyde (1.0 g, 3.9 mmol), piperidin-4-ylmethyl-carbamic acid tert-butyl ester (1.3 g, 5.9 mmol) and molecular sieves (1.0 g, crushed, 4Å) in $ClCH_2CH_2Cl$ (15 mL) was stirred at room temperature for 40 min. To the resulting mixture was added $NaBH(OAc)_3$ portion wise over 1.5 h (4 x 412 mg, 7.8 mmol). The mixture was stirred at room temperature for 24 h, filtered through diatomaceous earth and rinsed with CH_2Cl_2 (100 mL). The filtrate was washed with sat. aq. $NaHCO_3$ (1 x 50 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as a yellow semi-solid. The crude product was purified on SiO_2 (40 g; 0-100% acetone/CH_2Cl_2) to give a white foam (890 mg, 50% yield). MS (ESI): mass calculated for $C_{25}H_{31}N_3O_3S$, 453.6; m/z found, 454.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.0, 1H), 7.67 (d, J = 8.0, 1H), 7.41-7.36 (m, 3H), 7.32-7.24 (m, 3H), 4.59 (br s, 1 H), 3.50 (s, 2H), 3.06-3.00 (m, 2H), 2.94-2.88 (m, 2H), 1.97 (t, J = 11.4, 2H), 1.68 (d, J = 11.4, 2H), 1.44 (s, 9H), 1.22-1.33 (m, 2H).

B. C-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-methylamine. To a solution of {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-carbamic acid tert-butyl ester (866 mg, 1.9 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added 4 N HCl in dioxane (2.4 mL, 9.5 mmol) dropwise. The resulting mixture was stirred at room temperature for 24 h and concentrated under reduced pressure to yield the crude product as a white solid. The crude product was triturated with Et_2O (50 mL) and isolated by filtration to yield the desired product as a white powder (813 mg, 100% yield). MS (ESI): mass calculated for $C_{20}H_{23}N_3OS$, 353.5; m/z found, 354.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$):

7.80 (d, J = 8.0, 1H), 7.69 (d, J = 8.6, 2H), 7.60 (d, J = 8.0, 1H), 7.51 (d, J = 8.6, 1H), 7.42-7.38 (m, 1H), 7.33-7.28 (m, 1H), 4.37 (s, 2H), 3.78 (br d, J = 12.7, 1H), 2H), 3.13-3.04 (m, 2H), 2.89 (d, J = 6.6, 2H), 2.08-1.92 (m, 3H), 1.68-1.56 (m, 2H).

C. N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-methanesulfonamide. To a mixture of C-{1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-methylamine (150 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (400 µL, 2.86 mmol). The resulting mixture was cooled to 0 °C and CH_3SO_2Cl was added via syringe (41 µL, 0.52 mmol). The mixture was stirred at room temperature for 24 h, diluted with CH_2Cl_2 (10 mL) and washed with sat. aq. $NaHCO_3$ (1 x 5 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as a white solid. The crude product was purified on SiO_2 (10 g; 0-3% 2 M NH_3 in CH_3OH/CH_2Cl_2) to give a white solid (112 mg, 67% yield). MS (ESI): mass calculated for $C_{21}H_{25}N_3O_3S_2$, 431.6; m/z found, 432.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.0, 1H), 7.67 (d, J = 8.0, 1H), 7.42-7.36 (m, 3H), 7.33-7.25 (m, 3H), 4.25 (br t, J = 6.6, 1H), 3.51 (s, 2H), 3.04 (d, J = 6.6, 2H), 2.96 (s, 3H), 2.91-2.84 (m, 2H), 1.98 (t, J = 11.7, 2H), 1.74 (br d, J = 12.7, 2H), 1.60-1.48 (m, 2H), 1.36-1.24 (m, 2H).

EXAMPLE 259



3-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-oxazolidin-2-one.

A. 3-Piperidin-4-yl-oxazolidin-2-one hydrochloride salt. To a solution of 1-benzyl-4-piperidinone (10.3 g, 54 mmol) and ethanolamine (13.2 mL, 218 mmol) in CH_3OH (20 mL) was added sodium cyanoborohydride (10.2 g, 163 mmol) and trifluoromethanesulfonic acid (5 mL) and the reaction was stirred at 23 °C for 3 days. The mixture was cooled to 0 °C and 12 N HCl was slowly added until gas evolution ceased and the resulting mixture was stirred for a

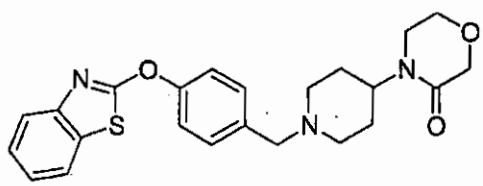
further 3 h. The mixture was filtered and the filtrate concentrated under reduced pressure. The crude oil was redissolved in H_2O (50 mL), the solution was made basic by the addition of 10 N NaOH. The mixture was extracted with CH_2Cl_2 (8 x 70 mL). The combined CH_2Cl_2 extracts were dried and concentrated under reduced pressure to yield the crude product (12.0 g, 95%). A solution of 2-(1-benzyl-piperidin-4-ylamino)-ethanol (3.6 g, 15.3 mmol) in $ClCH_2CH_2Cl$ (5 mL) was treated with carbonyl diimidazole (CDI) (2.6 g, 16 mmol) and the mixture stirred at 23 °C for 30 min. The mixture was diluted with CH_2Cl_2 (100 mL), washed with H_2O (1 x 50 mL) and sat. aq. $NaHCO_3$ (1 x 50 mL), dried, and concentrated under reduced pressure to yield 2.85 g (65%) of 3-(1-benzyl-piperidin-4-yl)-oxazolidin-2-one. To a solution of 3-(1-benzyl-piperidin-4-yl)-oxazolidin-2-one (2.3 g, 8.8 mmol) in $ClCH_2CH_2Cl$ (40 mL) was added α-chloroethyl acetylchloride (1.5 g, 10.6 mmol) and the mixture was heated to 100 °C for 90 min. The mixture was cooled to 23 °C and concentrated under reduced pressure. The crude residue was dissolved in CH_3OH and heated to reflux for 1 h. The mixture was cooled to 0 °C and concentrated under reduced pressure to yield the title compound (1.89 g, 99%). MS (ESI): exact mass calculated for $C_8H_{14}N_2O_2$, 170.1; m/z found, 171.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.97 (br s, 2H), 4.27 (dd, J = 9.1, 7.8, 2H), 3.80 (tt, J = 11.8, 4.2, 1H), 3.49 (dd, J = 8.0, 6.6, 1H), 3.30 (br d, J = 12.7, 2H), 2.97 (dt, J = 12.6, 2.3, 2H), 1.90 (ddd, J = 16.6, 13.0, 4.1, 2H), 1.86-1.75 (m, 2H).

B. [4-(Benzothiazol-2-yloxy)-phenyl]-methanol. To a mixture of 4-hydroxybenzyl alcohol (12 g, 97 mmol) in CH_3CN (200 mL) containing K_2CO_3 (22 g, 159 mmol) was added 2-chlorobenzothiazole (22 g, 130 mmol) and the mixture was heated to reflux for 72 h. The mixture was cooled to room temperature, filtered, and concentrated under reduced pressure to give the crude product as a golden oil. The crude oil was purified on SiO_2 (300 g; 5% acetone/CH_2Cl_2) to give a clear and colorless oil. (15 g, 60% yield). MS (ESI): exact mass calculated for $C_{14}H_{11}NO_2S$, 257.1; m/z found, 258.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.92 (d, J = 7.4, 1H), 7.69 (d, J = 8.0, 1H), 7.50-7.31 (m, 5H), 7.32 (t, J = 7.5, 1H), 5.32 (t, J = 5.7, 1H), 4.55 (d, J = 5.7, 2H).

C. 2-(4-Chloromethyl-phenoxy)-benzothiazole. To a mixture of [4-(benzothiazol-2-yloxy)-phenyl]-methanol (11 g, 43 mmol) in CH_2Cl_2 (100 mL) containing triethytlamine (9 mL, 65 mmol) at 5°C was added dropwise over 15 minutes thionyl chloride (4 mL g, 55 mmol). The ice bath was removed and the mixture warmed to room temperature and stirred for 24 hr. The mixture was washed once with saturated $K_2 CO_3$ (100 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a black oil. The crude oil was purified on SiO_2 (300 g; 100% CH_2Cl_2) to give a clear orange oil. (10 g, 84% yield). MS (ESI): exact mass calculated for $C_{14}H_{10}ClNOS$, 275.0; m/z found, 276.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.95 (d, J = 7.3, 1H), 7.70 (d, J = 7.6, 1H), 7.59 (d, J = 8.6, 2H), 7.47 (d, J = 8.6, 2H), 7.37 (t, J = 7.4, 1H), 7.33 (t, J = 7.5, 1H), 4.84 (s, 2H).

D. 3-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-oxazolidin-2-one. To a mixture of 2-(4-chloromethyl-phenoxy)-benzothiazole (670 mg, 2.4 mmol) in CH_3CN (15 mL) containing K_2CO_3 (544 mg, 3.9 mmol) was added 3-piperidin-4-yl-oxazolidin-2-one hydrochloride salt (355 mg, 1.7 mmol) and the mixture was heated to 60 °C for 24 h. The mixture was cooled to room temperature, filtered, and concentrated under reduced pressure to give the crude product as a golden oil. The crude oil was purified on SiO_2 (12 g; acetone) to give a white solid (591 mg, 84% yield). MS (ESI): mass calculated for $C_{22}H_{23}N_3O_3S$, 409.2; m/z found, 410.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 8.7, 1H), 7.70 (d, J = 7.5, 1H), 7.48-7.37 (m, 5H), 7.33 (d, J = 8.0, 1H), 4.25 (t, J = 7.7, 2H), 3.60-3.42 (m, 5H), 2.85 (d, J = 11.5, 2H), 2.04 (t, J =11.4, 2H), 1.78-1.58 (m, 4H).

EXAMPLE 260



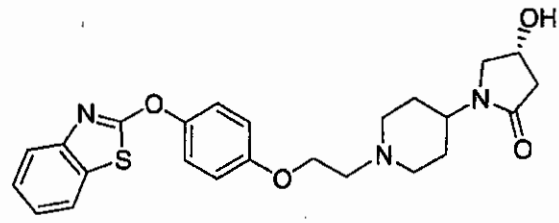
4-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-morpholin-3-one.

A. 4-Piperidin-4-yl-morpholin-3-one. To a solution of 1-benzyl-4-piperidinone (10.3 g, 54 mmol) and ethanolamine (13.2 mL, 218 mmol) in CH_3OH (20 mL) was added sodium cyanoborohydride (10.2 g, 163 mmol) and trifluoromethanesulfonic acid (5 mL) and the reaction mixture was stirred at 23 °C for 3 days. The mixture was cooled to 0 °C and 12 N HCl was slowly added until gas evolution ceased and the resulting mixture was stirred for a further 3 h. The mixture was filtered and the filtrate concentrated. The crude oil was redissolved in H_2O (50 mL), and the solution was made basic by the addition of 10 N NaOH. The mixture was extracted with CH_2Cl_2 (8 x 70 mL). The combined CH_2Cl_2 extracts were dried and concentrated under reduced pressure to yield 12.0 g (95% yield) crude product. A 0 °C solution of 2-(1-benzyl-piperidin-4-ylamino)-ethanol (2.13 g, 9.1 mmol) in ethanol (11 mL) and H_2O (5 mL) was treated simultaneously with chloroacetyl chloride (1.8 mL, 22.7 mmol) and 35% aq. NaOH solution and the mixture was stirred below 20 °C for 3 h. The reaction was diluted with H_2O (20 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine, dried, and concentrated to yield 1.83 g (66% yield) of 4-(1-benzyl-piperidin-4-yl)-morpholin-3-one. To a solution of 4-(1-benzyl-piperidin-4-yl)-morpholin-3-one (1.1 g, 3.9 mmol) in $ClCH_2CH_2Cl$ (20 mL) was added α-chloroethyl acetylchloride (660 mg, 4.6 mmol) and the reaction mixture was heated to 100 °C for 16 h. The mixture was cooled to 23 °C and concentrated under reduced pressure. The resulting crude material was purified on SiO_2 (12 g, 0-10% 2 M ammonia in CH_3OH/CH_2Cl_2) to yield 282 mg (53% yield) of 4-piperidin-4-yl-morpholin-3-one. MS (ESI): exact mass calculated for $C_8H_{14}N_2O_2$, 184.1; m/z found, 185.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 3.72 (s, 2H), 2.94 (t, J = 6.6, 2H), 2.55 (t, J = 3.6, 2H), 2.46 (tt, J = 10.3, 3.7, 1H), 1.92 (dd, J = 12.3, 2.3, 2H), 1.82-1.70 (m, 2H), 1.70-1.60 (m, 1H), 1.40-1.02 (m, 4H).

B. 4-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-morpholin-3-one. The title compound was prepared according to EXAMPLE 259, step D. MS (ESI): exact mass calculated for $C_{24}H_{27}N_3O_3S_1$, 423.16; m/z found, 424.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (dd, J = 8.1, 0.6, 1H), 7.70 (dd, J = 7.9, 0.7, 1H), 7.45-7.40 (m, 2H), 7.36-7.28 (m, 4H), 4.57 (tt, J = 12.1, 4.2, 1H), 4.22 (s, 2H), 3.90 (t, J = 4.9, 2H), 3.56 (s, 2H), 3.34 (t, J = 5.1, 2H), 3.01 (br d, J = 11.6, 2H),

2.18 (ddd, *J* = 11.7, 11.7, 2.2, 2H), 1.79 (dddd, *J* = 12.1, 12.1, 12.0, 3.8, 2H), 1.72-1.65 (m, 2H).

EXAMPLE 261



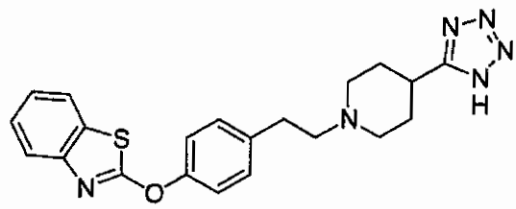
(*R*) 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one.

A. (R)- 4-Hydroxy-1-piperidin-4-yl-pyrrolidin-2-one acetic acid salt. A solution of 4-amino-1-benzylpiperidine (1.0 g, 5.2 mmol) and *N,N*-diisopropylethylamine (2.3 mL, 13.1 mmol) in CH_3CN (12 mL) was treated with (*R*)-4-bromo-3-hydroxybutyrate (1.4 g, 6.8 mmol) and the mixture was heated at 65 °C for 48 h. The mixture was cooled and diluted with ethyl acetate (70 mL) and washed with H_2O (20 mL). The organic layer was dried and concentrated under reduced pressure and the crude residue purified on SiO_2 (12 g, 0-5% 2 M ammonia in CH_3OH/CH_2Cl_2). The product was dissolved in ethanol (20 mL) and heated to 80 °C for 48 h. The mixture was concentrated under reduced pressure and the crude residue purified on SiO_2 (12 g, 0-5% 2 M ammonia in CH_3OH/CH_2Cl_2) to give 346 mg (25% yield) of 1-(1-benzyl-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one. A solution of 1-(1-benzyl-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one (346 mg, 1.3 mmol) in ethanol (7 mL) was treated with $Pd(OH)_2$ (60 mg) and the mixture charged with hydrogen gas on a Parr apparatus to 50 psi and shaken for 5 days. The mixture was filtered through diatomaceous earth and concentrated to give 280 mg (91% yield) of the title compound, which was used without purification in subsequent reactions. MS (ESI): exact mass calculated for $C_9H_{16}N_2O_2$, 184.1; m/z found, 185.2 $[M+H]^+$.

B. (*R*) 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one. The title compound was prepared according to EXAMPLE 24 using 4-hydroxy-1-piperidin-4-yl-pyrrolidin-2-one acetic acid salt. MS (ESI): exact mass calculated for $C_{24}H_{27}N_3O_4S_1$, 453.2; m/z found, 454.5

$[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (dd, J = 8.1, 0.5, 1H), 7.69 (dd, J = 8.0, 0.7, 1H), 7.42 (dt, J = 8.5, 1.3, 1H), 7.34-7.27 (m, 5H), 7.02-6.97 (m, 2H), 4.58-4.53 (m, 1H), 4.18-4.04 (m, 3H), 3.62 (dd, J = 10.7, 5.6, 1H), 3.34 (dd, J = 10.7, 2.2, 1H), 3.15-3.08 (m, 1H), 2.87 (t, J = 5.7, 2H), 2.75 (dd, J = 17.2, 6.6, 1H), 2.44 (dd, J = 17.2, 2.6, 1H), 2.34-2.24 (m, 2H), 1.90-1.68 (m, 3H).

EXAMPLE 262



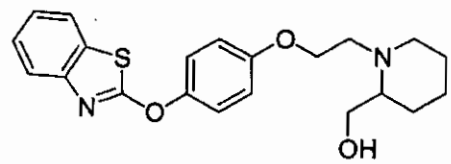
2-(4-{2-[4-(1H-Tetrazol-5-yl)-piperidin-1-yl]-ethyl}-phenoxy)-benzothiazole.

A. [4-(Benzothiazol-2-yloxy)-phenyl]-acetaldehyde. A solution of (4-hydroxy-phenyl)-acetic acid methyl ester (11.2 g, 62 mmol) and 2-chlorobenzothiazole (9.5 g mL, 56 mmol) in CH_3CN was treated with finely powdered Cs_2CO_3 (27 g, 84 mmol), and the resulting mixture was stirred at 40 °C for 17 h and 60 °C for 2 h. The reaction mixture was filtered through diatomaceous earth, and the filtrate was concentrated under reduced pressure. The crude solid was purified by dissolving in ethyl acetate (350 mL) and washing with 10% NaOH (3 x 30 mL), 0.5 M citric acid (1 x 30 mL), sat. aq. $NaHCO_3$ (1 x 30 mL), brine (1 x 30 mL), then dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide 16 g (95% yield) of [4-(benzothiazol-2-yloxy)-phenyl]-acetic acid methyl ester as a white solid. A solution of [4-(benzothiazol-2-yloxy)-phenyl]-acetic acid methyl ester (5.4 g, 18 mmol) in 80 mL of toluene at –90 °C was treated by dropwise addition of a 1.0 M solution of diisobutyl aluminum hydride in hexanes (27 mL, 27 mmol). The reaction was slowly warmed to –68 °C over 30 min and then quenched by the addition of methanol (2.0 mL). The reaction mixture was warmed to –20 °C and diluted with diethyl ether (100 mL) and 2.0 M HCl (60 mL) and stirred vigorously for 30 min. The organic layer was separated, washed with sat. aq. $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated to yield the title compound (4.84 g, 99% yield).

B. 2-(4-{2-[4-(1H-Tetrazol-5-yl)-piperidin-1-yl]-ethyl}-phenoxy)-benzothiazole.

A solution of [4-(benzothiazol-2-yloxy)-phenyl]-acetaldehyde (628 mg, 2.3 mmol) and 4-(1H-tetrazol-5-yl)-piperidine (443 mg, 2.34 mmol) in CH_2Cl_2 (10 mL) containing triethylamine (360 µL, 2.6 mmol) was treated with sodium triacetoxyborohydride (599 mg, 2.7 mmol) and the mixture was stirred at room temperature for 24 h. The mixture was washed with sat. aq. $NaHCO_3$ (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a white solid. The solid was washed with diethyl ether and air dried to give the product as a white solid (214 mg, 23% yield). MS (ESI): mass calculated for $C_{21}H_{22}N_6OS$, 406.2; m/z found, 407.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.93 (d, J = 7.9, 1H), 7.69 (d, J = 7.7, 1H), 7.48-7.30 (m, 6H), 3.10 (d, J = 11.6, 2H), 3.08-2.97 (m, 1H), 2.87 (t, J = 6.7, 2H), 2.72 (t, J = 8.6, 2H), 2.34 (t, J = 11.0, 2H), 2.01 (d, J = 11.2, 2H), 1.79 (q, J = 9.9, 2H).

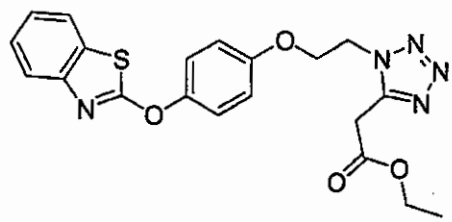
EXAMPLE 263



(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-2-yl)-methanol.

The title compound was prepared according to the procedure for EXAMPLE 24 using piperidin-2-yl-methanol. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_3S$, 384.2; m/z found, 385.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.91 (d, J = 7.9, 1H), 7.68 (d, J = 8.0, 1H), 7.42 (t, J = 7.3, 1H), 7.37 (d, J = 9.0, 2H), 7.31 (t, J = 8.1, 1H), 7.05 (d, J = 9.1, 2H), 4.43 (t, J = 5.3, 1H), 4.08 (t, J = 6.2, 2H), 3.60-3.51 (m, 1H), 3.48-3.39 (m, 1H), 3.17-3.09 (m, 1H), 2.94-2.84 (m, 1H), 2.80-2.70 (m, 1H), 2.33 (t, J = 10.4, 2H), 1.62 (d, J = 9.3, 2H), 1.58-1.47 (m, 1H), 1.47-1.35 (m, 1H), 1.35-1.20 (m, 2H).

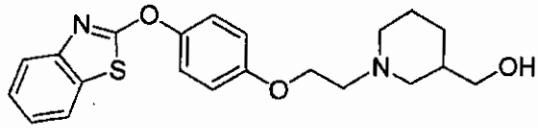
EXAMPLE 264



(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-1H-tetrazol-5-yl)-acetic acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 24 using (1H-tetrazol-5-yl)-acetic acid ethyl ester. MS (ESI): mass calculated for $C_{20}H_{19}N_5O_4S$, 425.1; m/z found, 426.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.91 (d, J = 8.0, 1H), 7.67 (d, J = 7.6, 1H), 7.46-7.36 (m, 3H), 7.32 (t, J = 8.4, 1H), 7.03 (d, J = 9.1, 2H), 4.88 (t, J = 5.0, 2H), 4.43 (t, J = 5.0, 2H), 4.35 (s, 2H), 4.14 (q, J = 7.1, 2H), 1.20 (t, J = 7.1, 3H).

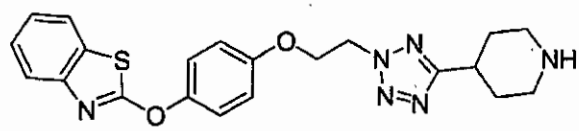
EXAMPLE 265



(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-3-yl)-methanol.

The title compound was prepared according to the procedure for EXAMPLE 24 using piperidin-3-yl-methanol. MS (ESI): exact mass calculated for $C_{21}H_{24}N_2O_3S_1$, 384.2; m/z found, 385.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (d, J = 8.1, 1H), 7.68 (d, J = 7.9, 1H), 7.42 (dt, J = 8.4, 1.2, 1H), 7.34-7.26 (m, 3H), 7.02-6.97 (m, 2H), 4.15 (t, J = 5.9, 2H), 3.68 (dd, J = 10.6, 5.2, 1H), 3.56 (dd, J = 10.4, 6.3, 1H), 3.00 (d, J = 5.3, 1H), 2.84 (t, J = 5.9, 2H), 2.83-2.79 (m, 1H), 2.75-2.60 (m, 1H), 2.30 (t, J = 9.5, 1H), 2.16 (t, J = 9.5, 1H), 1.92-1.78 (m, 2H), 1.77-1.68 (m, 1H), 1.68-1.60 (m, 1H), 1.24-1.12 (m, 1H).

EXAMPLE 266

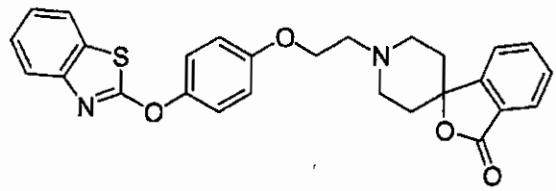


2-{4-[2-(5-Piperidin-4-yl-tetrazol-2-yl)-ethoxy]-phenoxy}-benzothiazole hydrochloride.

A. 4-(2-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-2H-tetrazol-5-yl)-piperidine-1-carboxylic acid tert-butyl ester. To a stirred solution of 2-[4-(2-bromo-ethoxy)-phenoxy]-benzothiazole (EXAMPLE 9; 500 mg, 1.4 mmol) and 4-(2H-tetrazol-5-yl)-piperidine-1-carboxylic acid tert-butyl ester (404 mg, 1.6 mmol) in CH_3CN (10 mL) was added Cs_2CO_3 (537 mg, 1.7 mmol). The mixture was heated at 60 °C for 20 h and then filtered. The filtrate was concentrated under reduced pressure to a clear golden oil, which was purified on SiO_2 (40 g; 0-15% acetone/CH_2Cl_2) to give a white solid (483 mg, 65% yield). TLC (SiO_2, 15% acetone/CH_2Cl_2): R_f = 0.84. MS (ESI): mass calculated for $C_{26}H_{30}N_6O_4S$, 522.2; m/z found, 523.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.90 (d, J = 7.7, 1H), 7.67 (d, J = 7.9, 1H), 7.42 (t, J = 7.1, 1H), 7.36 (d, J = 6.8, 2H), 7.31 (t, J = 8.1, 1H), 7.01 (d, J = 6.9, 2H), 5.05 (t, J = 4.7, 2H), 4.57 (t, J = 4.8, 2H), 3.92 (d, J = 12.4, 2H), 3.20-3.12 (m, 1H), 2.96 (br.s, 2H), 1.97 (dd, J = 13.3, 3, 2H), 1.65-1.52 (m, 2H), 1.40 (s, 9H).

B. 2-{4-[2-(5-Piperidin-4-yl-tetrazol-2-yl)-ethoxy]-phenoxy}-benzothiazole hydrochloride. To a stirred solution of 4-(2-{2-[4-(benzothiazol-2-yloxy)-phenoxy]-ethyl}-2H-tetrazol-5-yl)-piperidine-1-carboxylic acid tert-butyl ester (440 mg, 0.84 mmol) in 88% formic acid (7.5 mL) was added concentrated HCl (75 µL, 0.009 mmol). The mixture was stirred at room temperature for 20 h and concentrated under reduced pressure to give a clear, colorless oil. The oil was dried under high vacuum for 2 h and a white solid was obtained (337 mg, 99% yield). MS (ESI): mass calculated for $C_{21}H_{22}N_6O_2S$, 422.2; m/z found, 423.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.92 (d, J = 7.9, 1H), 7.67 (d, J = 8.0, 1H), 7.42 (t, J = 7.8, 1H), 7.39 (d, J = 9.4, 2H), 7.32 (t, J = 7.4, 1H), 5.08 (t, J = 4.7, 2H), 4.58 (t, J = 4.8, 2H), 3.40-3.22 (m, 4H), 3.03 (q, J = 15.1, 2H), 2.16 (d, J = 14.1, 2H), 1.92 (q, J = 14.3, 2H).

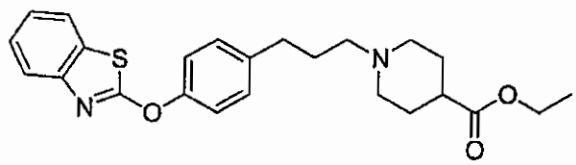
EXAMPLE 267



7-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-spiro-[3-phthalide]-piperidine.

The title compound was prepared according to the procedure for EXAMPLE 24 using 4-spiro-[3-phthalide]-piperidine. MS (ESI): mass calculated for $C_{27}H_{24}N_2O_4S$, 472.2; m/z found, 473.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.92 (d, J = 7.9, 1H), 7.83 (d, J = 7.7, 1H), 7.82-7.75 (m, 2H), 7.70 (d, J = 10.2, 1H), 7.61 (t, J = 11.6, 1H), 7.48-7.38 (m, 3H), 7.32 (t, J = 8.2, 1H), 7.10 (d, J = 9.1, 2H), 4.19 (t, J = 5.7, 2H), 3.05 (d, J = 13.0, 2H), 2.86 (t, J = 5.6, 2H), 2.50-2.44 (m, 2H), 2.28 (t, J = 13.5, 2H), 1.65 (d, J = 12.5, 2H).

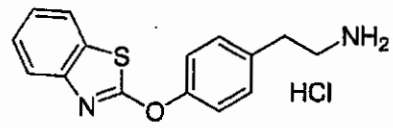
EXAMPLE 268



1-{3-[4-(Benzothiazol-2-yloxy)-phenyl]-propyl}-piperidine-4-carboxylic acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 35 using piperidine-4-carboxylic acid ethyl ester for step A and 2-chlorobenzothiazole for step C. MS (ESI): mass calculated for $C_{24}H_{28}N_2O_3S$, 424.2; m/z found, 425.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.92 (d, J = 7.9, 1H), 7.68 (d, J = 8.0, 1H), 7.43 (t, J = 8.1, 1H), 7.38-7.28 (m, 5H), 4.05 (q, J = 7.1, 2H), 2.78 (d, J = 11.3, 2H), 2.63 (t, J = 7.5, 2H), 2.25 (t, J = 7.0, 3H), 1.93 (t, J = 13.2, 2H), 1.84-1.68 (m, 4H), 1.54 (q, J = 14.9, 2H), 1.18 (t, J = 7.1, 3H).

EXAMPLE 269



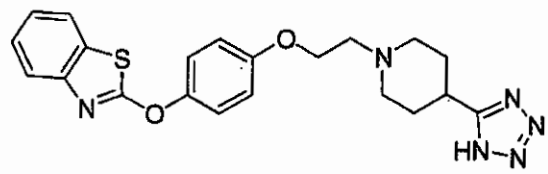
2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamine hydrochloride.

A. [2-(4-Hydroxy-phenyl)-ethyl]-carbamic acid tert-butyl ester. To a stirring solution of di-tert-butyl dicarbonate (34.2 g, 157 mmol) in THF (200 mL) was added tyramine (21.3 g, 155 mmol) in THF (100 mL) over 1 h. The mixture was stirred for 2.5 h and concentrated under reduced pressure to give a clear golden oil which was purified on SiO_2 (300 g; 0-25% acetone/CH_2Cl_2). The desired fractions were combined and concentrated under reduced pressure to give the product as a clear pink oil (37 g, 100% yield). TLC (SiO_2, 5% acetone/CH_2Cl_2): R_f = 0.31. MS (ESI): mass calculated for $C_{13}H_{19}NO_3$, 237.1; m/z found, 260.2 $[M+Na]^+$. ^1H NMR (400 MHz, DMSO-d_6): 9.16 (s, 1H), 6.96 (d, J = 8.4, 2H), 6.82 (s, 1H), 6.66 (d, J = 8.4, 2H), 3.05 (q, J = 8.3, 2H), 2.56 (t, J = 8.1, 2H), 1.37 (s, 9H).

B. {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-carbamic acid tert-butyl ester. The title compound was prepared following the procedure from EXAMPLE 30, step B using [2-(4-hydroxy-phenyl)-ethyl]-carbamic acid tert-butyl ester to give a white solid (9 g, 56% yield). TLC (SiO_2, CH_2Cl_2): R_f = 0.19. MS (ESI): mass calculated for $C_{20}H_{22}N2O_3S$, 370.1; m/z found, 371.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.92 (d, J = 7.9, 1H), 7.68 (d, J = 8.0, 1H), 7.48-7.30 (m, 6H), 7.34 (t, J = 7.8, 1H), 3.09 (d, J = 7.1, 2H), 2.75 (t, J = 7.4, 2H), 1.38 (s, 9H).

C. 2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamine hydrochloride. The title compound was prepared according to the procedure for EXAMPLE 266, step B to give a white solid (6.4 g, 100% yield). MS (ESI): mass calculated for $C_{15}H_{14}N_2OS$, 270.1; m/z found, 271.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.05 (br s, 2H), 7.94 (d, J = 7.8, 1H), 7.68 (d, J = 7.8, 1H), 7.53-7.39 (m, 5H), 7.34 (t, J = 7.9, 1H), 3.09 (t, J = 6.9, 2H), 2.95 (t, J = 8.6, 2H).

EXAMPLE 270



2-(4-{2-[4-(1H-Tetrazol-5-yl)-piperidin-1-yl]-ethoxy}-phenoxy)-benzothiazole.

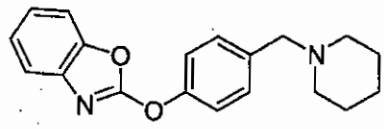
A. [4-(Benzothiazol-2-yloxy)-phenoxy]-acetic acid methyl ester. To a stirring mixture of sodium hydride (7.5 g, 187.5 mmol) in DMSO (100 mL) was added hydroquinone (10.0 g, 91.2 mmol) over 30 minutes. The mixture was then heated to 80 °C for 2 h and cooled to room temperature. To the stirring mixture was added 2-chlorobenzothiazole (11.3 mL, 91.3 mmol) over 30 minutes and the mixture was stirred at room temperature for 24 h. To the mixture was added methyl-2-bromoacetate (8.6 mL, 90.8 mmol) over 30 minutes and the mixture stirred for 24 h. To the mixture was added H_2O (1 L) and the product extracted with Et_2O (2 x 500 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a beige solid. The solid was stirred in CH_2Cl_2 (200 mL) and filtered to give the product as a white solid (24.2 g, 84% yield). MS (ESI): mass calculated for $C_{16}H_{13}NO_4S$, 315.1; m/z found, 316.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.92 (d, J = 8.0, 1H), 7.66 (d, J = 8.1, 1H), 7.47-7.40 (m, 3H), 7.32 (t, J = 7.5, 1H), 7.07 (d, J = 8.6, 2H), 4.87 (s, 2H), 3.73 (s, 3H).

B. [4-(Benzothiazol-2-yloxy)-phenoxy]-acetaldehyde. To a stirring solution of [4-(benzothiazol-2-yloxy)-phenoxy]-acetic acid methyl ester (1.0 g, 3.17 mmol) in THF (15 mL) at –78 °C was added DIBAL-H (5 mL, 5 mmol) while maintaining the temperature below –75 °C. The mixture was stirred at –72 °C for 4 h and quenched with H2O (10 mL), extracted with CH_2Cl_2 (2 x 10 mL), dried (MgSO4), and concentrated under reduced pressure to give a clear golden oil (708 mg, 78% yield). MS (ESI): mass calculated for $C_{15}H_{11}NO_3S$, 285.1; m/z found, 286.3 $[M+H]^+$.

C. 2-(4-{2-[4-(1H-Tetrazol-5-yl)-piperidin-1-yl]-ethoxy}-phenoxy)-benzothiazole. The title compound was prepared according to the procedure for EXAMPLE 262, step B using 4-(1H-tetrazol-5-yl)-piperidine. MS (ESI): mass calculated

for $C_{21}H_{22}N_6O_2S$; 422.2; m/z found, 422.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.93 (d, J = 7.8, 1H), 7.68 (d, J = 7.9, 1H), 7.49-7.40 (m, 3H), 7.33 (t, J = 7.3, 1H), 7.14 (d, J = 9.0, 2H), 4.43 (t, J = 4.3, 2H), 3.62-3.43 (m, 4H), 3.25-3.10 (m, 3H), 2.25 (d, J = 12.0, 2H), 2.18-2.02 (m, 2H).

EXAMPLE 271

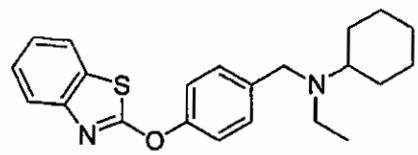


2-(4-Piperidin-1-ylmethyl-phenoxy)-benzooxazole.

A. 4-Piperidin-1-ylmethyl-phenol. A mixture of 4-hydroxybenzaldehyde (10 g, 82 mmol), piperidine (16 mL, 164 mmol), and molecular sieves (10 g, crushed, 4Å) in $ClCH_2CH_2Cl$ (150 mL) was stirred at room temperature for 40 min. To the resulting mixture was added $NaBH(OAc)_3$ portion wise over 1.5 h (7 x 5 g, 164 mmol). The mixture was stirred at room temperature for 24 h. The resulting mixture was diluted with CH_2Cl_2, (300 mL) filtered through diatomaceous earth and rinsed with additional CH_2Cl_2 (100 mL). The filtrate was washed with sat. aq. $NaHCO_3$ (3 x 150 mL), and extracted with 25% isopropanol/$CHCl_3$, dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as a orange semi-solid. The crude product was purified on SiO_2 (120 g; 0-100% acetone/CH_2Cl_2) to give a yellow solid (3.08 g, 48% yield). MS (ESI): mass calculated for $C_{12}H_{17}NO$, 191.1; m/z found, 192.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.18 (d, J = 8.4, 2H), 6.75 (d, J = 8.4, 2H), 3.83 (s, 2H), 2.81 (br s, 4H), 1.77 (quint, J = 5.7, 4H), 1.54 (br s, 2H).

B. 2-(4-Piperidin-1-ylmethyl-phenoxy)-benzooxazole. The title compound was prepared according to the procedure for EXAMPLE 13, step B using 4-piperidin-1-ylmethyl-phenol. MS (ESI): mass calculated for $C_{19}H_{20}N_2O_2S$, 308.2; m/z found, 309.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.64 (d, J = 3.1 Hz, 1H), 7.52 (d, J = 8.9 Hz, 1H), 7.3 (q, J = 8.3 Hz, 4H), 7.34-7.26 (m, 2H), 3.45 (s, 2H), 2.33 (br.s, 4H), 1.57-1.46 (m, 4H), 1.44-1.32 (m, 2H).

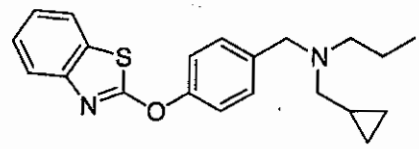
EXAMPLE 272



[4-(Benzothiazol-2-yloxy)-benzyl]-cyclohexyl-ethyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using cyclohexyl-ethyl-amine. MS (ESI): mass calculated for $C_{22}H_{26}N_2OS$, 366.2; m/z found, 367.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.93 (d, J = 8.5, 1H), 7.70 (d, J = 8.0, 1H), 7.45 (t, J = 8.5, 3H), 7.37 (d, J = 8.6, 2H), 7.33 (t, J = 8.3, 1H), 3.63 (s, 2H), 2.58-2.41 (m, 3H), 1.76 (t, J = 11.9, 4H), 1.58 (d, J = 12.1, 1H), 1.32-1.01 (m, 5H), 0.95 (t, J = 7.1, 3H).

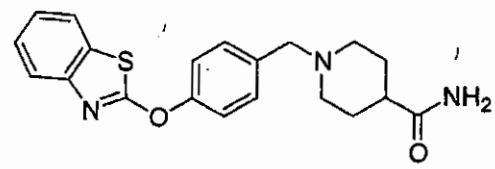
EXAMPLE 273



[4-(Benzothiazol-2-yloxy)-benzyl]-cyclopropylmethyl-propyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using (2-cyclopropyl-methyl)-ethyl-amine. MS (ESI): mass calculated for $C_{21}H_{24}N_2OS$, 352.2; m/z found, 353.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 8.0, 1H), 7.70 (d, J = 8.1, 1H), 7.45 (t, J = 8.5, 3H), 7.39 (d, J = 8.6, 2H), 7.33 (t, J = 8.0, 1H), 3.66 (s, 2H), 2.53-2.44 (m, 3H), 2.32 (d, J = 6.5, 2H), 1.54-1.42 (m, 2H), 1.32-1.01 (m, 5H), 0.85 (d, J = 7.3, 4H), 0.45 (d, J = 9.7, 2H), 0.06 (t, J = 6.2, 2H).

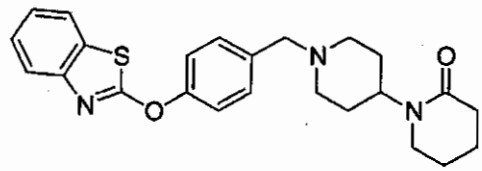
EXAMPLE 274



1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidine-4-carboxylic acid amide.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using piperidine-4-carboxylic acid amide. MS (ESI): mass calculated for $C_{20}H_{21}N_3O_2S$, 367.1; m/z found, 368.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 7.4, 1H), 7.70 (d, J = 7.9, 1H), 7.48-7.38 (m, 5H), 7.33 (d, J = 7.1, 1H), 7.22 (s, 1H), 6.73 (s, 1H), 3.49 (s, 2H), 2.83 (d, J = 11.4, 2H), 2.14-2.02 (m, 1H), 2.00-1.93 (m, 2H), 1.73-1.62 (m, 2H), 1.58 (t, J = 15.4, 2H).

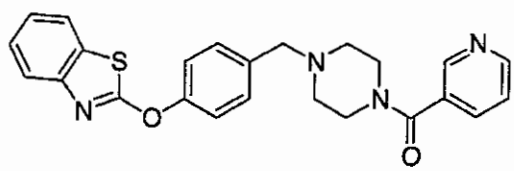
EXAMPLE 275



1'-[4-(Benzothiazol-2-yloxy)-benzyl]-[1,4']bipiperidinyl-2-one.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using [1,4']bipiperidinyl-2-one. MS (ESI): mass calculated for $C_{24}H_{27}N_3O_2S$, 421.2; m/z found, 422.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 8.8, 1H), 7.70 (d, J = 8.6, 1H), 7.48-7.38 (m, 5H), 7.33 (d, J = 9.0, 1H), 4.37-4.25 (m, 1H), 3.52 (s, 2H), 3.16 (t, J = 5.2, 2H), 2.89 (d, J =11.2, 2H), 2.22 (t, J = 6.6, 2H), 2.03 (t, J = 11.1, 2H), 1.78-1.58 (m, 6H), 1.45 (d, J = 10.8, 2H).

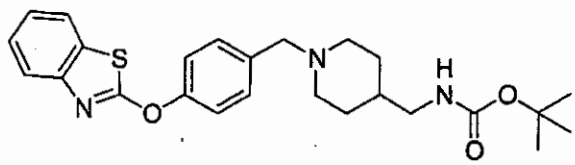
EXAMPLE 276



{4-[4-(Benzothiazol-2-yloxy)-benzyl]-piperazin-1-yl}-pyridin-3-yl-methanone.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using piperazin-1-yl-pyridin-3-yl-methanone. MS (ESI): mass calculated for $C_{24}H_{22}N_4O_2S$, 430.2; m/z found, 431.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.65 (d, J = 4.8, 1H), 8.61 (d, J = 1.9, 1H), 7.94 (d, J = 7.9, 1H), 7.84 (d, J = 7.8, 1H), 7.69 (d, J = 8.0, 1H), 7.60-7.40 (m, 6H), 7.33 (d, J = 8.3, 1H), 3.64 (br s, 2H), 3.58 (s, 2H), 3.37 (br s, 2H), 2.41 (br s, 4H).

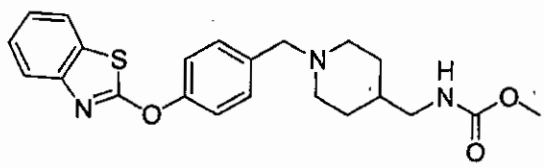
EXAMPLE 277



{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-carbamic acid tert-butyl ester.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using piperidin-4-ylmethyl-carbamic acid tert-butyl ester. MS (ESI): mass calculated for $C_{25}H_{31}N_3O_3S$, 453.2; m/z found, 454.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 7.3, 1H), 7.70 (d, J = 7.9, 1H), 7.48-7.37 (m, 5H), 7.33 (d, J = 8.2, 1H), 6.85 (t, J = 5.9, 1H), 3.48 (s, 2H), 2.86-2.76 (m, 4H), 1.90 (t, J =11.1, 2H), 1.56 (d, J = 11.8, 2H), 1.37 (s, 10H), 1.11 (t, J = 9.9, 2H).

EXAMPLE 278

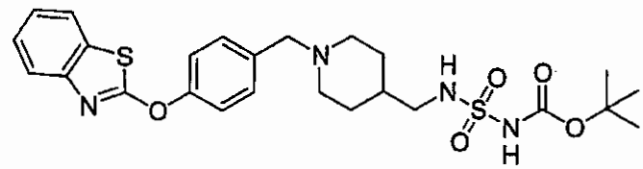


{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-carbamic acid methyl ester.

The title compound was prepared according to the procedure for EXAMPLE 258, step C using methyl chloroformate. MS (ESI): mass calculated for $C_{22}H_{25}N_3O_3S$, 411.2; m/z found, 412.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6):

7.94 (d, J = 7.9, 1H), 7.70 (d, J = 8.0, 1H), 7.48-7.36 (m, 5H), 7.33 (d, J = 8.0, 1H), 7.17 (t, J = 5.6, 1H), 3.51 (s, 3H), 3.48 (s, 2H), 2.87 (t, J = 6.2, 2H), 2.80 (d, J =11.1, 2H), 1.90 (t, J = 10.5, 2H), 1.60 (t, J = 12.8, 2H), 1.38 (br s, 1H), 1.20-1.06 (m, 2H).

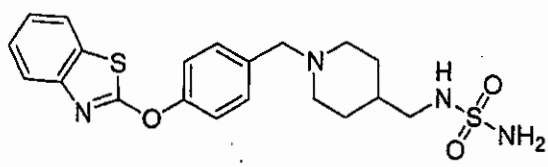
EXAMPLE 279



N-{C-[[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl]-methylamino sulfonyl}-carbamic acid tert-butyl ester

To a stirring solution of C-{1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-methylamine (EXAMPLE 258, step B, 657 mg, 1.5 mmol) in CH_2Cl_2 (15 mL) containing triethylamine (1 mL, 7.2 mmol) was added carbamic acid, N-(sulfonyl chloride) tert butyl ester (440 mg, 2.1 mmol). The mixture was stirred for 48 h and brought up in CH_2Cl_2 (50 mL) and washed once with H_2O (75 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a clear and colorless oil. The oil was purified on SiO_2 (12 g, 0-50% acetone/CH_2Cl_2) and the desired fractions combined and concentrated under reduced pressure to give a white solid (112 mg, 14% yield). TLC (SiO_2, 50% acetone/CH_2Cl_2): R_f = 0.40. MS (ESI): mass calculated for $C_{25}H_{32}N_4O_5S_2$, 532.2; m/z found, 533.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 10.74 (br s, 1H), 7.90 (d, J = 7.9, 1H), 7.66 (d, J = 8.0, 1H), 7.54 (br s, 1H), 7.44-7.34 (m, 5H), 7.30 (d, J = 8.3, 1H), 3.48 (s, 2H), 2.84-2.70 (m, 4H), 1.90 (t, J =10.4, 2H), 1.64 (d, J = 11.4, 2H), 1.38 (s, 10H), 1.16-1.02 (m, 2H).

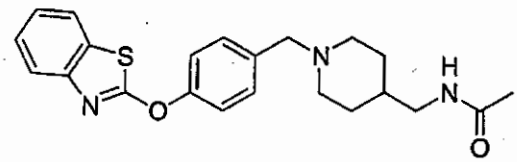
EXAMPLE 280



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-sulfamide hydrochloride

The title compound was prepared from EXAMPLE 279 following the procedure for EXAMPLE 266, step B. MS (ESI): mass calculated for $C_{20}H_{24}N_4O_3S_2$, 432.1; m/z found, 433.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 10.08 (br s, 1H), 7.80 (d, J = 8.2, 1H), 7.76-7.68 (m, 3H), 7.58 (d, J = 8.6, 2H), 7.45 (t, J = 8.4, 2H), 7.36 (t, J = 8.8, 2H), 6.70-6.50 (br s, 2H), 4.33 (d, J = 5.4, 2H), 3.00-2.86 (br s, 1H), 2.77 (t, J = 6.2, 2H), 1.91 (d, J = 13.4, 2H), 1.71 (br s, 1H), 1.50-1.36 (m, 2H), 1.34-1.26 (m, 1H).

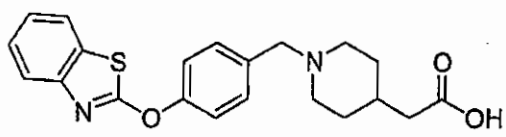
EXAMPLE 281



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-acetamide.

The title compound was prepared according to the procedure for EXAMPLE 258, step C using acetyl chloride. MS (ESI): mass calculated for $C_{22}H_{25}N_3O_2S$, 395.2; m/z found, 396.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 7.8, 1H), 7.83 (t, J = 5.5, 1H), 7.70 (d, J = 8.0, 1H), 7.48-7.36 (m, 5H), 7.33 (d, J = 8.2, 1H), 3.48 (s, 2H), 2.93 (t, J = 6.2, 2H), 2.81 (d, J = 11.4, 2H), 1.91 (t, J = 11.3, 2H), 1.80 (s, 3H), 1.61 (d, J = 11.0, 2H), 1.38 (br s, 1H), 1.20-1.06 (m, 2H).

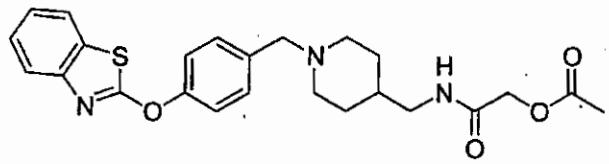
EXAMPLE 282



{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-acetic acid.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using piperidin-4-yl-acetic acid ethyl ester and EXAMPLE 250, step D. MS (ESI): mass calculated for $C_{21}H_{22}N_2O_3S$, 382.1; m/z found, 383.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 10.1 (br s, 1H), 7.97 (d, J = 7.9, 1H), 7.70 (d, J = 7.6, 3H), 7.58 (br s, 2H), 7.45 (t, J = 7.2, 1H), 7.36 (t, J = 7.3, 1H), 4.31 (br s, 1H), 2.98 (br s, 3H), 2.20 (d, J = 5.6, 3H), 1.87 (br s, 4H), 1.51 (br s, 2H).

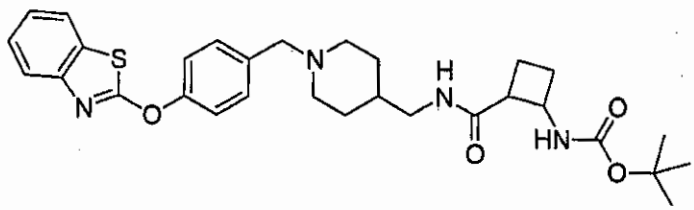
EXAMPLE 283



Acetic acid ({1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-carbamoyl)-methyl ester.

The title compound was prepared according to the procedure for EXAMPLE 258, step D using acetic acid [(piperidin-4-ylmethyl)-carbamoyl]-methyl ester and EXAMPLE 253, step D. MS (ESI): mass calculated for $C_{24}H_{27}N_3O_4S$, 453.2; m/z found, 454.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.01 (t, J = 5.8, 1H), 7.94 (d, J = 7.5, 1H), 7.70 (d, J = 8.0, 1H), 7.80-7.36 (m, 5H), 7.33 (t, J = 7.2, 1H), 4.43 (s, 2H), 3.48 (s, 2H), 2.98 (t, J = 6.3, 2H), 2.81 (d, J = 11.4, 2H), 2.08 (s, 3H), 1.91 (t, J = 11.2, 2H), 1.60 (d, J = 11.2, 2H), 1.42 (br s, 1H), 1.20-1.08 (m, 2H).

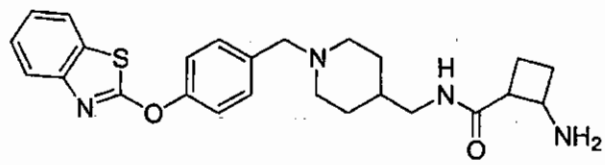
EXAMPLE 284



[2-({1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-carbamoyl)-cyclobutyl]-carbamic acid tert-butyl ester.

The title compound was prepared from EXAMPLE 258, step B following EXAMPLE 257, step C using 2-tert-butoxycarbonylamino-cyclobutanecarboxylic acid. MS (ESI): mass calculated for $C_{30}H_{38}N_4O_4S$, 550.3; m/z found, 551.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 7.9, 1H), 7.70 (d, J = 8.0, 1H), 7.47-7.35 (m, 7H), 7.33 (t, J = 7.3, 1H), 3.47 (s, 2H), 2.95 (t, J = 6.1, 2H), 2.78 (t, J = 9.6, 2H), 2.45-2.35 (m, 2H), 2.13 (s, 1H), 2.05-1.95 (m, 2H), 1.93-1.70 (m, 4H), 1.59 (d, J = 10.9, 2H), 1.38 (s, 9H), 1.20-1.05 (m, 2H).

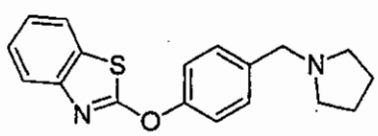
EXAMPLE 285



2-Amino-cyclobutanecarboxylic acid {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-amide dihydrochloride.

The title compound was prepared according to the procedure for EXAMPLE 266, step B. MS (ESI): mass calculated for $C_{25}H_{30}N_4O_2S$, 450.2; m/z found, 451.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.78-8.55 (m, 4H), 7.97 (d, J = 8.1, 1H), 7.78 (d, J = 8.6, 3H), 7.71 (d, J = 7.8, 1H), 7.45 (t, J = 8.5, 1H), 7.36 (t, J = 7.1, 1H), 4.32 (s, 2H), 3.20-3.05 (m, 2H), 3.00-2.85 (m, 2H), 2.472 (d, J = 4.7, 2H), 2.62-2.50 (m, 2H), 2.65-2.42 (m, 2H), 2.38-2.05 (m, 1H), 2.02-1.70 (m, 6H), 1.68-1.50 (s, 2H).

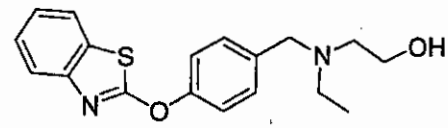
EXAMPLE 286



2-(4-Pyrrolidin-1-ylmethyl-phenoxy)-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using pyrrolidine. MS (ESI): mass calculated for $C_{18}H_{18}N_2OS$, 310.1; m/z found, 311.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 9.0, 1H), 7.70 (d, J = 8.0, 1H), 7.48-7.37 (m, 5H), 7.33 (t, J = 7.7, 1H), 3.62 (s, 2H), 2.49-2.40 (m, 4H), 1.78-1.65 (m, 4H).

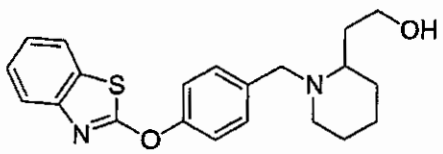
EXAMPLE 287



2-{[4-(Benzothiazol-2-yloxy)-benzyl]-ethyl-amino}-ethanol.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using 2-ethylamino-ethanol. MS (ESI): mass calculated for $C_{18}H_{20}N_2O_2S$, 328.1; m/z found, 329.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 8.0, 1H), 7.70 (d, J = 7.7, 1H), 7.50-7.36 (m, 5H), 7.33 (t, J = 7.7, 1H), 4.39 (t, J = 5.4, 1H), 3.63 (s, 2H), 3.49 (q, J = 6.4, 2H), 2.57-2.45 (m, 4H), 1.00 (t, J = 7.1, 3H).

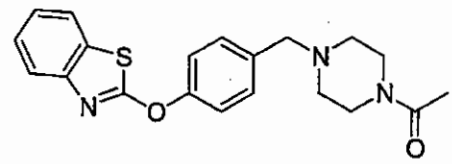
EXAMPLE 288



2-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-2-yl}-ethanol.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using 2-piperidin-2-yl-ethanol. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_2S$, 368.2; m/z found, 369.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.93 (d, J = 8.0, 1H), 7.70 (d, J = 7.7, 1H), 7.48-7.36 (m, 5H), 7.33 (t, J = 6.9, 1H), 4.42 (s, 1H), 3.92 (d, J = 14.0, 1H), 3.50 (br s, 2H), 3.31 (d, J = 6.4, 1H), 2.70-2.60 (m, 1H), 2.14-2.03 (m, 1H), 1.87-1.75 (m, 1H), 1.70-1.55 (m, 3H), 1.53-1.27 (m, 5H).

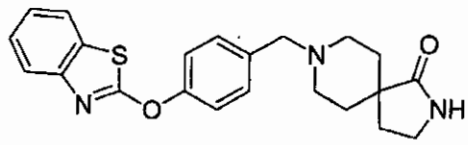
EXAMPLE 289



1-{4-[4-(Benzothiazol-2-yloxy)-benzyl]-piperazin-1-yl}-ethanone.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using 1-piperazin-1-yl-ethanone. MS (ESI): mass calculated for $C_{20}H_{21}N_3O_2S$, 367.1; m/z found, 368.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 8.0, 1H), 7.70 (d, J = 7.5, 1H), 7.48-7.39 (m, 5H), 7.33 (t, J = 7.7, 1H), 3.55 (s, 2H), 3.50-3.40 (m, 4H), 2.40 (t, J = 4.9, 2H), 2.33 (t, J = 5.0, 2H), 1.99 (s, 3H).

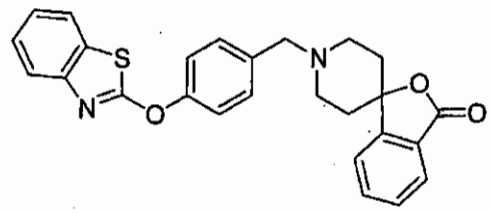
EXAMPLE 290



8-[4-(Benzothiazol-2-yloxy)-benzyl]-2,8-diaza-spiro[4.5]decan-1-one.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using 2,8-diaza-spiro[4.5]decan-1-one. MS (ESI): mass calculated for $C_{22}H_{23}N_3O_2S$, 393.2; m/z found, 394.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 7.4, 1H), 7.70 (d, J = 8.0, 1H), 7.54 (s, 1H), 7.48-7.36 (m, 5H), 7.33 (t, J = 8.2, 1H), 3.51 (s, 2H), 3.15 (t, J = 6.8, 2H), 2.75(d, J = 11.6, 2H), 2.05 (t, J = 10.0, 2H), 1.91 (t, J = 6.8, 2H), 1.70 (t, J = 12.6, 2H), 1.33 (d, J = 12.8, 2H).

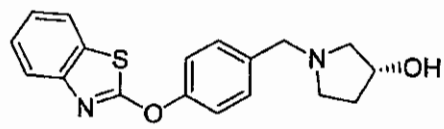
EXAMPLE 291



Spiro[isobenzofuran-1(3H), 4'-piperidin]-3-one, 1'-[4-(Benzothiazol-2-yloxy)-benzyl]

The title compound was prepared according to the procedure for EXAMPLE 259, step D using spiro[isobenzofuran-1(3H), 4'-piperidin]-3-one. MS (ESI): mass calculated for $C_{26}H_{22}N_2O_3S$, 442.1; m/z found, 443.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.95 (d, J = 7.9, 1H), 7.83 (d, J = 7.6, 1H), 7.82-7.76 (m, 2H), 7.70 (d, J = 8.0, 1H), 7.61 (t, J = 7.8, 1H), 7.56-7.48 (m, 2H), 7.47-7.40 (m, 3H), 7.33 (t, J = 7.4, 1H), 3.66 (s, 2H), 2.90 (d, J = 11.1, 2H), 2.41 (t, J = 11.0, 2H), 2.28 (t, J = 13.3, 2H), 1.66 (d, J = 12.6, 2H).

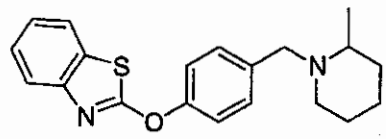
EXAMPLE 292



(*R*)-1-[4-(Benzothiazol-2-yloxy)-benzyl]-pyrrolidin-3-ol.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using (R)-pyrrolidin-3-ol. MS (ESI): mass calculated for $C_{18}H_{18}N_2O_2S$, 326.1; m/z found, 327.2 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 8.0, 1H), 7.70 (d, J = 8.1, 1H), 7.48-7.36 (m, 5H), 7.33 (t, J = 7.2, 1H), 4.72 (d, J = 4.5, 1H), 4.27-4.16 (m, 1H), 3.60 (q, J = 13.2, 2H), 2.73-2.65 (m, 1H), 2.60 (q, J = 8.1, 1H), 2.47-2.38 (m, 1H), 2.36-2.30 (m, 1H), 2.07-1.95 (m, 1H), 1.62-1.50 (m, 1H).

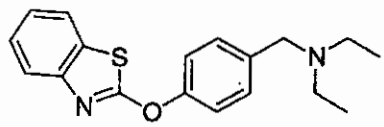
EXAMPLE 293



2-[4-(2-Methyl-piperidin-1-ylmethyl)-phenoxy]-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using 2-methyl-piperidine. MS (ESI): mass calculated for $C_{20}H_{22}N_2OS$, 338.2; m/z found, 339.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 8.0, 1H), 7.70 (d, J = 8.1, 1H), 7.30-7.33 (m, 5H), 7.33 (t, J = 7.9, 1H), 3.96 (d, J = 13.9, 1H), 3.19 (d, J = 13.9, 1H), 2.70-2.60 (m, 1H), 2.40-2.30 (m, 1H), 1.98 (t, J = 13.0, 1H), 1.68-1.56 (m, 2H), 1.54-1.34 (m, 2H), 1.32-1.24 (m, 2H), 1.11 (d, J = 6.2, 3H).

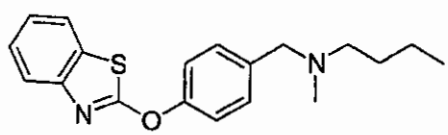
EXAMPLE 294



[4-(Benzothiazol-2-yloxy)-benzyl]-diethyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using diethylamine. MS (ESI): mass calculated for $C_{18}H_{20}N_2OS$, 312.1; m/z found, 313.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 7.9, 1H), 7.70 (d, J = 8.0, 1H), 7.48-7.36 (m, 5H), 7.33 (t, J = 7.2, 1H), 3.57 (s, 2H), 2.48 (q, J = 7.1, 4H), 1.00 (t, J = 7.1, 6H).

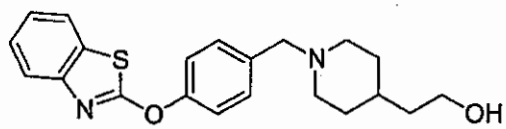
EXAMPLE 295



[4-(Benzothiazol-2-yloxy)-benzyl]-butyl-methyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using butyl-methyl-amine. MS (ESI): mass calculated for $C_{19}H_{22}N_2OS$, 326.2; m/z found, 327.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 7.9, 1H), 7.70 (d, J = 7.5, 1H), 7.48-7.36 (m, 5H), 7.33 (t, J = 8.0, 1H), 3.49 (s, 2H), 2.34 (t, J = 7.1, 2H), 2.13 (s, 3H), 1.50-1.40 (m, 2H), 1.38-1.24 (m, 2H), 0.88 (t, J = 7.3, 3H).

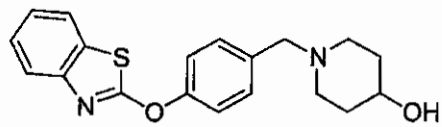
EXAMPLE 296



2-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-ethanol.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using 2-piperidin-4-yl-ethanol. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_2S$, 368.2; m/z found, 369.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.74 (d, J = 7.9, 1H), 7.49 (d, J = 8.0, 1H), 7.30-7.16 (m, 5H), 7.13 (t, J = 7.9, 1H), 4.13 (t, J = 5.1, 1H), 3.27 (s, 2H), 3.23 (q, J = 6.2, 2H), 2.59 (d, J = 11.1, 2H), 1.72 (t, J = 10.3, 2H), 1.42 (d, J = 12.1, 2H), 1.16 (t, J = 3.8, 3H), 1.00-0.85 (m, 2H).

EXAMPLE 297

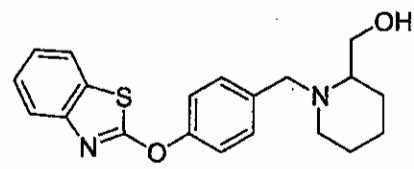


1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using piperidin-4-ol. MS (ESI): mass calculated for $C_{19}H_{20}N_2O_2S$, 340.1; m/z found, 341.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 7.9, 1H), 7.68 (d, J = 8.0, 1H), 7.46-7.36 (m, 5H), 7.32 (t, J = 8.1, 1H), 4.60 (d, J = 4.9, 1H), 3.58-3.40 (m, 3H), 2.80 (d, J = 9.9, 1H), 2.65 (d, J = 10.7, 1H),

1.87 (t, *J* = 9.2, 1H), 1.80 (d, *J* = 8.6, 1H), 1.71 (t, *J* = 9.8, 1H), 1.62 (d, *J* = 13.3, 1H), 1.48-1.38 (m, 1H), 1.12-1.00 (m, 1H).

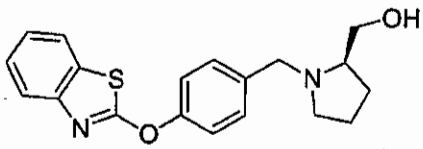
EXAMPLE 298



{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-2-yl}-methanol.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using piperidin-2-yl-methanol. MS (ESI): mass calculated for $C_{20}H_{22}N_2O_2S$, 354.1; m/z found, 355.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.98 (d, *J* = 7.2, 1H), 7.74 (d, *J* = 8.0, 1H), 7.53-7.42 (m, 5H), 7.37 (t, *J* = 8.3, 1H), 4.60 (t, *J* = 5.2, 1H), 4.18 (d, *J* = 14.1, 1H), 3.75-3.65 (m, 1H), 3.56-3.46 (m, 1H), 3.37 (d, *J* = 3.8, 1H), 2.72 (d, *J* = 11.9, 1H), 2.36 (d, *J* = 4.8, 1H), 2.07 (t, *J* = 9.7, 1H), 1.72 (t, *J* = 13.2, 2H), 1.58-1.26 (m, 4H).

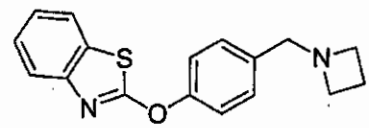
EXAMPLE 299



(*R*)-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-pyrrolidin-2-yl}-methanol.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using (*R*)-pyrrolidin-2-yl-methanol. MS (ESI): mass calculated for $C_{19}H_{20}N_2O_2S$, 340.1; m/z found, 340.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.97 (d, *J* = 7.2, 1H), 7.73 (d, *J* = 7.8, 1H), 7.50-7.38 (m, 5H), 7.36 (t, *J* = 7.9, 1H), 4.90 (t, *J* = 5.4, 1H), 4.14 (d, *J* = 13.4, 1H), 3.55-3.48 (m, 1H), 3.42 (d, *J* = 13.4, 2H), 2.84 (t, *J* = 6.6, 1H), 2.68-2.58 (m, 1H), 2.20 (q, *J* = 8.6, 1H), 1.95-1.83 (m, 1H), 1.72-1.55 (m, 3H).

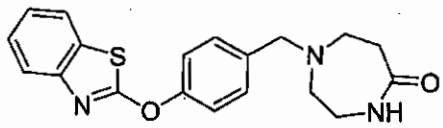
EXAMPLE 300



2-(4-Azetidin-1-ylmethyl-phenoxy)-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using azetidine. MS (ESI): mass calculated for $C_{17}H_{16}N_2OS$, 296.1; m/z found, 297.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.80 (d, J = 8.5, 1H), 7.56 (d, J = 8.0, 1H), 7.35-7.24 (m, 5H), 7.19 (t, J = 7.3, 1H), 3.43 (s, 2H), 3.02 (t, J = 7.0, 4H), 1.92-1.80 (m, 2H).

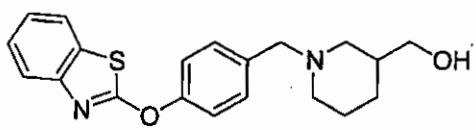
EXAMPLE 301



1-[4-(Benzothiazol-2-yloxy)-benzyl]-[1,4]diazepan-5-one.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using [1,4]diazepan-5-one. MS (ESI): mass calculated for $C_{19}H_{19}N_3O_2S$, 353.1; m/z found, 354.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.94 (d, J = 7.9, 1H), 7.69 (d, J = 7.9, 1H), 7.57 (t, J = 5.4, 1H), 7.44-7.33 (m, 5H), 7.33 (t, J = 8.2, 1H), 3.62 (s, 2H), 3.18-3.10 (m, 2H), 2.58-2.40 (m, 6H).

EXAMPLE 302

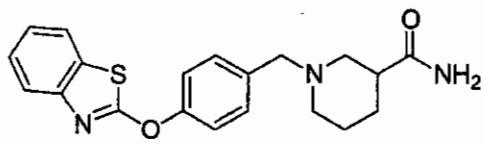


{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-3-yl}-methanol.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using piperidin-3-yl-methanol. MS (ESI): mass calculated for

$C_{20}H_{22}N_2O_2S$, 354.1; m/z found, 355.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.98 (d, J = 7.2, 1H), 7.74 (d, J = 7.9, 1H), 7.50-7.42 (m, 5H), 7.38 (t, J = 8.2, 1H), 4.46 (t, J = 5.3, 1H), 3.52 (d, J = 3.4, 2H), 3.36-3.29 (m, 1H), 3.27-3.18 (m, 1H), 2.92 (d, J = 8.1, 1H), 2.77 (d, J = 10.8, 1H), 1.96 (d, J = 12.8, 1H), 1.75-1.60 (m, 4H), 1.58-1.45 (m, 1H), 1.00-0.85 (m, 1H).

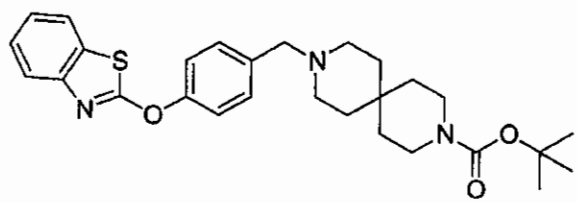
EXAMPLE 303



1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidine-3-carboxylic acid amide.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using piperidine-3-carboxylic acid amide. MS (ESI): mass calculated for $C_{20}H_{21}N_3O_2S$, 367.1; m/z found, 368.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.70 (d, J = 7.8, 1H), 7.46 (d, J = 8.0, 1H), 7.25-7.00 (m, 7H), 6.53 (s, 1H), 3.26 (d, J = 2.9, 2H), 2.57 (d, J = 10.3, 1H), 2.49 (d, J = 11.3, 1H), 2.15-2.00 (m, 1H), 1.78 (t, J = 10.7, 1H), 1.69 (t, J = 9.4, 1H), 1.51 (d, J = 10.0, 1H), 1.40 (d, J = 12.9, 1H), 1.22 (q, J = 12.6, 1H), 1.09 (q, J = 12.2, 1H).

EXAMPLE 304

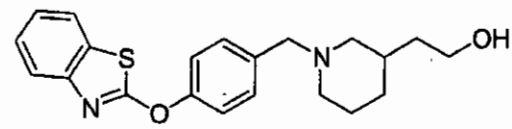


9-[4-(Benzothiazol-2-yloxy)-benzyl]-3,9-diaza-spiro[5.5]undecane-3-carboxylic acid tert-butyl ester.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using 3,9-diaza-spiro[5.5]undecane-3-carboxylic acid tert-butyl ester. MS (ESI): mass calculated for $C_{28}H_{35}N_3O_3S$, 493.2; m/z found, 494.5 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.13 (d, J = 7.9, 1H), 7.89 (d, J = 8.0,

1H), 7.68-7.56 (m, 5H), 7.53 (t, *J* = 7.1, 1H), 3.70 (s, 2H), 3.51-3.45 (m, 4H), 2.60-2.50 (m, 4H), 1.66 (t, *J* = 5.3, 4H), 1.58 (s, 9H), 1.54 (t, *J* = 5.4, 4H).

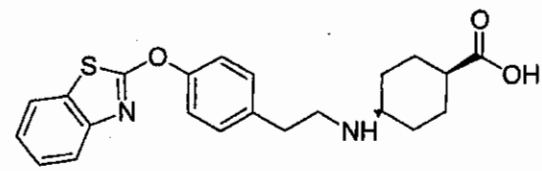
EXAMPLE 305



2-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-3-yl}-ethanol.

The title compound was prepared according to the procedure for EXAMPLE 259, step D using 2-piperidin-3-yl-ethanol. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_2S$, 368.2; m/z found, 369.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 7.71 (d, *J* = 8.4, 1H), 7.47 (d, *J* = 7.9, 1H), 7.25-7.15 (m, 5H), 7.10 (t, *J* = 8.1, 1H), 4.12 (t, *J* = 5.1, 1H), 3.33-3.15 (m, 4H), 2.58-2.42 (m, 2H), 1.67 (t, *J* = 9.6, 1H), 1.53-1.33 (m, 4H), 1.30-1.00 (m, 3H), 0.70-0.58 (m, 1H).

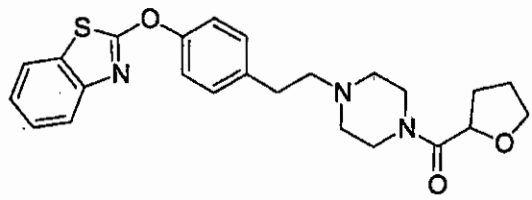
EXAMPLE 306



cis-4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-cyclohexanecarboxylic acid trifluoromethanesulfonate salt.

The title compound was prepared according to the procedure for EXAMPLE 262, step B using cis-4-amino-cyclohexanecarboxylic acid. MS (ESI): exact mass calculated for $C_{22}H_{24}N_2O_3S$, 396.2; m/z found, 397.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 9.15, (s, 1H), 7.75 (d, *J* = 7.6, 1H), 7.72 (dd, *J* = 8.0, 0.7, 1H), 7.43 (dt, *J* = 7.2, 1.2, 1H), 7.37-7.29 (m, 5H), 5.10 (br s, 1H), 3.29 (br s, 2H), 3.10 (t, *J* = 7.4, 3H), 2.73 (br s, 1H), 2.24 (br d, *J* = 10.6, 2H), 2.09 (br d, *J* = 9.3, 2H), 1.72-1.52 (m, 3H).

EXAMPLE 307

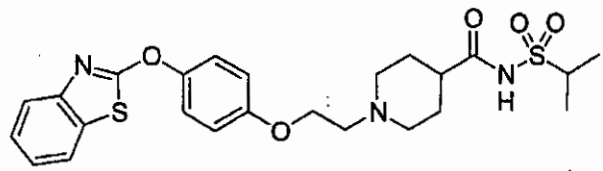


(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(tetrahydro-furan-2-yl)-methanone.

A. 2-[4-(2-Piperazin-1-yl-ethyl)-phenoxy]-benzothiazole bis trifluoromethane sulfonate. 4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester was prepared according to Example 262, step B, using piperazine-1-carboxylic acid tert-butyl ester. A solution of 4-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester (3.9 g, 8.9 mmol) in CH_2Cl_2 (5 mL) with a solution of 50% trifluoromethansulfonic acid in CH_2Cl_2 (35 ml) and stirring at 23 °C for 4h. The reaction was concentrated and the residue suspended in diethyl ether, filtered and dried to give the title compound as a white solid (5.4 g, 94% yield). MS (ESI): exact mass calculated for $C_{19}H_{21}N_3O_1S_1$, 339.1; m/z found, 340.4 $[M+H]^+$. ^1H NMR (400 MHz, D_6-DMSO): 9.50-9.30 (br. s, 1H), 7.94 (dd, *J* =7.9, 0.6, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.48-7.41 (m, 5H), 7.39-7.30 (m, 1H), 4.15-3.50 (br. s, 1H), 3.45-3.32 (m, 8H), 3.32-3.20 (m, 2H), 3.01 (dd, *J*= 8.8, 5.2 Hz, 2H).

B. (4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(tetrahydro-furan-2-yl)-methanone. The title compound was prepared according to the procedure for Example 257 step C, using tetrahydro-furan-2-carboxylic acid and triethylamine. MS (ESI): exact mass calculated for $C_{24}H_{27}N_3O_3S$, 437.2; m/z found, 438.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (d, *J* = 7.3, 1H), 7.71 (dd, *J* = 7.8, 0.8, 1H), 7.42 (dt, *J* = 7.3, 1.2, 1H), 7.33-7.26 (m, 5H), 4.65 (dd, *J* = 7.0, 5.3, 1H), 3.99 (ddd, *J* = 7.7, 7.1, 6.7, 1H), 3.92-3.86 (m, 1H), 3.82-3.72 (m, 2H), 3.76 (s, 1H), 3.70-3.58 (m, 2H), 2.90 (dd, *J* = 10.3, 7.3, 2H), 2.70 (dd, *J* = 8.6, 5.6, 2H), 2.64-2.54 (m, 3H), 2.38-2.28 (m, 1H), 2.14-1.90 (m, 4H).

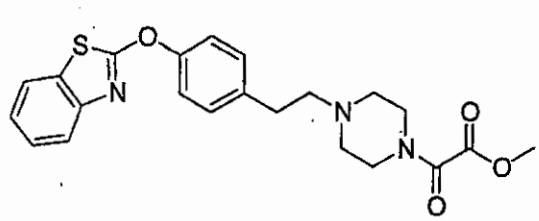
EXAMPLE 308



Propane-2-sulfonic acid (1-{2-[4-(benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carbonyl)-amide.

A solution of 1-{2-[4-(benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carboxylic acid amide (Example 22, 197 mg, 0.5 mmol) in THF (5 mL) was treated with NaH (14 mg, 0.6 mmol) and isopropylsulfonyl chloride (86 mg, 0.6 mmol) and the reaction was stirred at 60 °C for 16 h. The reaction was cooled and quenched by the addition of CH_3OH (5 mL) follwed by H_2O (5 mL)and the pH was adjusted to pH 7. The solution was extracted with ethyl acetate (2 x 25 mL) and the ethyl acetate solution was washed with 1 M NaOH (2 x 30 mL). The combined base washes were neutralized by the addition of 2 M HCl and extracted with chloroform (2 x 30 mL). The chloroform solutions were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified on SiO_2 (4 g, 0-10% 2 M NH_3/CH_3OH:CH_2Cl_2) to give the title compound as a solid (45 mg, 18% yield). MS (ESI): exact mass calculated for $C_{24}H_{29}N_3O_5S_2$, 503.2; m/z found, 504.5 $[M+H]^+$. ^1H NMR (400 MHz, C_6D_6): 7.77 (d, J = 7.8, 1H), 7.20 (dd, J = 8.0, 0.8, 1H), 7.16-7.10 (m, 2H), 7.07 (dt, J = 8.3, 1.0, 1H), 6.90 (dt, J = 8.0, 1.0, 1H), 6.76 (d, J = 8.8, 1H), 6.13 (s, 1H), 3.98 (br s, 2H), 3.51 (sept., J = 6.8, 2H), 3.20 (br s, 2H), 2.82 (br s, 1H), 2.37-2.00 (m, 4H), 1.96-1.84 (m, 2H), 1.33 (d, J = 6.6, 6H) 1.38-1.28 (m, 2H).

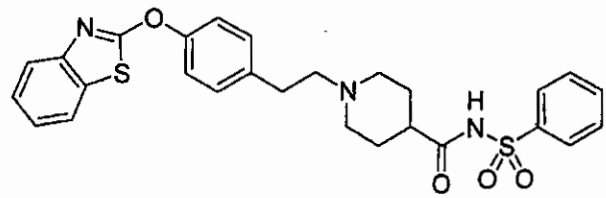
EXAMPLE 309



(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-oxo-acetic acid methyl ester.

A solution of 2-[4-(2-piperazin-1-yl-ethyl)-phenoxy]-benzothiazole bis-trifluoromethane sulfonate (296 mg, 0.52 mmol) in CH_2Cl_2 (3 mL) was treated with triethylamine (0.25 mL, 1.8 mmol), followed by addition of methyl chlorooxoacetate (0.07 mL, 0.8 mmol) and the reaction was stirred at 23 °C for 20 min. The reaction was diluted with CH_2Cl_2 (10 mL) and washed with sat. aq. $NaHCO_3$(10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound (234 mg, 99% yield). MS (ESI): exact mass calculated for $C_{22}H_{23}N_3O_4S$, 425.1; m/z found, 426.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.76 (d, J = 7.6, 0.5, 1H), 7.70 (d, J = 7.8, 1H), 7.41 (dt, J = 7.3, 1.0, 1H), 7.34-7.26 (m, 5H), 3.91 (s, 3H), 3.72 (t, J = 4.8, 2H), 3.51 (t, J = 4.8, 2H), 2.86, (dd, J = 10, 6.8, 2H), 2.70, (dd, J = 8.6, 5.6, 2H), 2.62-2.57 (m, 4H).

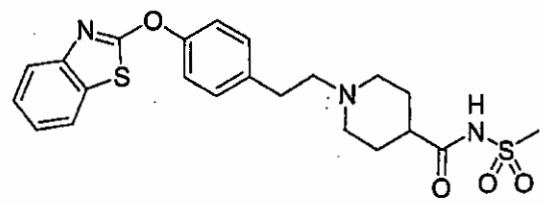
EXAMPLE 310



N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carbonyl)-benzenesulfonamide trifluoromethanesulfonate salt.

The title compound was prepared according to the procedure for Example 34, step B using benzene sulfonamide. MS (ESI): exact mass calculated for $C_{27}H_{27}N_3O_4S_2$, 521.1; m/z found, 522.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 8.60-8.00 (m, 2H), 7.82-7.76 (m, 1H), 7.73-7.57 (m, 4H), 7.48-7.28 (m, 5H), 3.70 (br s, 1H), 3.41-3.34 (m, 2H), 3.14-2.98 (m, 3H), 2.60 (br s, 1H), 2.08 (br d, J = 13.6, 2H), 1.86 (br s, 2H) 1.30 (br s, 2H), 0.94-0.88 (m, 2H).

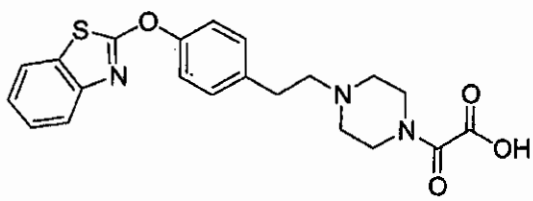
EXAMPLE 311



N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carbonyl)-methanesulfonamide trifluoromethanesulfonate salt.

The title compound was prepared according to the procedure for EXAMPLE 34, step B using methane sulfonamide. MS (ESI): exact mass calculated for $C_{22}H_{25}N_3O_4S_2$, 459.1; m/z found, 460.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.81 (d, J = 7.8, 1H), 7.62 (d, J = 8.1, 1H) 7.49-7.43 (m, 3H), 7.43-7.38 (m, 2H), 7.34 (t, J = 7.8, 1H), 3.80 (br d, J = 10.4, 1H), 3.48-3.40 (m, 2H), 3.33 (s, 3H), 3.28 (s, 2H), 3.20-3.04 (m, 3H), 2.70-2.60 (m, 1H), 2.21 (br d, J = 12.4, 2H), 2.06-1.93 (m, 2H).

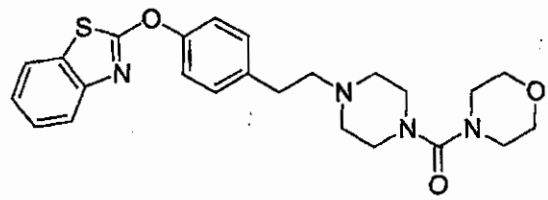
EXAMPLE 312



(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-oxo-acetic acid trifluoromethanesulfonate salt.

The title compound was prepared according to the procedure for Example 253, step D. MS (ESI): exact mass calculated for $C_{21}H_{21}N_3O_4S$, 411.1; m/z found, 412.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.75 (t, J = 8.3, 2H), 7.70 (dt, J = 8.0, 0.8, 1H), 7.28-7.22 (m, 5H), 4.28-3.88 (br m, 4H), 3.58-3.20 (br m, 6H), 3.16-3.04 (br m, 2H).

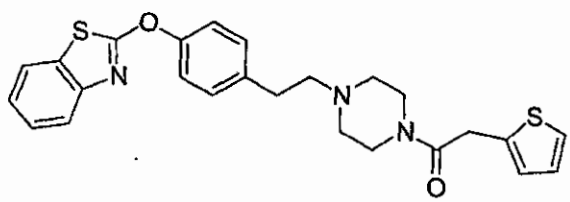
EXAMPLE 313



(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-morpholin-4-yl-methanone.

A solution of 2-[4-(2-piperazin-1-yl-ethyl)-phenoxy]-benzothiazole bis trifluoromethane sulfonate Example 307, step A (268 mg, 0.47 mmol) in CH_2Cl_2 (6 mL) was treated with PS-dimethylamine resin (1.3 g, 0.90 mmol) followed by 4-morpholine carbonyl chloride (0.07 mL, 0.6 mmol) and the reaction shaken for 1h. The reaction was treated with PS-isocyanate resin to scavenge excess isocyanate and after 15 min, the reaction was filtered and concentrated to give the title compound (225 mg, 99% yield). MS (ESI): exact mass calculated for $C_{24}H_{28}N_4O_3S_1$, 452.2; m/z found, 453.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (dd, J = 8.0, 0.5, 1H), 7.71 (dd, J = 7.8, 0.5, 1H), 7.42 (dt, J = 7.3, 1.2, 1H), 7.34-7.28 (m, 5H), 3.78-3.70 (m, 4H), 3.39 (br t, J = 4.3, 4H), 3.31 (t, J = 4.8, 4H), 2.90 (dd, J = 10.4, 7.3, 2H), 2.70 (dd, J = 8.3, 7.3, 2H), 2.59 (br s, 4H).

EXAMPLE 314

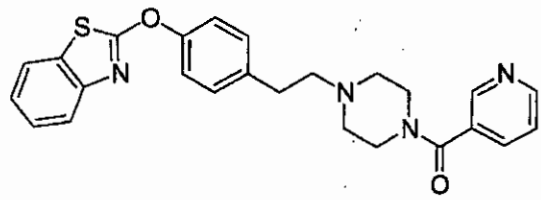


1-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-2-thiophen-2-yl-ethanone

The title compound was prepared according to the procedure for EXAMPLE 313 using 2-thiopheneacetyl chloride. MS (ESI): exact mass calculated for $C_{25}H_{25}N_3O_3S_2$, 463.1; m/z found, 464.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$):

7.77 (dd, *J* = 8.0, 0.5, 1H), 7.71 (dd, *J* = 7.8, 0.8, 1H), 7.43 (dt, *J* = 7.3, 1.2, 1H), 7.34-7.28 (m, 5H), 7.25 (dd, *J* = 5.3, 1.2, 1H), 7.00 (dd, *J* = 5.0, 3.2, 1H), 6.96-6.93 (m, 1H), 3.96 (d, *J* = 0.8, 2H), 3.74 (t, *J* = 4.8, 2H), 3.59 (t, *J* = 4.8, 2H), 2.86 (dd, *J* = 10.4, 7.6, 2H), 2.66 (dd, *J* = 8.3, 5.6, 2H), 2.55 (t, *J* = 5.3, 2H), 2.47 (t, *J* = 5.0, 2H).

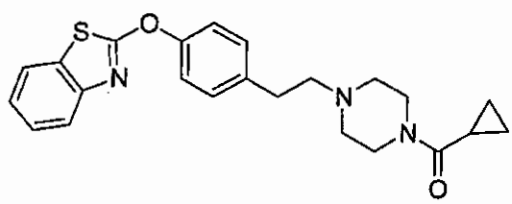
EXAMPLE 315



(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-pyridin-3-yl-methanone.

The title compound was prepared according to the procedure for EXAMPLE 313 using 2-nicotonyl chloride-hydrochloride. MS (ESI): exact mass calculated for $C_{25}H_{24}N_4O_2S$, 444.2; m/z found, 445.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.73-8.70 (m, 2H), 7.81 (dt, *J* = 7.9, 1.9, 1H), 7.77 (dd, *J* = 8.1, 0.5, 1H), 7.71 (ddd, *J* = 7.9, 0.7, 0.4, 1H), 7.45-7.39 (m, 2H), 7.34-7.28 (m, 5H), 3.90 (br s, 2H), 3.52 (br s, 2H), 2.92-2.85 (m, 2H), 2.71 (dd, *J* = 8.9, 5.6, 2H), 2.74-2.60 (m, 2H), 2.54 (br s, 2H).

EXAMPLE 316

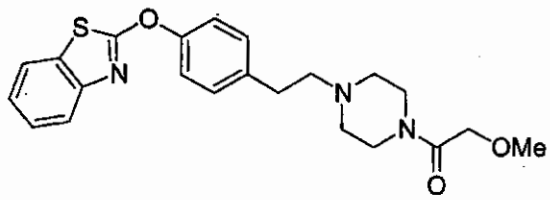


(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-cyclopropyl-methanone.

The title compound was prepared according to the procedure for EXAMPLE 313 using cyclopropane carbonylchloride. MS (ESI): exact mass calculated

for $C_{23}H_{25}N_3O_2S$, 407.2; m/z found, 408.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (dd, J = 8.1, 0.5, 1H), 7.71 (dd, J = 7.9, 0.8, 1H), 7.43 (dt, J = 7.4, 1.3, 1H), 7.34-7.28 (m, 5H), 3.74 (d, J = 16.0, 4H), 2.89 (dd, J = 9.4, 6.5, 2H), 2.70 (dd, J = 9.4, 6.5, 2H), 2.58 (br d, J = 20.8, 4H), 1.78 (tt, J = 8.0, 4.7, 1H), 1.06-1.01 (m, 2H), 0.83-0.78 (m, 2H).

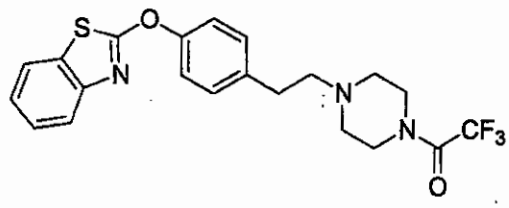
EXAMPLE 317



1-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-2-methoxy-ethanone.

A solution of 2-[4-(2-piperazin-1-yl-ethyl)-phenoxy]-benzothiazole bis trifluoromethane sulfonate Example 307, step A (200 mg, 0.35 mmol) in $CHCl_3$ (14 mL) was treated with PS-dimethylamine resin (740 mg, 1.0 mmol) and the reaction shaken for 1h. The resin was filtered, and the resulting solution of free base was treated with methoxy acetic acid (0.04 ml, 0.5 mmol) and PS-carbonyl diimidazole resin (500 mg, 0.6 mmol) and the reaction shaken for 1 h. The reaction was filtered and concentrated and the crude product was purified on SiO_2 (12 g, 0-10% 2M NH_3/MeOH : CH_2Cl_2) to give the title compound (143 mg, 99% yield). MS (ESI): exact mass calculated for $C_{22}H_{25}N_3O_2S$, 411.2; m/z found, 412.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (dd, J = 8.1, 0.6, 1H), 7.71 (dd, J = 7.9, 0.8, 1H), 7.42 (dt, J = 7.5, 1.3, 1H), 7.35-7.28 (m, 5H), 4.14 (s, 2H), 3.72 (t, J = 4.8, 2H), 3.58 (t, J = 4.8, 2H), 3.47 (s, 3H), 2.89 (dd, J = 10.6, 7.3, 2H), 2.70 (dd, J = 8.5, 5.6, 2H), 2.58 (t, J = 5.1, 4H).

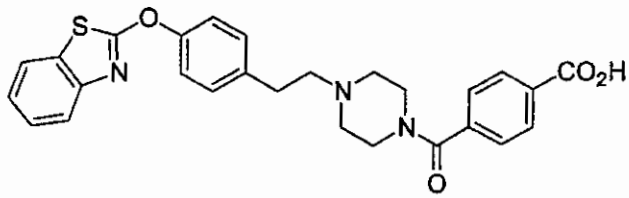
EXAMPLE 318



1-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-2,2,2-trifluoro-ethanone.

The title compound was prepared according to the procedure for EXAMPLE 317 using trifluromethanesulfonic acid. MS (ESI): exact mass calculated for $C_{21}H_{20}F_3N_3O_2S$, 435.1; m/z found, 436.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (dd, J = 8.2, 0.5, 1H), 7.71 (dd, J = 7.9, 0.7, 1H), 7.43 (dt, J = 8.5, 1.2, 1H), 7.35-7.28 (m, 5H), 4.14 (s, 2H), 3.76 (t, J = 4.8, 2H), 3.68 (t, J = 4.7, 2H), 2.88 (dd, J = 10.0, 7.0, 2H), 2.70 (dd, J = 8.7, 5.6, 2H), 2.62 (t, J = 4.6, 4H).

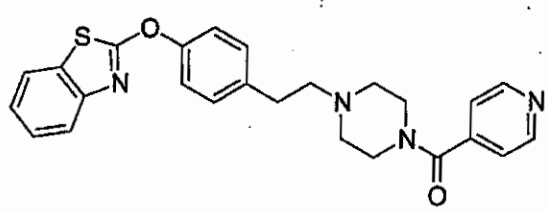
EXAMPLE 319



4-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazine-1-carbonyl)-benzoic acid.

The title compound was prepared according to the procedure for EXAMPLE 262, step A using terephthalic acid monomethyl ester and EXAMPLE 250, step D. MS (ESI): exact mass calculated for $C_{27}H_{25}N_3O_4S$, 487.2; m/z found, 488.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 8.00 (d, J = 8.3, 2H), 7.93 (dd, J = 8.0, 0.8, 1H), 7.69 (dd, J = 8.0, 0.4, 1H), 7.50 (d, J = 8.3, 2H), 7.43 (dt, J = 7.5, 1.3, 1H), 7.40-7.29 (m, 5H), 3.66 (br s, 2H), 3.30 (br s, 2H), 2.88 (dd, J = 7.0, 7.0, 2H), 2.60 (dd, J = 8.3, 8.3, 2H), 2.55 (br s, 2H), 2.44 (br s, 2H).

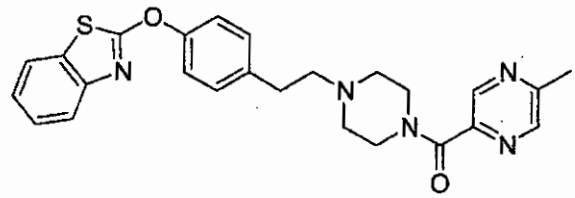
EXAMPLE 320



(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-pyridin-4-yl-methanone.

The title compound was prepared according to the procedure for EXAMPLE 317 using isonicotinic acid. MS (ESI): exact mass calculated for $C_{25}H_{24}N_4O_2S$, 444.2; m/z found, 445.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.74 (dd, J = 4.4, 1.6, 1H), 7.77 (dd, J = 8.1, 0.5, 1H), 7.71 (dd, J = 7.9, 0.8, 1H), 7.43 (dt, J = 7.4, 1.3, 1H), 7.45-7.39 (m, 2H), 7.35-7.28 (m, 7H), 3.87 (br s, 2H), 3.44 (br t, J = 3.9, 2H), 2.88 (dd, J = 10.1, 6.9, 2H), 2.71 (dd, J = 8.8, 5.5, 2H), 2.70-2.64 (m, 2H), 2.54-2.49 (m, 2H).

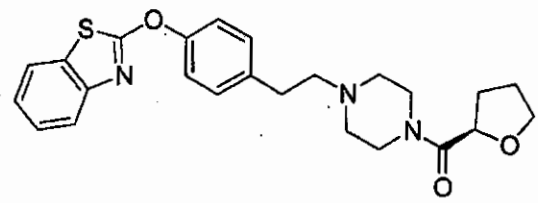
EXAMPLE 321



(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(5-methyl-pyrazin-2-yl)-methanone.

The title compound was prepared according to the procedure for EXAMPLE 317 using 5-methyl-pyrazine-2-carboxylic acid. MS (ESI): exact mass calculated for $C_{25}H_{25}N_5O_2S$, 444.2; m/z found, 445.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.89 (d, J =1.4, 1H), 8.45 (d, J =1.0, 1H), 7.76 (dd, J = 8.1, 0.5, 1H), 7.70 (dd, J = 8.0, 0.8, 1H), 7.43 (dt, J = 7.4, 1.3, 1H), 7.33-7.28 (m, 5H), 3.90 (br t, J = 4.7, 2H), 3.77 (br t, J = 4.8, 2H), 2.92 (dd, J = 10.5, 6.5, 2H), 2.80-2.72 (m, 2H), 2.69-2.64 (m, 2H), 2.66 (s, 3H).

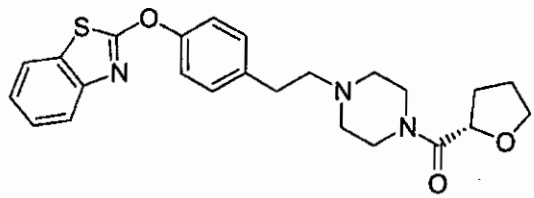
EXAMPLE 322



(*R*)-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(tetrahydro-furan-2-yl)-methanone.

The title compound was prepared according to the procedure for EXAMPLE 317 using 5-(*R*)-tetrahydro-furan-2-carboxylic acid. MS (ESI): exact mass calculated for $C_{24}H_{27}N_3O_3S$, 437.2; m/z found, 438.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (d, *J* = 7.3, 1H), 7.71 (dd, *J* = 7.8, 0.8, 1H), 7.42 (dt, *J* = 7.3, 1.2, 1H), 7.33-7.26 (m, 5H), 4.65 (dd, *J* = 7.0, 5.3, 1H), 3.99 (ddd, *J* = 7.1, 6.7, 6.7, 1H), 3.92-3.86 (m, 1H), 3.82-3.72 (m, 2H), 3.76 (s, 1H), 3.70-3.58 (m, 2H), 2.90 (dd, *J* = 10.3, 7.3, 2H), 2.70 (dd, *J* = 8.6, 5.6, 2H), 2.64-2.54 (m, 3H), 2.38-2.28 (m, 1H), 2.14-1.90 (m, 4H).

EXAMPLE 323

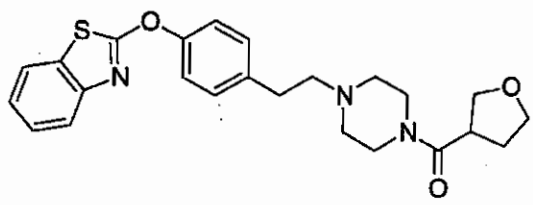


(*S*)-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(tetrahydro-furan-2-yl)-methanone.

The title compound was prepared according to the procedure for EXAMPLE 317 using 5-(*S*)-tetrahydro-furan-2-carboxylic acid. MS (ESI): exact mass calculated for $C_{24}H_{27}N_3O_3S$, 437.2; m/z found, 438.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (d, *J* = 7.3, 1H), 7.71 (dd, *J* = 7.8, 0.8, 1H), 7.42 (dt, *J* = 7.3, 1.2, 1H), 7.33-7.26 (m, 5H), 4.65 (dd, *J* = 7.0, 5.3, 1H), 3.99 (ddd, *J* = 7.1, 6.7, 6.7, 1H), 3.89 (ddd, *J* = 7.7, 7.5, 5.8, 1H), 3.82-3.72 (m, 2H), 3.76 (s, 1H),

3.70-3.58 (m, 2H), 2.90 (dd, *J* = 10.3, 7.3, 2H), 2.70 (dd, *J* = 8.6, 5.6, 2H), 2.64-2.54 (m, 3H), 2.38-2.28 (m, 1H), 2.14-1.90 (m, 4H).

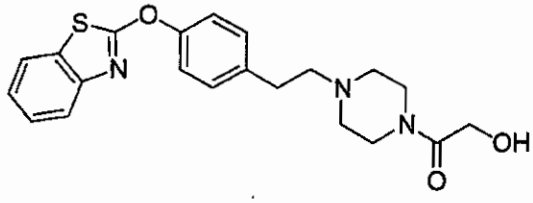
EXAMPLE 324



(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(tetrahydro-furan-3-yl)-methanone.

The title compound was prepared according to the procedure for EXAMPLE 317 using 5-tetrahydro-furan-3-carboxylic acid. MS (ESI): exact mass calculated for $C_{24}H_{27}N_3O_3S$, 437.2; m/z found, 438.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (dd, *J* = 8.1, 0.5, 1H), 7.71 (dd, *J* = 7.9, 0.8, 1H), 7.42 (dt, *J* = 7.5, 1.3, 1H), 7.33-7.26 (m, 5H), 4.06 (t, *J* = 8.2, 1H), 3.97-3.87 (m, 3H), 3.77-3.67 (m, 2H), 3.59 (t, *J* = 5.1, 1H), 3.35-3.24 (m, 1H), 2.88 (dd, *J* = 10.2, 7.3, 2H), 2.79 (dd, *J* = 8.5, 5.7, 2H), 2.60-2.50 (m, 4H), 2.29 (dddd, *J* = 12.6, 7.6, 6.4, 6.4, 1H), 2.17-2.08 (m, 1H).

EXAMPLE 325

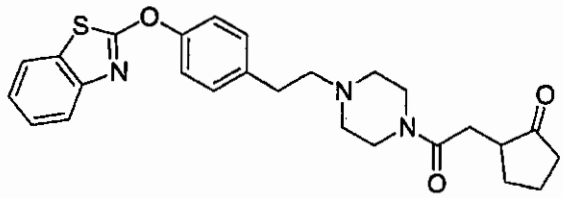


1-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-2-hydroxy-ethanone.

The title compound was prepared according to the procedure for EXAMPLE 317 using gylcolic acid. MS (ESI): exact mass calculated for $C_{21}H_{23}N_3O_3S$, 397.2; m/z found, 398.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (dd, *J* = 8.1, 0.5, 1H), 7.71 (dd, *J* = 8.0, 0.7, 1H), 7.43 (dt, *J* = 7.5, 1.3, 1H), 7.35-7.28 (m,

5H), 4.21 (s, 2H), 3.75 (t, J = 5.0, 2H), 3.68 (br s, 1H), 3.35 (t, J = 5.0, 2H), 2.88 (dd, J = 10.1, 7.0, 2H), 2.70 (dd, J = 8.6, 5.6, 2H), 2.58 (ddd, J = 8.4, 8.3, 5.2, 1H).

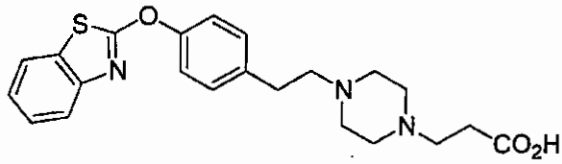
EXAMPLE 326



2-[2-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-2-oxo-ethyl]-cyclopentanone.

The title compound was prepared according to the procedure for EXAMPLE 317 using 5- (2-oxo-cyclopentyl)-acetic acid. MS (ESI): exact mass calculated for $C_{26}H_{29}N_3O_3S$, 463.2; m/z found, 464.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (d, J = 7.7, 1H), 7.71 (dd, J = 7.9, 0.7, 1H), 7.42 (dt, J = 7.5, 1.2, 1H), 7.33-7.28 (m, 5H), 3.80-3.64 (m, 2H), 3.54 (dd, J = 9.2, 3.9, 1H), 2.92-2.84 (m, 3H), 2.88 (dd, J = 10.1, 7.0, 2H), 2.68 (dd, J = 8.5, 5.6, 2H), 2.60-2.25 (m, 2H), 2.15-2.06 (m, 1H), 1.93-1.80 (m, 1H), 1.78-1.64 (m, 2H).

EXAMPLE 327

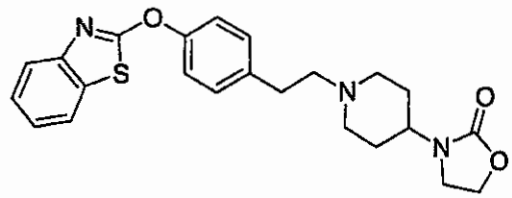


3-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-propionic acid trifluoromethansufonate salt.

The title compound was prepared according to the procedure for EXAMPLE 262, step A using 3-piperazin-1-yl-propionic acid. MS (ESI): exact mass calculated for $C_{21}H_{23}N_3O_3S_1$, 411.2; m/z found, 412.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 11.25 (br s, 1H), 7.76 (dd, J = 8.0, 0.5, 1H), 7.69 (dd, J = 7.8, 0.6, 1H), 7.42 (dt, J = 7.4, 1.2, 1H), 7.35-7.28 (m, 5H), 3.76 (s, 1H), 3.04 (t, J =

6.4, 4H), 2.91 (dd, *J* = 10.3, 5.4, 4H), 2.86-2.79 (m, 2H), 2.63 (t, *J* = 6.4, 1H), 2.08 (s, 4H).

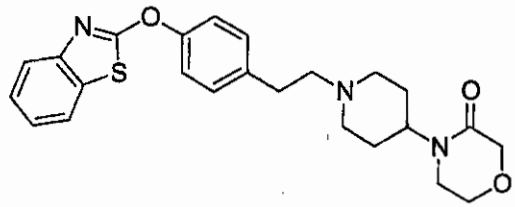
EXAMPLE 328



3-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-oxazolidin-2-one.

The title compound was prepared according to the procedure for EXAMPLE 262, step A using 3-piperidin-4-yl-oxazolidin-2-one hydrochloride salt and EXAMPLE 259, step A. MS (ESI): exact mass calculated for $C_{23}H_{25}N_3O_3S_1$, 423.2; m/z found, 424.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (dd, *J* = 8.1, 0.5, 1H), 7.69 (dd, *J* = 7.9, 1.1, 1H), 7.41 (dt, *J* = 8.5, 1.2, 1H), 7.35-7.28 (m, 5H), 4.36, (t, *J* = 7.8, 2H), 3.72 (t, *J* = 4.8, 2H), 3.86-3.76 (m, 1H), 3.57 (t, *J* = 8.1, 2H), 3.11 (br d, *J* = 11.8, 2H), 2.86 (dd, *J* = 11.0, 7.6, 2H), 2.66 (dd, *J* = 8.6, 5.2, 2H), 2.18 (dt, *J* = 11.7, 2.7, 2H), 1.89-1.72 (m, 4H).

EXAMPLE 329

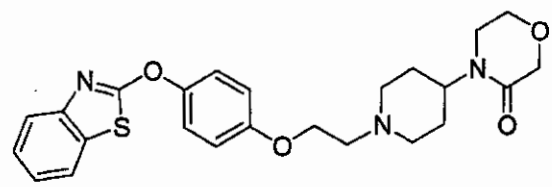


4-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-morpholin-3-one.

The title compound was prepared according to the procedure for EXAMPLE 262, step A using piperidin-4-yl-morpholin-3-one and EXAMPLE 260, step A. MS (ESI): exact mass calculated for $C_{24}H_{27}N_3O_3S_1$, 437.2; m/z found, 438.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.76 (d, *J* = 8.0, 1H), 7.70 (dd, *J* = 7.9, 0.7, 1H), 7.42 (dt, *J* = 7.4, 1.2, 1H), 7.33-7.28 (m, 5H), 4.57 (tt, *J* = 11.9, 4.3, 1H), 4.23 (s, 2H), 3.91, (t, *J* = 4.9, 2H), 3.34 (t, *J* = 5.1, 2H), 3.12 (br d, *J* =

11.6, 2H), 2.87 (dd, *J* = 10.9, 7.6, 2H), 2.67 (dd, *J* = 8.7, 5.2, 2H), 2.23 (ddd, *J* = 11.7, 11.6, 2.5, 2H), 1.82 (ddd, *J* = 24.1, 12.1, 3.8, 2H), 1.76-1.70 (m, 2H).

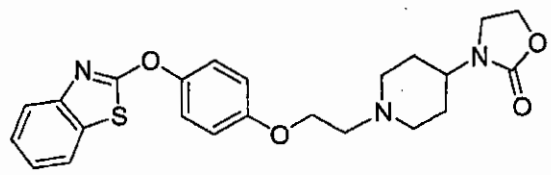
EXAMPLE 330



4-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-morpholin-3-one.

The title compound was prepared according to the procedure for EXAMPLE 17, step A using piperidin-4-yl-morpholin-3-one and EXAMPLE 260, step A. MS (ESI): exact mass calculated for $C_{24}H_{27}N_3O_4S_1$, 453.2; m/z found, 454.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.76 (dd, *J* = 8.1, 0.5, 1H), 7.68 (dd, *J* = 7.9, 0.7, 1H), 7.40 (dt, *J* = 7.4, 1.3, 1H), 7.31-7.28 (m, 3H), 7.02-6.96 (m, 2H), 4.57 (tt, *J* = 12.1, 4.2, 1H), 4.22 (s, 2H), 4.14 (t, *J* = 5.6, 2H), 3.90 (t, *J* = 5.0, 2H), 3.33 (t, *J* = 5.1, 2H), 3.12 (br d, *J* = 11.7, 2H), 2.87 (t, *J* = 5.7, 2H), 2.32 (ddd, *J* = 11.8, 11.8, 2.4, 2H), 1.82 (dddd, *J* = 12.2, 12.1, 12.1, 3.8, 2H), 1.75-1.68 (m, 2H).

EXAMPLE 331

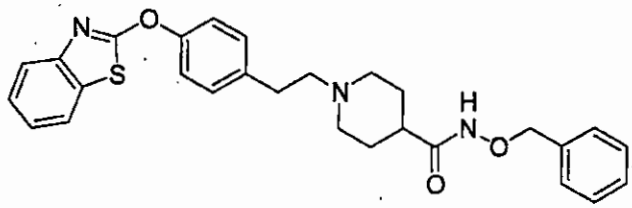


3-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-oxazolidin-2-one.

The title compound was prepared according to the procedure for EXAMPLE 17, step A using 3-piperidin-4-yl-oxazolidin-2-one hydrochloride salt and EXAMPLE 259, step A. MS (ESI): exact mass calculated for $C_{23}H_{25}N_3O_4S_1$, 439.2; m/z found, 440.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.76 (dd, *J* = 8.1, 0.7, 1H), 7.69 (dd, *J* = 8.0, 0.7, 1H), 7.42 (dt, *J* = 8.6, 1.3, 1H), 7.35-7.26 (m,

3H), 7.02-6.97 (m, 2H), 4.36 (dd, *J* = 8.7, 7.3, 2H), 4.14 (t, *J* = 5.7, 2H), 3.80 (ddd, *J* = 16.4, 11.0, 5.6, 1H), 3.60-3.53 (m, 2H), 3.12 (br d, *J* = 12.0, 2H), 2.87 (d, *J* = 5.7, 2H), 2.28 (ddd, *J* = 11.7, 11.6, 3.8, 2H), 1.90-1.74(m, 4H).

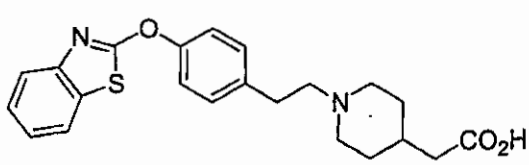
EXAMPLE 332



1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid benzyloxy-amide.

A solution of 1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid EXAMPLE 34, step A (383 mg, 1.0 mmol) in CH_2Cl_2 (10 mL) was treated with N-methylmorpholine (0.24 ml, 2.2 mmol) and cyanuric chloride (61 mg, 0.3 mmol) and the resulting solution stirred for 1 h, at which time the reaction was treated with O-benzyl hydroxylamine and stirred for 16h. The reaction was filtered through diatomaceous earth concentrated and purified on SiO_2 (12 g, 0-10% 2M NH_3/MeOH/CH_2Cl_2) to give the title compound (81 mg,17% yield). MS (ESI): exact mass calculated for $C_{28}H_{29}N_3O_3S_1$, 487.2; m/z found, 488.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.34 (br s, 1H), 7.76 (dd, *J* = 8.1, 0.5, 1H), 7.70 (dd, *J* = 7.9, 0.7, 1H), 7.45-7.39 (m, 6H), 7.34-7.28 (m, 4H), 4.96 (br s, 2H), 3.05 (br d, *J* = 11.6, 2H), 2.85 (dd, *J* = 10.6, 7.6, 2H), 2.63 (dd, *J* = 8.5, 5.5, 2H), 2.04 (ddd, *J* = 11.0, 11.0, 2.8, 2H), 1.91-1.76 (m, 2H).

EXAMPLE 333

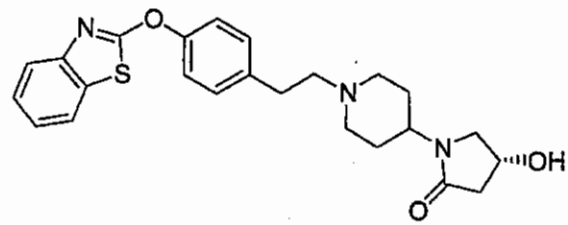


(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-acetic acid.

The title compound was prepared according to the procedure for EXAMPLE 262, step A using piperidin-4-yl-acetic acid ethyl ester and EXAMPLE 250, step

D. MS (ESI): exact mass calculated for $C_{22}H_{24}N_2O_3S_1$, 396.2; m/z found, 397.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 8.34 (br s, 1H), 7.82 (dd, *J* = 7.9, 0.6, 1H), 7.67 (dd, *J* = 8.1, 0.5, 1H), 7.53-7.33 (m, 6H), 3.78-3.66 (m, 2H), 3.46-3.38 (m, 2H), 3.22-3.14 (m, 2H), 3.14-3.07 (m, 2H), 2.39 (br d, *J* = 6.1, 1H), 2.20-2.08 (br s , 1H), 2.11 (br d, *J* = 13.5, 1H), 1.72-1.54 (m, 2H).

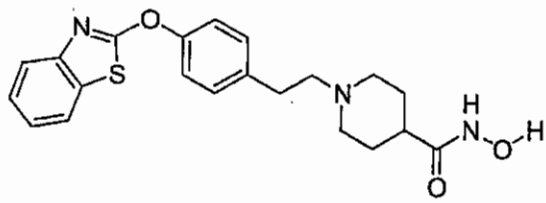
EXAMPLE 334



(*R*)-1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one

The title compound was prepared according to the procedure for EXAMPLE 262, step A using (R)-4-hydroxy-1-piperidin-4-yl-pyrrolidin-2-one acetic acid salt and EXAMPLE 261, step A. MS (ESI): exact mass calculated for $C_{24}H_{27}N_3O_3S_1$, 437.2; m/z found, 438.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (dd, *J* = 8.1, 0.5, 1H), 7.66 (dd, *J* = 7.9, 0.7, 1H), 7.40 (dt, *J* = 7.7, 1.3, 1H), 7.28-7.24 (m, 5H), 4.52 (ddd, *J* = 8.5, 5.9, 2.4, 1H), 4.11-4.00 (m, 1H), 3.60 (dd, *J* = 10.7, 5.6, 1H), 3.31 (dd, *J* = 10.7, 2.2, 1H), 3.12-3.04 (m, 2H), 2.83 (dd, *J* = 9.7, 6.5, 2H), 2.72 (dd, *J* = 17.2, 6.6, 1H), 2.63 (dd, *J* = 9.8, 6.4, 2H), 2.72 (dd, *J* = 17.2, 2.6, 1H), 2.21-2.12 (m, 2H), 1.85-1.67 (m, 4H).

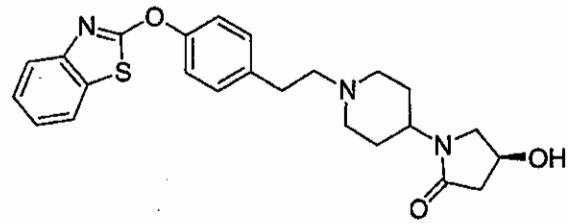
EXAMPLE 335



1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid hydroxyamide

The title compound was prepared according to the procedure for EXAMPLE 262, step A using piperidine-4-carboxylic acid hydroxyamide. MS (ESI): exact mass calculated for $C_{21}H_{23}N_3O_3S_1$, 397.2; m/z found, 398.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73-7.60 (m, 2H), 7.40-7.30 (m, 1H), 7.30-7.16 (m, 5H), 3.48-3.36 (br s, 2H), 3.10-2.95 (m, 4H), 2.80-2.50 (br m, 3H), 2.23-1.96 (br m, 5H).

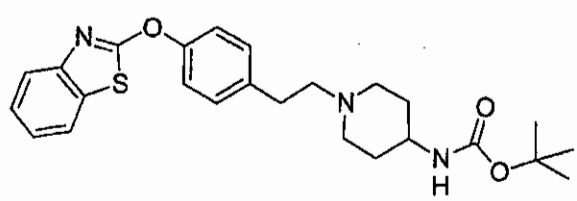
EXAMPLE 336



(*S*)-1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one.

The title compound was prepared according to the procedure for EXAMPLE 262, step A using (*S*)-4-hydroxy-1-piperidin-4-yl-pyrrolidin-2-one acetic acid salt, EXAMPLE 261, step A using (*S*)-4-bromo-3-hydroxybutyrate . MS (ESI): exact mass calculated for $C_{24}H_{27}N_3O_3S_1$, 437.2; m/z found, 438.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.77 (dd, *J* = 8.1, 0.5, 1H), 7.66 (dd, *J* = 7.9, 0.7, 1H), 7.40 (dt, *J* = 7.7, 1.3, 1H), 7.28-7.24 (m, 5H), 4.52 (ddd, *J* = 8.5, 5.9, 2.4, 1H), 4.11-4.00 (m, 1H), 3.60 (dd, *J* = 10.7, 5.6, 1H), 3.31 (dd, *J* = 10.7, 2.2, 1H), 3.12-3.04 (m, 2H), 2.83 (dd, *J* = 9.7, 6.5, 2H), 2.72 (dd, *J* = 17.2, 6.6, 1H), 2.63 (dd, *J* = 9.8, 6.4, 2H), 2.72 (dd, *J* = 17.2, 2.6, 1H), 2.21-2.12 (m, 2H), 1.85-1.67 (m, 4H).

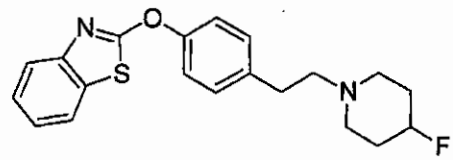
EXAMPLE 337



(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-carbamic acid tert-butyl ester.

The title compound was prepared according to the procedure for EXAMPLE 262, step A using piperidin-4-yl-carbamic acid tert-butyl ester. MS (ESI): exact mass calculated for $C_{25}H_{31}N_3O_3S_1$, 453.2; m/z found, 454.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (dd, J = 8.2, 0.6, 1H), 7.65 (dd, J = 7.9, 0.7, 1H), 7.39 (dt, J = 7.4, 1.3, 1H), 7.29-7.23 (m, 5H), 4.47 (br d, J = 6.6, 1H), 3.55-3.45 (m, 1H), 2.93 (br d, J = 11.3, 2H), 2.82 (dd, J = 11.0, 7.7, 2H), 2.60 (dd, J = 8.6, 5.3, 2H), 2.16 (t, J = 11.3, 2H), 1.97 (br d, J = 11.1, 2H), 1.45 (s, 9H).

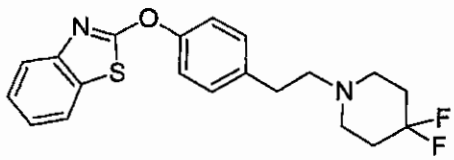
EXAMPLE 338



2-{4-[2-(4-Fluoro-piperidin-1-yl)-ethyl]-phenoxy}-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 262, step A using 4-fluoro piperidine. MS (ESI): exact mass calculated for $C_{20}H_{21}F_1N_3O_1S_1$, 356.1; m/z found, 357.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (dd, J = 8.1, 0.5, 1H), 7.65 (dd, J = 8.0, 0.7, 1H), 7.41-7.36 (m, 1H), 7.28-7.24 (m, 5H), 4.70 (dm, J = 48.6, 1H), 2.85 (dd, J = 10.9, 7.7, 2H), 2.71-2.63 (m, 2H), 2.62 (dd, J = 8.3, 5.4, 2H), 2.52-2.44 (m, 2H), 2.03-1.86 (m, 4H).

EXAMPLE 339

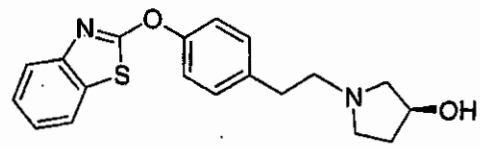


2-{4-[2-(4,4-Difluoro-piperidin-1-yl)-ethyl]-phenoxy}-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 262, step A using 4,4-difluoro piperidine. MS (ESI): exact mass calculated for $C_{20}H_{20}F_2N_3O_1S_1$, 374.1; m/z found, 375.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (dd, J = 8.1, 0.6, 1H), 7.65 (dd, J = 8.0, 0.7, 1H), 7.41-7.36 (m, 1H), 7.28-

7.24 (m, 5H), 2.82 (dd, *J* = 10.2, 6.4, 2H), 2.71-2.60 (m, 6H), 2.09-1.97 (m, 4H).

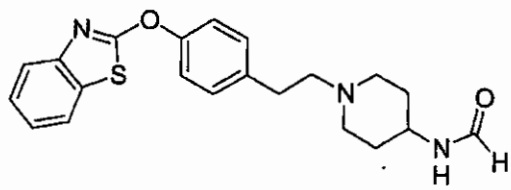
EXAMPLE 340



(*R*)-1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-pyrrolidin-3-ol.

The title compound was prepared according to the procedure for EXAMPLE 262, step A using (*R*)-3-hydroxypyrrolidine. MS (ESI): exact mass calculated for $C_{19}H_{20}N_2O_2S_1$, 340.1; m/z found, 341.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (dd, *J* = 8.0, 0.4, 1H), 7.66 (dd, *J* = 7.9, 0.8, 1H), 7.39 (dt, *J* = 7.4, 1.2, 1H), 7.31-7.24 (m, 5H), 4.36 (dddd, *J* = 7.3, 4.8, 2.2, 2.2, 1H), 2.96 (ddd, *J* = 8.5, 8.5, 5.1, 1H), 2.90-2.83 (m, 2H), 2.79-2.70 (m, 3H), 2.58 (dd, *J* = 10.0, 5.2, 2H), 2.36 (ddd, *J* = 8.8, 8.8, 6.5, 1H), 2.21 (dddd, *J* = 13.7, 8.6, 7.2, 5.1, 1H), 1.82-1.73 (m, 1H).

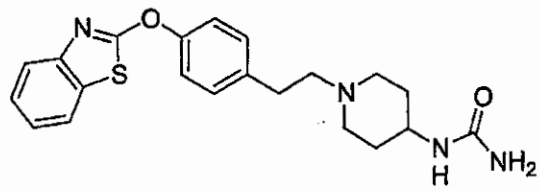
EXAMPLE 341



N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-formamide.

The title compound was prepared from EXAMPLE 337 following the procedure for EXAMPLE 266, step B and EXAMPLE 317. MS (ESI): exact mass calculated for $C_{21}H_{23}N_3O_2S_1$, 381.2; m/z found, 382.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.16 (s, 1H), 7.72 (d, *J* = 8.6, 1H), 7.65 (dd, *J* = 7.9, 0.7, 1H), 7.42-7.36 (m, 1H), 7.31-7.23 (m, 5H), 4.03-3.93 (m, 1H), 3.13-3.03 (m, 2H), 2.90 (dd, *J* = 11.1, 7.2, 2H), 2.75-2.69 (m, 2H), 2.34 (t, *J* = 9.2, 2H), 2.08-2.00 (m, 2H), 1.72-1.60 (m, 2H).

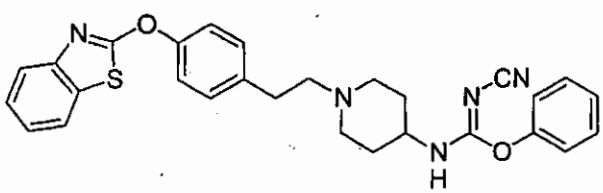
EXAMPLE 342



(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-urea

1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ylamine hydrochloride was prepared from (1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-carbamic acid tert-butyl ester EXAMPLE 337 following the procedure for EXAMPLE 266, step B. The resulting amine hydrochloride (227 mg, 0.58 mmol) in CH_2Cl_2 (5 mL) was treated with pyridine (0.14 mL, 1.7 mmol), trimethylisocyanate (0.09 ml, 0.64 mmol), and triethylamine (0.08 mL, 0.58 mmol) and the reaction stirred for 16h. The reaction was diluted with CH_2Cl_2 (25 mL) and washed with $NaHCO_3$ (30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified on SiO_2 (12 g, 0-10% [2 M NH_3] CH_3OH/CH_2Cl_2) to give the title compound (134 mg, 58% yield). MS (ESI): exact mass calculated for $C_{21}H_{24}N_4O_2S_1$, 396.2; m/z found, 397.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.7, 1H), 7.65 (dd, J = 7.9, 0.7, 1H), 7.42-7.36 (m, 1H), 7.31-7.23 (m, 5H), 4.93 (d, J = 8.0, 1H), 4.78 (s, 2H), 3.93 (br d, J = 11.7, 1H), 2.82 (dd, J = 10.7, 7.6, 2H), 2.60 (dd, J = 8.5, 5.4, 2H), 2.16 (t, J = 11.3, 2H), 1.97 (dd, J = 12.7, 3.1, 2H), 1.47 (dddd, J = 12.8, 12.6, 12.6, 3.7, 2H).

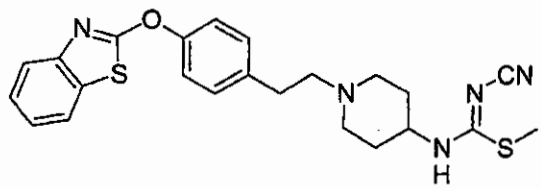
EXAMPLE 343



1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-3-cyano-2-phenyl-isourea

The 1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ylamine hydrochloride was prepared from (1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-carbamic acid tert-butyl ester EXAMPLE 337 by removal of the Boc group according to EXAMPLE 266, step B. The free base was prepared by suspending 1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ylamine hydrochloride (1.3 g, 3.3 mmol) in CH_2Cl_2 (20 mL) and washing with a solution of saturated $NaHCO_3$ (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give 1.0 g (83% yield) of 1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ylamine free base. A solution of 1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl amine (145 mg, 0.4 mmol) in ethanol (5 mL) was treated with diphenyl cyanocarbodiimidate (319 mg. 1.34 mmol) and heated to 80 °C for 16h. The reaction was concentrated under reduced pressure and purified on SiO_2 (12 g, 0-10% [2 M NH_3 CH_3OH]/CH_2Cl_2) to give of the title compound (173 mg, 85% yield). MS (ESI): exact mass calculated for $C_{28}H_{27}N_5O_2S_1$, 496.2; m/z found, 498.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.7, 1H), 7.66 (dd, J = 7.9, 0.7, 1H), 7.45-7.36 (m, 4H), 7.31-7.24 (m, 5H), 7.08 (d, J = 7.8, 2H), 6.36 (br d, J = 6.5, 1H), 3.87-3.76 (m, 1H), 3.02 (br d, J = 11.2, 2H), 2.83 (dd, J = 8.4, 7.3, 2H), 2.64 (dd, J = 8.6, 5.4, 2H), 2.21 (t, J = 11.1, 2H), 2.07 (d, J = 11.0, 2H), 1.76 (dd, J = 20.7, 10.4, 2H).

EXAMPLE 344

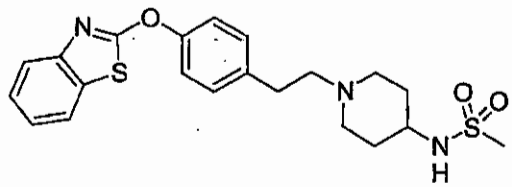


1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-3-cyano-2-methyl-isothiourea.

The 1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ylamine hydrochloride was prepared from (1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-carbamic acid tert-butyl ester EXAMPLE 337 by removal of the Boc group according to EXAMPLE 266, step B. The free base was prepared

according to EXAMPLE 343. A solution of 1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl amine (145 mg, 0.4 mmol) in ethanol (5 mL) was treated with dimethyl-N-cyanodithioiminocarbonate (180 mg. 1.34 mmol) and heated to 80 °C for 16h. The reaction was concentrated under reduced pressure and purified on SiO_2 (12 g, 0-10% 2M $NH_3/CH_3OH/CH_2Cl_2$) to give of the title compound (143 mg, 69% yield). MS (ESI): exact mass calculated for $C_{23}H_{25}N_5O_1S_2$, 451.2; m/z found, 452.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (dd, J = 8.1, 0.5, 1H), 7.66 (dd, J = 7.9, 0.7, 1H), 7.41-7.36 (m, 2H), 7.29-7.24 (m, 5H), 6.13 (br d, J = 196, 2H), 2.97 (br d, J = 12.0, 2H), 2.82 (dd, J = 10.3, 7.3, 2H), 2.62 (dd, J = 8.5, 5.5, 2H), 2.60-2.44 (br s, 3H), 2.18 (t, J = 11.5, 2H), 2.03 (d, J = 13.5, 2H), 1.7-1.55 (m, 2H).

EXAMPLE 345

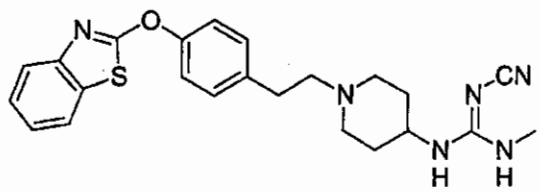


N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-methanesulfonamide.

The 1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ylamine hydrochloride was prepared from (1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-carbamic acid tert-butyl ester EXAMPLE 337 by removal of the Boc group according to EXAMPLE 266, step B. The free base was prepared according to EXAMPLE 343. The free base (240 mg, 0.68 mmol) in CH_2Cl_2 (7 mL) was treated with triethylamine (142 µL, 1.0 mmol) followed by methanesulfonyl chloride (77 µL, 1.0 mmol) and the solution stirred for 16 h. The reaction was diluted with CH_2Cl_2 (20 mL) and washed $NaHCO_3$ solution (30 mL). The organic layer was dried and concentrated under reduced pressure then purified on SiO_2 (12 g, 0-10% 2M NH_3/MeOH : CH_2Cl_2) to give 168 mg (57% yield) of the title compound. MS (ESI): exact mass calculated for $C_{21}H_{25}N_3O_3S_2$, 431.1; m/z found, 432.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.0, 1H), 7.65 (dd, J = 7.9, 0.7, 1H), 7.42-7.36 (m, 1H), 7.29-7.24

(m, 5H), 4.45 (d, J = 7.6, 1H), 3.42-3.31 (m, 1H), 2.99 (s, 3H), 2.93 (br d, J = 12.0, 2H), 2.81 (dd, J = 10.6, 7.5, 2H), 2.60 (dd, J = 8.5, 5.4, 2H), 2.18 (t, J = 11.0, 2H), 2.02 (d, J = 12.5, 2H), 1.47 (dddd, J = 11.2, 11.1, 11.1, 3.7, 2H).

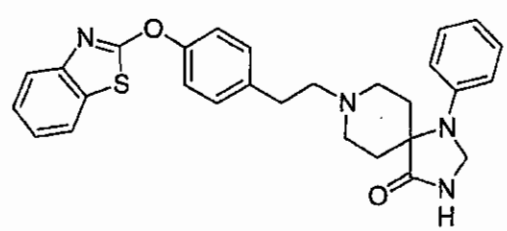
EXAMPLE 346



1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-3-cyano-2-methyl-guanidine.

A solution of 1-(1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-3-cyano-2-phenyl-isourea, EXAMPLE 343, (76 mg, 0.15 mmol) in ethanol (3 mL) was treated with a solution of 40% methylamine in water (0.2 ml) and the solution stirred at 80 °C for 1 h. The reaction was cooled to 23 °C and concentrated under reduced pressure to give a crude solid that was purified on SiO_2 (4 g, 0-10% 2M NH_3/MeOH : CH_2Cl_2) to give 50 mg (76% yield) of the title compound. MS (ESI): exact mass calculated for $C_{23}H_{26}N_6O_1S_1$, 434.2; m/z found, 435.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.67 (dd, J = 7.9, 0.7, 1H), 7.42-7.36 (m, 2H), 7.29-7.24 (m, 5H), 5.67 (br s, 1H), 4.75 (br s, 1H), 3.63 (br s, 1H), 2.94 (br d, J = 11.9, 2H), 2.86 (d, J = 4.9, 2H), 2.82 (dd, J = 10.4, 7.4, 2H), 2.61 (dd, J = 8.5, 5.5, 2H), 2.18 (t, J = 11.4, 2H), 2.05-1.96 (m, 2H), 2.61 (dddd, J = 12.3, 12.3, 12.3, 3.6, 2H).

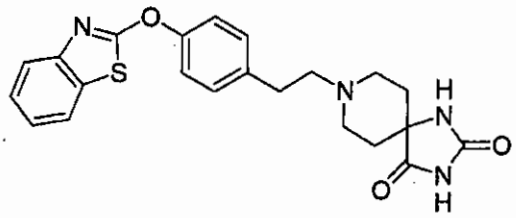
EXAMPLE 347



8-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one.

The title compound was prepared according to the procedure for EXAMPLE 262, step A using 1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one. MS (ESI): exact mass calculated for $C_{28}H_{28}N_4O_2S_1$, 484.2; m/z found, 485.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (dd, J = 8.0, 0.5, 1H), 7.66 (dd, J = 7.9, 0.7, 1H), 7.52 (s, 1H), 7.42-7.36 (m, 1H), 7.34-7.24 (m, 6H), 6.91 (d, J = 8.0, 1H), 6.87 (t, J = 7.3, 1H), 4.75 (s, 2H), 2.95-2.85 (m, 4H), 2.76-2.66 (m, 4H), 1.76 (d, J = 13.9, 2H).

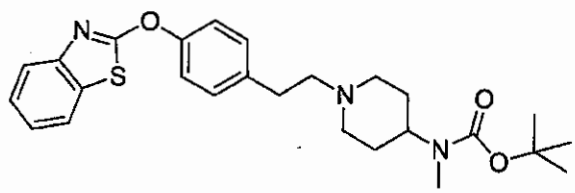
EXAMPLE 348



8-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-1,3,8-triaza-spiro[4.5]decane-2,4-dione.

The title compound was prepared according to the procedure for EXAMPLE 262, step A using 1,3,8-triaza-spiro[4.5]decane-2,4-dione. MS (ESI): exact mass calculated for $C_{22}H_{22}N_4O_3S_1$, 422.1; m/z found, 423.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (dd, J = 8.1, 0.5, 1H), 7.67 (dd, J = 7.9, 1.1, 1H), 7.42-7.36 (m, 1H), 7.34-7.24 (m, 5H), 3.0 (ddd, J = 9.2, 4.3, 4.3, 2H), 2.86 (dd, J = 10.6, 6.9, 2H), 2.69 (dd, J = 9.0, 5.3, 2H), 2.72 (t, J = 10.2, 2H), 2.19-2.10 (m, 2H), 1.75 (d, J = 13.6, 2H).

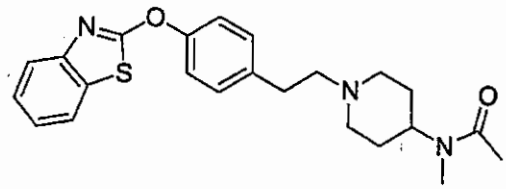
EXAMPLE 349



(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-methyl-carbamic acid tert-butyl ester.

The title compound was prepared according to the procedure for EXAMPLE 262, step A using methyl-piperidin-4-yl-carbamic acid tert-butyl ester. MS (ESI): exact mass calculated for $C_{26}H_{23}N_3O_3S_1$, 467.2; m/z found, 468.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (dd, J = 8.1, 0.5, 1H), 7.66 (dd, J = 7.9, 0.7, 1H), 7.41-7.36 (m, 1H), 7.29-7.25 (m, 5H), 4.10-3.95 (br m, 1H), 3.07 (d, J = 11.6, 2H), 2.83 (dd, J = 11.1, 7.8, 2H), 2.75 (s, 3H), 2.61 (d, J = 8.6, 5.2, 2H), 2.11 (t, J = 10.9, 2H), 2.19-2.10 (m, 2H), 1.77 (dddd, J = 12.1, 12.0, 12.0, 3.3, 2H), 1.70-1.64 (m, 2H), 1.47 (s, 9H).

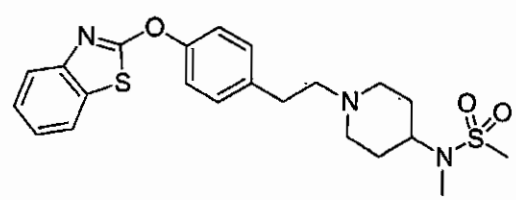
EXAMPLE 350



N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-N-methyl-acetamide.

The title compound was prepared from EXAMPLE 349 following EXAMPLE 266, step B, EXAMPLE 343 and EXAMPLE 345 using acetyl chloride. MS (ESI): exact mass calculated for $C_{23}H_{27}N_3O_2S_1$, 409.2; m/z found, 410.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (dd, J = 8.1, 0.6, 1H), 7.66 (dd, J = 8.0, 1.1, 1H), 7.41-7.36 (m, 1H), 7.31-7.25 (m, 5H), 4.53 (tt, J = 12.0, 4.2, 0.5H), 3.54 (tt, J = 11.7, 4.0, 0.5H), 3.15-3.04 (m, 2H), 2.90-2.78 (m, 5H), 2.70-2.58 (m, 2H), 2.24-2.06 (m, 5H), 2.00-1.96 (m, 1H), 1.82-1.60 (m, 3H).

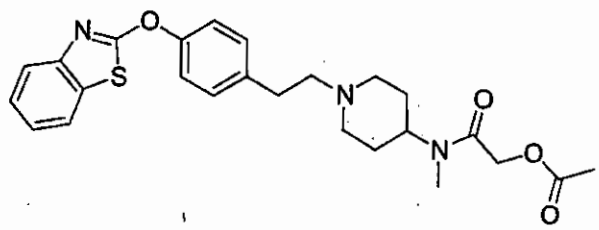
EXAMPLE 351



N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-N-methyl-methanesulfonamide.

The title compound was prepared from EXAMPLE 349 following EXAMPLE 266, step B, EXAMPLE 343 and EXAMPLE 345 using methanesulfonyl chloride. MS (ESI): exact mass calculated for $C_{25}H_{29}N_3O_4S$, 467.2; m/z found, 468.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.1, 1H), 7.66 (dd, J = 7.9, 0.7, 1H), 7.42-7.36 (m, 1H), 7.29-7.24 (m, 5H), 3.78 (tt, J = 11.9, 4.2, 1H), 3.08 (dd, J = 9.6, 2.1, 1H), 2.84 (s, 3H), 2.82 (s, 3H), 2.83-2.79 (m, 2H), 2.61 (dd, J = 8.5, 5.3, 2H), 2.18 (ddd, J = 11.8, 11.8, 2.2, 2H), 1.86 (dddd, J = 12.2, 12.0, 12.0, 3.4, 2H), 1.76-1.69 (m, 2H).

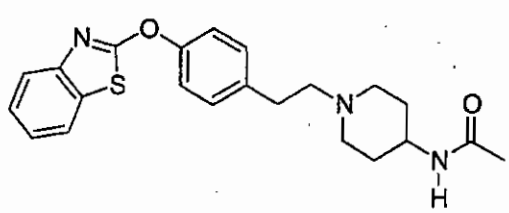
EXAMPLE 352



Acetic acid [(1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-methyl-carbamoyl]-methyl ester.

The title compound was prepared from EXAMPLE 349 following EXAMPLE 266, step B, EXAMPLE 343 and EXAMPLE 345 using acetic acid chlorocarbonylmethyl ester. MS (ESI): exact mass calculated for $C_{23}H_{27}N_3O_2S_1$, 467.2; m/z found, 468.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (dd, J = 8.1, 0.5, 1H), 7.66 (d, J = 7.9, 1H), 7.42-7.36 (m, 1H), 7.29-7.24 (m, 5H), 4.76 (s, 0.6H), 4.71 (s, 1.4H), 4.48 (tt, J = 12.0, 4.3, 0.7 H), 3.36 (tt, J = 11.6, 4.4, 0.3 H), 3.16-3.04 (m, 2H), 2.90-2.78 (m, 5H), 2.68-2.58 (m, 2H), 2.19 (s, 3H), 2.19-2.05 (m, 2H), 2.01-1.84 (m, 1H), 1.82-1.60 (m, 3H).

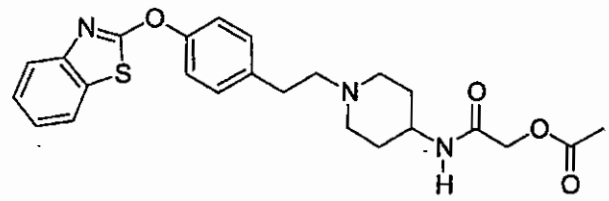
EXAMPLE 353



N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-N-acetamide.

The title compound was prepared from EXAMPLE 337 following EXAMPLE 266, step B, EXAMPLE 343 and EXAMPLE 345 using acetyl chloride. MS (ESI): exact mass calculated for $C_{25}H_{29}N_3O_4S$, 395.2; m/z found, 396.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.0, 1H), 7.66 (dd, J = 7.9, 0.6, 1H), 7.42-7.36 (m, 1H), 7.29-7.24 (m, 5H), 5.48 (d, J = 7.8, 1H), 3.87-3.77 (m 1H), 2.95 (dd, J = 11.6, 2H), 2.83 (dd, J = 10.8, 7.6, 2H), 2.62 (dd, J = 8.5, 5.3, 2H), 2.18 (d, J = 11.4, 2H), 2.00-1.94 (m, 2H), 1.98 (m, 2H), 1.49 (dddd, J = 12.3, 12.2, 12.2, 3.6, 2H).

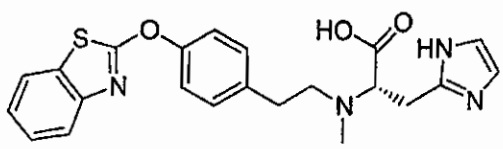
EXAMPLE 354



Acetic acid (1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ylcarbamoyl)-methyl ester.

The title compound was prepared from EXAMPLE 337 according to EXAMPLE 266, step B, EXAMPLE 343 and EXAMPLE 354 using acetic acid chlorocarbonylmethyl ester. MS (ESI): exact mass calculated for $C_{24}H_{27}N_3O_4S$, 453.2; m/z found, 454.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (dd, J = 8.2, 0.6, 1H), 7.67 (dd, J = 7.9, 0.7, 1H), 7.42-7.36 (m, 1H), 7.29-7.24 (m, 5H), 6.05 (d, J = 8.0, 1H), 4.54 (s, 2H), 3.96-3.85 (m 1H), 3.00 (d, J = 8.2, 0.6, 2H), 2.85 (dd, J = 10.6, 7.4, 2H), 2.85 (dd, J = 10.6, 7.4, 2H), 2.66 (dd, J = 8.6, 5.3, 2H), 2.23 (t, J = 11.4, 2H), 2.18 (s, 3H), 1.98 (d, J = 9.7, 2H), 1.57 (dddd, J = 12.4, 12.4, 12.3, 3.6, 2H).

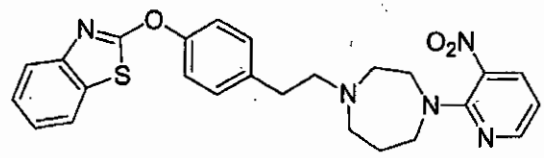
EXAMPLE 355



(*S*)-2-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-methyl-amino)-3-(1H-imidazol-2-yl)-propionic acid.

The title compound was prepared according to the procedure for EXAMPLE 262, step A using (*S*)-3-(1H-imidazol-2-yl)-2-methylamino-propionic acid. MS (ESI): exact mass calculated for $C_{22}H_{22}N_4O_3S_1$, 422.1; m/z found, 423.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 8.85, (s, 1H), 7.81 (dd, *J* = 7.9, 0.6, 1H), 7.72 (dd, *J* = 8.1, 0.5, 1H), 7.58-7.42 (m, 4H), 7.39-7.34 (m, 3H), 4.34, (dd, *J* = 9.3, 4.9, 3H), 3.71-3.42, (m, 4H), 3.35-3.32 (m, 2H), 3.20 (d, *J* = 8.6, 2H), 3.08 (s, 3H).

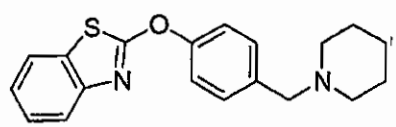
EXAMPLE 356



2-(4-{2-[4-(3-Nitro-pyridin-2-yl)-[1,4]diazepan-1-yl]-ethyl}-phenoxy)-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 262, step A using 1-(3-nitro-pyridin-2-yl)-[1,4]diazepane. MS (ESI): exact mass calculated for $C_{25}H_{25}N_5O_3S_1$, 475.2; m/z found, 476.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.36 (dd, *J* = 4.5, 1.7, 1H), 8.14 (dd, *J* = 8.1, 1.7, 1H), 7.77 (dd, *J* = 8.1, 0.5, 1H), 7.70 (dd, *J* = 8.0, 0.7, 1H), 7.45-7.40 (m, 1H), 7.29-7.24 (m, 5H), 6.73 (dd, *J* = 8.0, 4.4, 1H), 3.80-3.75 (br s, 2H), 3.47-3.40 (br s, 2H), 3.07-3.01 (br s, 2H), 2.95-2.88 (m, 2H), 2.86-2.79 (m, 4H), 2.20-2.10 (br s, 2H).

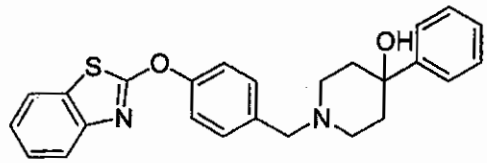
EXAMPLE 357



2-(4-Piperidin-1-ylmethyl-phenoxy)-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 251, step B using piperidine. MS (ESI): mass calculated for $C_{19}H_{20}N_2OS$, 324.4; m/z found, 325.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.75 (d, J = 8.2, 1H), 7.73 (d, J = 8.2, 1H), 7.36-7.42 (m, 3H), 7.24-7.32 (m, 3H), 3.49 (s, 2H), 2.39 (br s, 3H), 1.56-1.64 (m, 5H), 1.40-1.48 (m, 2H).

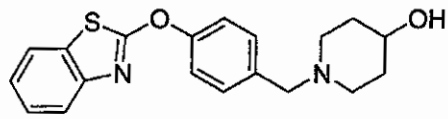
EXAMPLE 358



1-[4-(Benzothiazol-2-yloxy)-benzyl]-4-phenyl-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 251, step B using 4-phenyl-piperidin-4-ol. MS (ESI): mass calculated for $C_{25}H_{24}N_2O_2S$, 416.5; m/z found, 417.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.75 (d, J = 8.0, 1H), 7.66 (d, J = 8.0, 1H), 7.55-7.51 (m, 2H), 7.47-7.25 (m, 9H), 3.63 (s, 2H), 2.85-2.77 (m, 2H), 2.50 (dt, J = 11.8, 2.5, 2H), 2.18 (dt, J = 13.0, 4.4, 2H), 1.80-1.74 (m, 2H), 1.55 (br s, 1H).

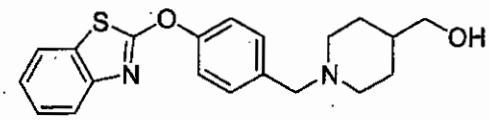
EXAMPLE 359



1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ol.

The title compound was prepared according to the procedure for EXAMPLE 251, step B using 4-piperidinol. MS (ESI): mass calculated for $C_{19}H_{20}N_2O_2S$, 340.4; m/z found, 341.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.0, 1H), 7.67 (d, J = 8.0, 1H), 7.42-7.36 (m, 3H), 7.32-7.24 (m, 3H), 3.68-3.64 (m, 1H), 3.46 (s, 2H), 2.81-2.25 (m, 2H), 2.20-2.15 (m, 2H), 1.95-1.90 (m, 2H), 1.67-1.58 (m, 3H).

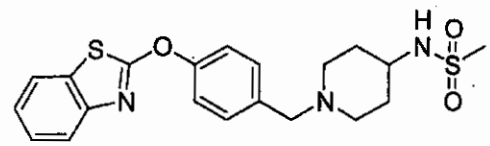
EXAMPLE 360



{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-methanol.

The title compound was prepared according to the procedure for EXAMPLE 251, step B using piperidin-4-yl-methanol. MS (ESI): mass calculated for $C_{20}H_{22}N_2O_2S$, 354.5; m/z found, 355.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.0, 1H), 7.67 (d, J = 8.0, 1H), 7.42-7.37 (m, 3H), 7.32-7.25 (m, 3H), 3.54 (s, 2H), 3.51 (d, J = 6.5, 2H), 2.97-2.90 (m, 2H), 2.01 (dt, J = 11.6, 2.4, 3H), 1.73 (d, J = 12.1, 2H), 1.58-1.47 (m, 1H), 1.37-1.26 (m, 2H).

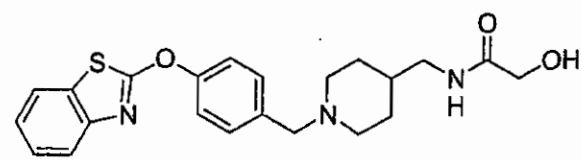
EXAMPLE 361



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-methanesulfonamide.

The title compound was prepared according to the procedure for EXAMPLE 253, step A and B followed by EXAMPLE 258 step C. MS (ESI): mass/ calculated for $C_{20}H_{23}N_3O_3S_2$, 417.6; m/z found, 418.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.0, 1H), 7.68 (d, J = 8.0, 1H), 7.42-7.36 (m, 3H), 7.35-7.25 (m, 3H), 4.32-4.5 (m, 1H), 3.58 (s, 2H), 3.43-3.32 (m, 1H), 2.99 (s, 3H), 2.87-2.80 (m, 2H), 2.18-2.10 (m, 2H), 2.04-1.96 (m, 2H), 1.64-1.54 (m, 2H).

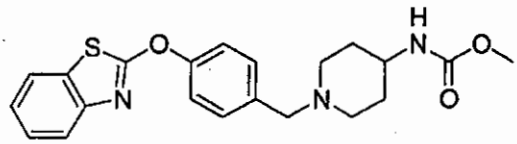
EXAMPLE 362



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-2-hydroxy-acetamide.

The title compound was prepared according to the procedure for EXAMPLE 258, step A and B followed by EXAMPLE 253 step C using glycolic acid. MS (ESI): mass calculated for $C_{22}H_{25}N_3O_3S$, 411.5; m/z found, 412.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.2, 1H), 7.67 (d, J = 8.2, 1H), 7.42-7.37 (m, 3H), 7.32-7.25 (m, 3H), 4.11 (s, 2H), 3.51 (s, 2H), 3.24 (t, J = 6.3, 2H), 2.88-2.94 (m, 2H), 2.20 (d, J = 11.5, 1H), 2.02-1.92 (m, 2H), 1.72-1.65 (m, 2H), 1.62-1.50 (m, 2H), 1.36-1.26 (m, 2H).

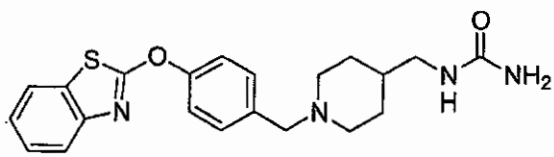
EXAMPLE 363



{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-carbamic acid methyl ester.

The title compound was prepared according to the procedure for EXAMPLE 253, step A and B followed by EXAMPLE 258 step C using methyl isocyanate. MS (ESI): mass calculated for $C_{21}H_{23}N_3O_3S$, 397.5; m/z found, 398.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.0, 1H), 7.67 (d, J = 8.0, 1H), 7.42-7.36 (m, 3H), 7.32-7.24 (m, 3H), 4.57 (br s, 1H), 3.66 (s, 3H), 3.51 (s, 2H), 2.85-2.79 (m, 2H), 2.18-2.09 (m, 2H), 1.98-1.90 (m, 2H), 1.51-1.40 (m, 2H).

EXAMPLE 364

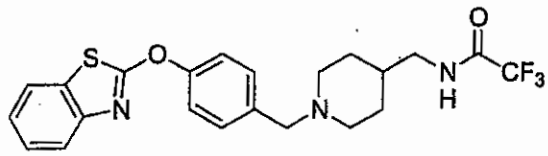


{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-urea.

The title compound was prepared according to the procedure for EXAMPLE 258, step A, B and C using trimethylsilyl isocyanate. MS (ESI): mass

calculated for $C_{21}H_{24}N_4O_2S$, 396.5; m/z found, 397.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.0, 1H), 7.67 (d, J = 8.0, 1H), 7.42-7.36 (m, 3H), 7.32-7.24 (m, 3H), 4.64 (br s, 1H), 4.35 (s, 2H), 3.50 (s, 2H), 3.07 (br t, J = 6.3, 2H), 2.94-2.88 (m, 2H), 1.86-2.01 (m, 2H), 1.72-1.66 (m, 2H), 1.56-1.44 (s, 1H), 1.24-1.23 (m, 2H).

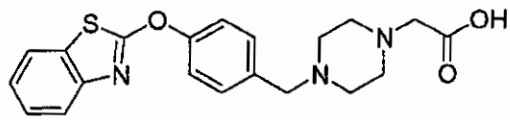
EXAMPLE 365



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylmethyl}-2,2,2-trifluoro-acetamide

The title compound was prepared according to the procedure for EXAMPLE 258, step A and B and EXAMPLE 257, step C using trifluoroacetic acid. MS (ESI): mass calculated for $C_{22}H_{22}F_3N_3O_2S$, 449.5; m/z found, 450.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.0, 1H), 7.67 (d, J = 8.0, 1H), 7.42-7.36 (m, 3H), 7.32-7.24 (m, 3H), 6.41 (br s, 1H), 3.51 (s, 2H), 3.28 (t, J = 6.46, 2H), 2.92 (d, J = 11.5, 2H), 2.02-1.94 (m, 2H), 1.74-1.54 (m, 3H), 1.38-1.27 (m, 2H).

EXAMPLE 366

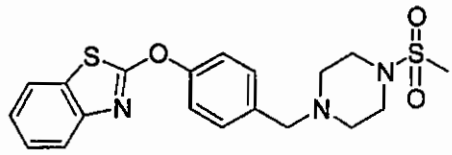


{4-[4-(Benzothiazol-2-yloxy)-benzyl]-piperazin-1-yl}-acetic acid.

The title compound was prepared according to the procedure for EXAMPLE 259, step C and D and EXAMPLE 250, step D using piperazin-1-yl-acetic acid. MS (ESI): mass calculated for $C_{20}H_{21}N_3O_3S$, 383.5; m/z found, 384.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.77 (d, J = 8.0, 1H), 7.62 (d, J = 8.0, 1H), 7.50-

7.46 (m, 2H), 7.42-7.26 (m, 4H), 6.67 (s, 2H), 3.60 (s, 2H), 3.34 (br s, 4H), 2.77 (br s, 4H).

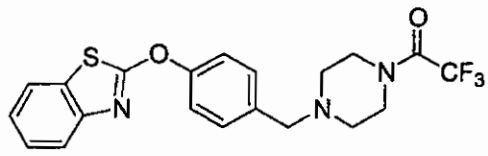
EXAMPLE 367



2-[4-(4-Methanesulfonyl-piperazin-1-ylmethyl)-phenoxy]-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 257, step A and B and EXAMPLE 258 step C. MS (ESI): mass calculated for $C_{19}H_{21}N_3O_3S_2$, 403.53; m/z found, 404.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.0, 1H), 7.68 (d, J = 8.0, 1H), 7.42-7.36 (m, 3H), 7.35-7.26 (m, 3H), 3.57 (s, 2H), 3.26 (br t, J = 4.7, 4H), 2.79 (s, 3H), 2.58 (br t, J = 4.7, 4H).

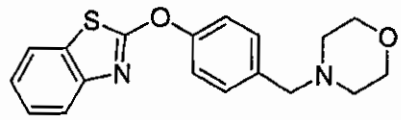
EXAMPLE 368



1-{4-[4-(Benzothiazol-2-yloxy)-benzyl]-piperazin-1-yl}-2,2,2-trifluoro-ethanone.

The title compound was prepared according to the procedure for EXAMPLE 257, step A, B and C using trifluoroacetic acid. MS (ESI): mass calculated for $C_{20}H_{18}F_3N_3O_2S$, 421.44; m/z found, 422.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.0, 1H), 7.68 (d, J = 8.0, 1H), 7.42-7.27 (m, 6H), 3.74-3.70 (m, 2H), 3.65-3.60 (m, 2H), 3.57 (s, 2H), 2.56-2.50 (m, 4H).

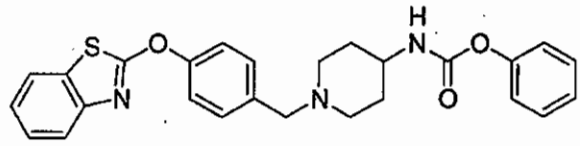
EXAMPLE 369



2-(4-Morpholin-4-ylmethyl-phenoxy)-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 259, step C and D using morpholine. MS (ESI): mass calculated for $C_{18}H_{18}N_2O_2S$, 326.42; m/z found, 327.4 $[M+H]^+$. ^1H NMR (500 MHz, $CDCl_3$): 7.74 (d, J = 7.7, 1H), 7.67 (d, J = 7.7, 1H), 7.42-7.37 (m, 3H), 7.33-7.25 (m, 3H), 3.72 (t, J = 3.7, 4H), 3.52 (s, 2H), 2.46 (br s, 4H).

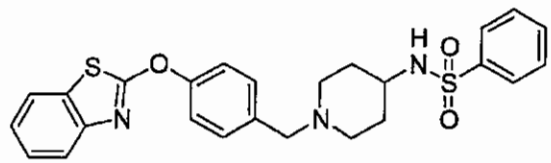
EXAMPLE 370



{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-carbamic acid phenyl ester.

The title compound was prepared according to the procedure for EXAMPLE 253, step A and B followed by EXAMPLE 258 step C using phenyl isocyanate. MS (ESI): mass calculated for $C_{26}H_{25}N_3O_3S$, 459.57; m/z found, 460.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.0, 1H), 7.67 (d, J = 8.0, 1H), 7.42-7.10 (m, 11H), 4.95 (br d, J = 7.8, 1H), 3.67-3.58 (m, 1H), 3.53 (s, 2H), 2.88-2.82 (m, 2H), 2.21-2.06 (m, 2H), 2.03-1.99 (m, 2H), 1.61-1.44 (m, 2H).

EXAMPLE 371

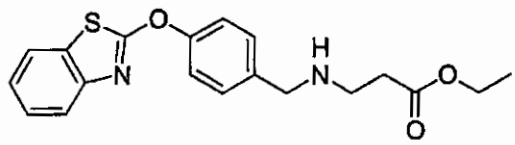


N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-benzenesulfonamide.

The title compound was prepared according to the procedure for EXAMPLE 253, step A and B followed by EXAMPLE 258, step C using benzenesulfonyl chloride. MS (ESI): mass calculated for $C_{25}H_{25}N_3O_3S_2$, 479.62; m/z found, 480.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.86-7.84 (m, 2H), 7.75 (d, J = 8.0,

1H), 7.67 (d, J = 8.0, 1H), 7.60-7.48 (m, 3H), 7.41-7.24 (m, 6H), 4.56 (br d, J = 7.8, 1H), 3.48 (s, 2H), 3.26-3.16 (m, 1H), 2.76-2.68 (m, 2H), 2.06-1.97 (m, 2H), 1.78-1.70 (m, 1H), 1.52-1.42 (m, 2H).

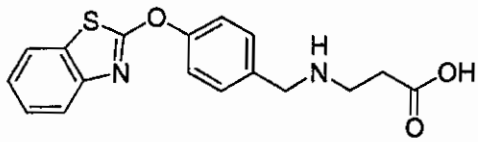
EXAMPLE 372



3-[4-(Benzothiazol-2-yloxy)-benzylamino]-propionic acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 251, step A and B using 3-amino-propionic acid ethyl ester. MS (ESI): mass calculated for $C_{19}H_{20}N_2O_3S$, 356.45; m/z found, 357.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.0, 1H), 7.67 (d, J = 8.0, 1H), 7.44-7.25 (m, 6H), 4.21 (br s, 1H), 4.15 (q, J = 7.2, 2H), 3.87 (s, 2H), 2.95 (t, J = 6.3, 2H), 2.58 (t, J = 6.3, 2H), 1.26 (t, J = 7.2, 3H).

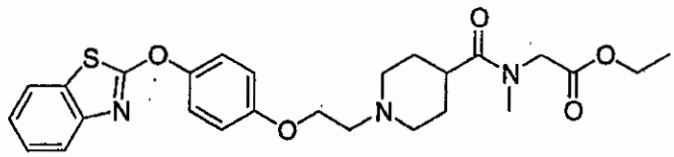
EXAMPLE 373



3-[4-(Benzothiazol-2-yloxy)-benzylamino]-propionic acid.

The title compound was prepared according to the procedure for EXAMPLE 372, and EXAMPLE 250, step D. MS (ESI): mass calculated for $C_{17}H_{16}N_2O_3S$, 328.39; m/z found, 329.3 $[M+H]^+$. ^1H NMR (400 MHz, DMSO): 7.87 (d, J = 8.0, 1H), 7.62 (d, J = 8.0, 1H), 7.44-7.23 (m, 6H), 3.77 (s, 2H), 2.72 (t, J = 6.6, 2H), 2.29 (t, J = 6.6, 2H).

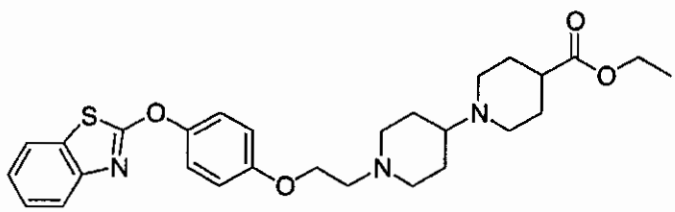
EXAMPLE 374



[(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carbonyl)-methyl-amino]-acetic acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 18, step A and EXAMPLE 20 using 3-methylamino-propionic acid ethyl ester. MS (ESI): mass calculated for $C_{26}H_{31}N_3O_5S$, 497.62; m/z found, 498.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.0, 1H), 7.65 (d, J = 8.0, 1H), 7.41-7.35 (m, 1H), 7.28-7.23 (m, 3H), 6.99-6.94 (m, 2H), 4.28-4.08 (m, 5H), 3.12 (s, 3H), 3.10-3.04 (m, 1H), 2.98-2.81 (m, 4H), 2.62-2.53 (m, 1H), 2.24-2.12 (m, 2H), 1.97-1.83 (m, 2H), 1.81-1.64 (m, 2H), 1.32-1.24 (m, 3H).

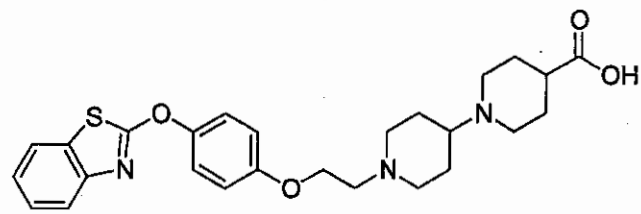
EXAMPLE 376



1'-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-[1,4']bipiperidinyl-4-carboxylic acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 9 and EXAMPLE 24 using [1,4']bipiperidinyl-4-carboxylic acid ethyl ester. MS (ESI): mass calculated for $C_{28}H_{35}N_3O_4S$, 509.67; m/z found, 510.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.0, 1H), 7.65 (d, J = 8.0, 1H), 7.41-7.35 (m, 1H), 7.29-7.23 (m, 3H), 6.99-6.92 (m, 2H), 4.16-4.08 (m, 4H), 3.10-3.04 (m, 2H), 2.92-2.86 (m, 2H), 2.80 (t, J = 5.9, 1H), 2.36-2.20 (m, 4H), 2.16-2.07 (m, 2H), 1.95-1.87 (m, 2H), 1.82-1.57 (m, 7H), 1.24 (t, J = 7.0, 3H).

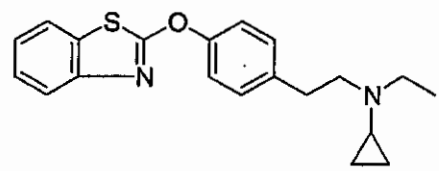
EXAMPLE 377



1'-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-[1,4']bipiperidinyl-4-carboxylic acid.

The title compound was prepared according to the procedure for EXAMPLE 376 and EXAMPLE 250, step D. MS (ESI): mass calculated for $C_{26}H_{31}N_3O_4S$, 481.62; m/z found, 482.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.76 (d, J = 8.0, 1H), 7.64 (d, J = 8.0, 1H), 7.44-7.38 (m, 1H), 7.32-7.27 (m, 3H), 7.08-7.03 (m, 2H), 4.17 (t, J = 5.4, 2H), 3.44-3.36 (m, 2H), 3.24-3.19 (m, 2H), 3.05-2.84 (m, 5H), 2.40-2.20 (m, 3H), 2.14-2.04 (m, 4H), 1.86-1.72 (m, 4H).

EXAMPLE 378



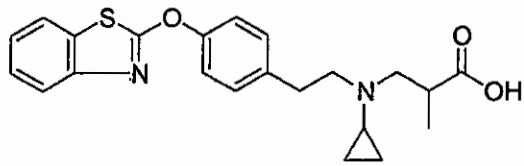
{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-ethyl-amine.

A. {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amine. A mixture of [4-(benzothiazol-2-yloxy)-phenyl]-acetaldehyde (Example 262 step A, 4.2 g, 15.6 mmol), cyclopropylamine (5.4 mL, 78.0 mmol) and acetic acid (4.5 mL, 78 mmol) in CH_2Cl_2 (156 mL) was stirred at room temperature for 1 h. To the resulting mixture was added $NaBH(OAc)_3$ (6.61 g, 31.2 mmol). The mixture was stirred at room temperature for 24 h, filtered through diatomaceous earth, rinsed with CH_2Cl_2 (200 mL), washed with 1N NaOH (3 x 50 mL), and concentrated under reduced pressure to yield the crude product as a yellow oil. The crude product was purified on SiO_2 (330 g; 0-10% CH_3OH/CH_2Cl_2) to give a clear oil which crystallized on standing (3.4 g, 71% yield). MS (ESI): mass calculated for $C_{18}H_{18}N_2OS$, 310.11; m/z found, 311.2 $[M+H]^+$. ^1H NMR (400

MHz, $CDCl_3$): 7.76 (d, *J* = 8.1, 1H), 7.62 (d, *J* = 8.1, 1H), 7.46-7.27 (m, 6H), 3.41 (t, *J* = 7.6, 2H), 3.08 (t, *J* = 7.6, 2H), 2.38-2.76 (m, 1H), 0.95-0.89 (m, 4H).

B. {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-ethyl-amine. A mixture of acetaldehyde (180 µL, 3.2 mmol), {2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amine (500 mg, 1.6 mmol) in CH_2Cl_2 (32 mL) was stirred at room temperature for 1 h. To the resulting mixture was added $NaBH(OAc)_3$ (1.02 g, 4.8 mmol). The mixture was stirred at room temperature for 24 h, filtered through diatomaceous earth, rinsed with CH_2Cl_2 (100 mL), and concentrated under reduced pressure to yield the crude product as a yellow oil. The crude product was purified on SiO_2 (40 g; 0-10% CH_3OH/CH_2Cl_2) to give a clear oil (465 mg, 86% yield). MS (ESI): mass calculated for $C_{20}H_{22}N_2OS$, 338.15; m/z found, 339.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.66 (d, *J* = 8.1, 1H), 7.58 (d, *J* = 8.1, 1H), 7.31 (t, *J* = 8.1, 1H), 7.23-7.15 (m, 5H), 2.80 (s, 4H), 2.72 (dd, *J* = 7.3, 7.1, 2H), 1.78-1.70 (m, 1H), 1.05 (t, *J* = 7.1, 3H), 0.50-0.36 (m, 4H).

EXAMPLE 379



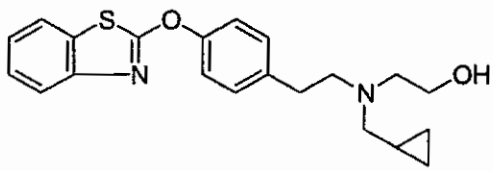
3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-2-methyl-propionic acid trifluoromethansulfonic acid salt.

A. 3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-2-methyl-propionic acid methyl ester. To a solution of {2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amine (500 mg, 1.6 mmol) in CH_3CN (10 mL) at room temperature was added *N,N*-diisopropylethylamine (349 µL, 2 mmol), followed by 3-bromo-2-methyl-propionic acid methyl ester (362 mg, 2 mmol). The resulting mixture was heated at 60 °C overnight. The mixture was cooled and dissolved in CH_2Cl_2 (100 mL), washed with sat. aq. $NaHCO_3$ (1 x 25 mL) and H_2O (2 x 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as a off-white solid. The crude product was

purified on SiO_2 (40 g; 0-10% CH_3OH/CH_2Cl_2) to give a pale off-white solid (158 mg, 39% yield). MS (ESI): mass calculated for $C_{23}H_{26}N_2O_3S$, 410.17; m/z found, 411.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.73 (d, J = 8.3, 1H), 7.65 (d, J = 8.3, 1H), 7.38 (t, J = 8.1, 1H), 7.28-7.23 (m, 5H), 3.66 (s, 3H), 3.01 (dd, J = 8.8, 3.8, 1H), 2.89-2.76 (m, 5H), 3.60 (dd, J = 6.6, 6.1, 1H), 1.84-1.78 (m, 1H), 1.12 (d, J = 7.1, 3H), 0.51-0.30 (m, 4H).

B. 3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-2-methyl-propionic acid trifluoromethansulfonic acid salt. To a solution of 3-({2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-2-methyl-propionic acid methyl ester (158 mg, 0.38 mmol) in 3:1:1 THF/CH_3OH (13 mL), was added a solution of lithium hydroxide (37 mg, 1.54 mmol) in H_2O (3 mL). The reaction solution was stirred at room temperature for 16 h and then concentrated under reduced pressure. The residue was dissolved in CH_3OH and purified by reversed-phase HPLC. The desired fractions were collected and concentrated under reduced pressure, giving the the title compound as a clear oil (179 mg, 92% yield). MS (ESI): mass calculated for $C_{22}H_{24}N_2O_3S$, 396.15; m/z found, 397.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.78 (d, J = 8.3, 1H), 7.64 (d, J = 8.1, 1H), 7.51-7.27 (m, 6H), 3.83 (t, J = 12.4, 1H), 3.55 (t, J = 8.1, 2H), 3.37 (d, J = 13.1, 1H), 3.25 (t, J = 8.8, 2H), 3.21-3.11 (m, 1H), 2.99-2.90 (m, 1H), 1.33 (d, J = 7.3, 3H), 1.17-0.97 (m, 4H).

EXAMPLE 380

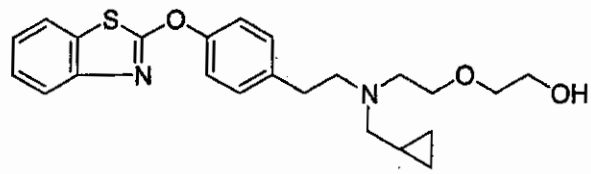


2-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-ethanol.

The title compound was prepared according to the procedure for EXAMPLE 378, step A using cyclopropyl-methylamine and EXAMPLE 379, step A using 2-bromoethanol. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_2S$, 368.16; m/z found, 369.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.70 (d, J = 8.1, 1H), 7.62

(d, J = 8.1, 1H), 7.34 (t, J = 7.3, 1H), 7.27-7.18 (m, 5H), 3.56 (t, J = 5.3, 2H), 2.92-2.86 (m, 2H), 2.84-2.73 (m, 4H), 2.49 (d, J = 6.6, 2H), 0.92-0.81 (m, 1H), 0.55-0.49 (m, 2H), 0.16-0.09 (m, 2H).

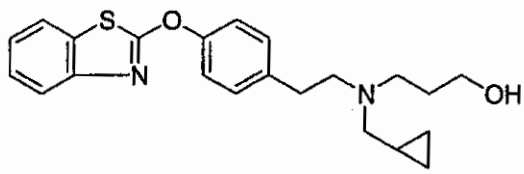
EXAMPLE 381



2-[2-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-ethoxy]-ethanol.

The title compound was prepared according to the procedure for EXAMPLE 380. MS (ESI): mass calculated for $C_{23}H_{28}N_2O_3S$, 412.18; m/z found, 413.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.64 (d, J = 8.3, 2H), 7.41 (d, J = 8.3, 2H), 7.31 (t, J = 8.3, 1H), 7.25-7.17 (m, 3H), 4.08 (br s, 1H), 3.84-3.68 (m, 6H), 3.59-3.49 (m, 2H), 3.26-3.16 (m, 2H), 1.11-0.99 (m, 1H), 0.79-0.70 (m, 2H), 0.55-0.48 (m, 2H).

EXAMPLE 382

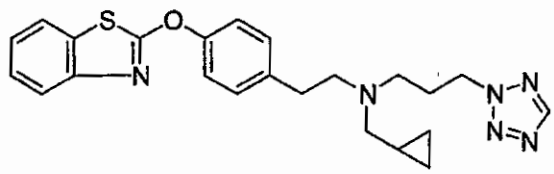


3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propan-1-ol.

The title compound was prepared according to the procedure for EXAMPLE 378, steps A using cyclopropyl-methylamine and EXAMPLE 379, step A using 3-bromo-propan-1-ol. MS (ESI): mass calculated for $C_{22}H_{26}N_2O_2S$, 382.17; m/z found, 383.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.70 (d, J = 8.1, 1H), 7.62 (d, J = 8.1, 1H), 7.34 (t, J = 8.1, 1H), 7.27-7.18 (m, 5H), 3.77 (t, J = 5.3,

2H), 2.84-2.76 (m, 6H), 2.43 (d, *J* = 6.6, 2H), 1,72-1,65 (m, 2H), 0.94-0.83 (m, 1H), 0.57-0.49 (m, 2H), 0.18-0.11 (m, 2H).

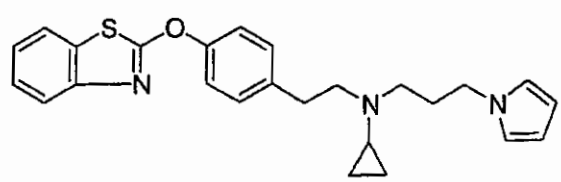
EXAMPLE 383



{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-(3-tetrazol-2-yl-propyl)-amine trifluoromethansulfonic acid salt.

To a solution of 3-({2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propan-1-ol (Example 382, 220 mg, 0.58 mmol) and 2H-tetrazole (61 mg, 0.87 mmol) in CH_2Cl_2 (12 mL) was added polymer-supported triphenylphosphine (290 mg, 0.87 mmol) and di-tert-butyl azodicarboxylate (200 mg, 0.87 mmol). The reaction mixture was stirred at room temperature for 1 h, filtered and the collected solids were washed with CH_2Cl_2 (10 mL). The filtrate was concentrated under reduced pressure to yield the crude product as a light yellow oil. The crude product was dissolved in CH_3OH and purified by reversed-phase HPLC. The desired fractions were collected and concentrated under reduced pressure, giving the title compound as a clear oil (100 mg, 40% yield). MS (ESI): mass calculated for $C_{23}H_{26}N_6OS$, 434.19; m/z found, 435.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.75 (s, 1H), 7.75 (d, *J* = 8.1, 1H), 7.60 (d, *J* = 8.1, 1H), 7.45-7.32 (m, 5H), 7.28 (t, *J* = 8.1, 1H), 3.54-3.40 (m, 4H), 3.29-3.25 (m, 2H), 3.19 (d, *J* = 7.3, 2H), 3.09 (t, *J* = 8.6, 2H), 2.56-2.47 (m, 2H), 1.16-1.05 (m, 1H), 0.78-0.71 (m, 2H), 0.46-0.40 (m, 2H).

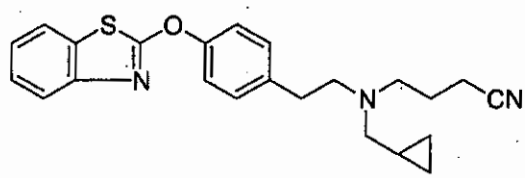
EXAMPLE 384



{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-(3-pyrrol-1-yl-propyl)-amine.

The title compound was prepared according to the procedure for EXAMPLE 379, step A using 1-(3-bromo-propyl)-1H-pyrrole. MS (ESI): mass calculated for $C_{25}H_{27}N_3OS$, 417.19; m/z found, 418.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.65 (d, J = 7.6, 1H), 7.57 (d, J = 8.1, 1H), 7.30 (t, J = 8.1, 1H), 7.21-7.13 (m, 5H), 6.57 (t, J = 2.0, 2H), 6.07 (t, J = 2.0, 2H), 3.80 (t, J = 7.1, 2H), 2.80-2.69 (m, 4H), 2.57 (t, J = 7.1, 2H), 1.98-1.88 (m, 2H), 1.74-1.67 (m, 1H), 0.47-0.40 (m, 2H), 0.37-0.31 (m, 2H).

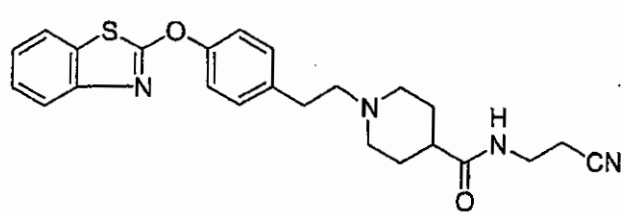
EXAMPLE 385



4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-butyronitrile.

The title compound was prepared according to the procedure for EXAMPLE 378, step A using cyclopropyl-methylamine and EXAMPLE 319, step A using 4-bromo-butyronitrile. MS (ESI): mass calculated for $C_{23}H_{25}N_3OS$, 391.17; m/z found, 392.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.70 (d, J = 8.1, 1H), 7.63 (d, J = 8.1, 1H), 7.35 (t, J = 8.1, 1H), 7.27-7.20 (m, 5H), 2.77-2.73 (m, 4H), 2.64 (t, J = 6.6, 2H), 2.39 (d, J = 6.3, 2H), 2.29 (t, J = 6.8, 2H), 1.74-1.66 (m, 2H), 0.89-0.78 (m, 1H), 0.55-0.48 (m, 2H), 0.13-0.08 (m, 2H).

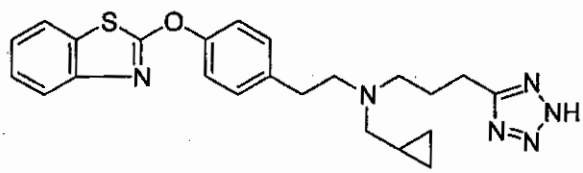
EXAMPLE 386



1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid (2-cyano-ethyl)-amide.

The title compound was prepared according to the procedure for EXAMPLE 33, step B, using 3-amino-propionitrile. MS (ESI): mass calculated for $C_{24}H_{26}N_4O_2S$, 434.18; m/z found, 435.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, J = 8.3, 1H), 7.67 (d, J = 8.1, 1H), 7.40 (t, J = 8.1, 1H), 7.32-7.24 (m, 5H), 6.39 (t, J = 6.6, 1H), 3.51(dd, J = 6.3, 6.1, 2H), 3.11-3.00 (m, 2H), 2.89-2.82 (m, 2H), 2.69-2.58 (m, 4H), 2.23-2.13 (m, 1H), 2.08 (t, J = 12.1, 2H), 1.94-1.76 (m, 4H).

EXAMPLE 387

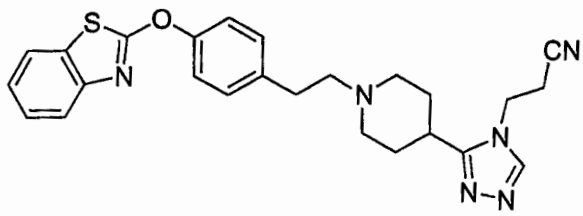


{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-[3-(2H-tetrazol-5-yl)-propyl]-amine.

To a solution of 4-({2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-butyronitrile (Example 385, 250 mg, 0.6 mmol) in toluene (32 mL) at room temperature was added trimethylaluminum (2.0 M solution in toluene, 1.53 mL, 3.08 mmol), followed by azidotrimethylsilane (404 µL, 3.08 mmol). The resulting mixture was heated at 80 °C for 18 h. The mixture was cooled to room temperature and diluted with CH_2Cl_2 (200 mL), washed with sat. aq. $NaHCO_3$ (1 x 25 ml) and H_2O (2 x 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as an off-white solid. The crude product was purified on SiO_2 (40 g; 0-20% CH_3OH/CH_2Cl_2) to give an off-white solid (246 mg, 88% yield). MS (ESI): mass calculated for $C_{23}H_{26}N_6OS$, 434.19; m/z found, 435.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 11.25 (br s, 1H), 7.54 (dd, J = 7.8, 5.0, 2H), 7.23 (dd, J = 8.1, 7.3, 1H), 7.19-7.09 (m, 5H), 3.23-3.11 (m, 4H), 3.01-2.90 (m, 4H), 2.83 (d,

J = 7.3, 2H), 2.18-2.07 (m, 2H), 1.01-0.91 (m, 1H), 0.57-0.50 (m, 2H), 0.25-0.18 (m, 2H).

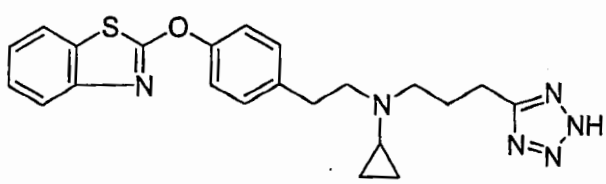
EXAMPLE 388



3-[5-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-tetrazol-1-yl]-propionitrile.

To a stirred suspension of 1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid (2-cyano-ethyl)-amide (Example 386, 500 mg, 1.15 mmol) and triphenylphosphine (755 mg, 2.88 mmol) in anhydrous CH_3CN (10 mL) at 0 °C were added diisopropyl azodicarboxylate (567 µL, 2.88 mmol) and 2 min later, azidotrimethylsilane (399 µL, 3.04 mmol) over 20 min. The reaction mixture was allowed to warm to room temperature over 30 min then was stirred for an additional 14 h. The reaction mixture was added to ice H_2O (20 mL) and extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified on SiO_2 (40 g; 0-15% CH_3OH/CH_2Cl_2) to give an off-white solid (439 mg, 83% yield). MS (ESI): mass calculated for $C_{24}H_{25}N_7OS$, 459.18; m/z found, 460.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, *J* = 8.1, 1H), 7.66 (d, *J* = 8.1, 1H), 7.38 (t, *J* = 7.8, 1H), 7.31-7.23 (m, 5H), 4.62 (t, *J* = 6.8, 2H), 3.20-3.10 (m, 4H), 3.04-2.94 (m, 1H), 2.91-2.82 (m, 2H), 2.73-2.64 (m, 2H), 2.25 (t, *J* = 10.9, 2H), 2.18-2.05 (m, 2H), 2.04-1.95 (m, 2H).

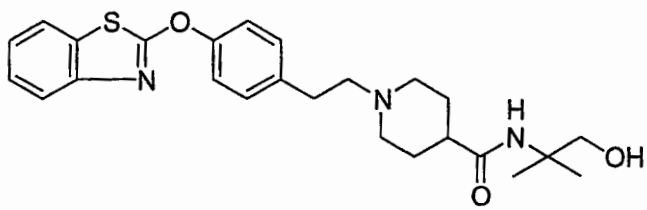
EXAMPLE 389



{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-[3-(2H-tetrazol-5-yl)-propyl]-amine.

The title compound was prepared according to the procedure for EXAMPLE 387. MS (ESI): mass calculated for $C_{20}H_{24}N_6OS$, 420.17; m/z found, 421.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 13.02 (br s, 1H), 7.50 (dd, J = 8.1, 3.5, 2H), 7.20 (t, J = 8.1, 1H), 7.12-7.04 (m, 5H), 2.95-2.77 (m, 8H), 2.06-1.93 (m, 3H), 0.60-0.48 (m, 4H).

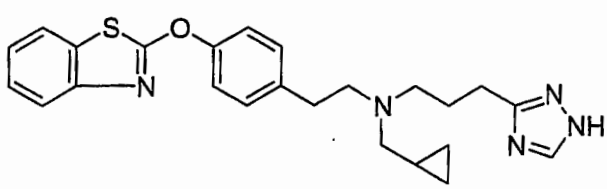
EXAMPLE 390



1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide.

The title compound was prepared according to the procedure for EXAMPLE 33, steps B and C using 2-amino-2-methyl-propan-1-ol. MS (ESI): mass calculated for $C_{25}H_{31}N_3O_3S$, 453.21; m/z found, 454.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.75 (d, J = 8.1, 1H), 7.68 (d, J = 8.1, 1H), 7.40 (t, J = 8.1, 1H), 7.32-7.25 (m, 5H), 5.83 (s, 1H), 5.06 (br s, 1H), 3.59 (s, 2H), 3.14-3.06 (m, 2H), 2.91-2.84 (m, 2H), 2.70-2.63 (m, 2H), 2.20-2.10 (m, 3H), 1.95-1.74 (m, 4H), 1.32 (s, 6H).

EXAMPLE 391

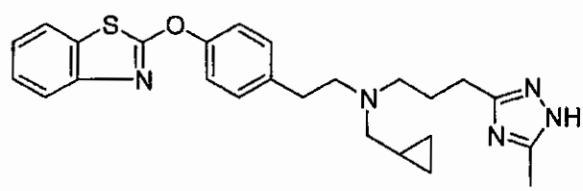


{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-[3-(1H-[1,2,4]triazol-3-yl)-propyl]-amine trifluoromethansulfonic acid salt.

A. 4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-butyrimidic acid ethyl ester hydrochloride salt. A solution of 4-({2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-butyronitrile (Example 385, 932 mg, 2.38 mmol) in absolute ethanol (5 mL) and diethyl ether (10 mL) was treated with bubbled hydrogen chloride gas for 1 h. The resulting suspention was filtered and washed with ether to give the title compound (1.12 g, 92% yield). Due to instability, the crude material was used immediately without purification.

B. {2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-[3-(1H-[1,2,4]triazol-3-yl)-propyl]-amine trifluoromethansulfonic acid salt. To a solution of 4-({2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-butyrimidic acid ethyl ester hydrochloride salt (511 mg, 1 mmol) in ethanol (4.5 mL) was added triethylamine (375 µL, 2.7 mmol), followed by a solution of formic hydrazide (60 mg, 1 mmol) in ethanol (4.5 mL). The resulting mixture was stirred at room temperature for 2 h and then at reflux for 1 h. The mixture was cooled and diluted with CH_2Cl_2 (1500 mL), washed with sat. aq. $NaHCO_3$ (1 x 25 mL) and H_2O (2 x 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as a off-white solid. The crude product was purified on SiO_2 (40 g; 0-15% CH_3OH/CH_2Cl_2) to give a off-white solid (317 mg, 73% yield). MS (ESI): mass calculated for $C_{24}H_{27}N_5OS$, 433.19; m/z found, 434.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.91 (s, 1H), 7.68 (d, J = 7.8, 1H), 7.63 (d, J = 8.1, 1H), 7.34 (t, J = 8.1, 1H), 7.25-7.19 (m, 5H), 2.90-2.76 (m, 6H), 2.72 (t, J = 6.3, 2H), 2.46 (d, J = 6.6, 2H), 2.00-1.90 (m, 2H), 0.93-0.82 (m, 1H), 0.56-0.49 (m, 2H), 0.16-0.10 (m, 2H).

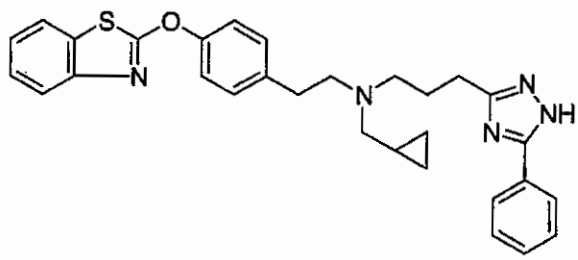
EXAMPLE 392



{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-[3-(5-methyl-1H-[1,2,4]triazol-3-yl)-propyl]-amine.

The title compound was prepared according to the procedure for EXAMPLE 391, step B using acetic hydrazide. MS (ESI): mass calculated for $C_{25}H_{29}N_5OS$, 447.21; m/z found, 448.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.65 (dd, J = 8.1, 8.1, 2H), 7.35 (t, J = 8.1, 1H), 7.27-7.21 (m, 5H), 3.01-2.94 (m, 2H), 2.93-2.84 (m, 4H), 2.81 (t, J = 6.6, 2H), 2.61 (d, J = 6.8, 2H), 2.37 (s, 3H), 2.07-1.97 (m, 2H), 1.01-0.89 (m, 1H), 0.62-0.53 (m, 2H), 0.25-0.17 (m, 2H).

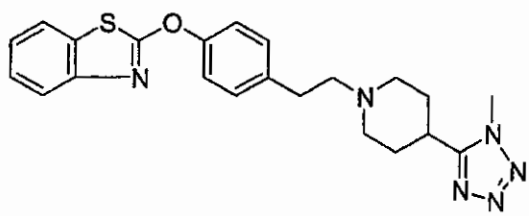
EXAMPLE 393



{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-[3-(5-phenyl-1H-[1,2,4]triazol-3-yl)-propyl]-amine.

The title compound was prepared according to the procedure for EXAMPLE 391, step B using benzoic acid hydrazide. MS (ESI): mass calculated for $C_{30}H_{31}N_5OS$, 509.22; m/z found, 510.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 8.06 (dd, J = 16.8, 0.5, 2H), 7.70 (d, J = 8.1, 1H), 7.63 (d, J = 8.1, 1H), 7.42-7.30 (m, 4H), 7.28-7.20 (m, 5H), 2.99-2.87 (m, 6H), 2.85 (t, J = 6.6, 2H), 2.58 (d, J = 6.8, 2H), 2.09-2.00 (m, 2H), 1.00-0.89 (m, 1H), 0.61-0.53 (m, 2H), 0.23-0.16 (m, 2H).

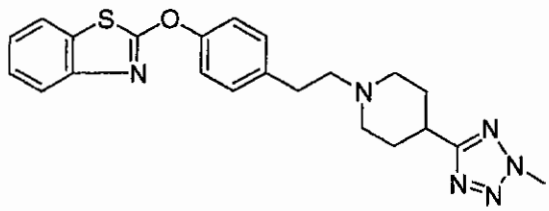
EXAMPLE 394



2-(4-{2-[4-(1-Methyl-1H-tetrazol-5-yl)-piperidin-1-yl]-ethyl}-phenoxy)-benzothiazole trifluoroacetic acid salt.

To a solution of 2-(4-{2-[4-(1H-tetrazol-5-yl)-piperidin-1-yl]-ethyl}-phenoxy)-benzothiazole (Example 262, 80 mg, 1.97 mmol) in DMF (20 mL) was added K_2CO_3 (256 mg, 1.85 mmol) and dimethyl carbonate (360 µL, 4.27 mmol). The reaction mixture was stirred at room temperature for 18 h, filtered and concentrated under reduced pressure. The crude product was dissolved in CH_3OH and purified by reversed-phase HPLC. The desired fractions were collected and concentrated under reduced pressure, giving the title compound as a colorless oil (289 mg, 27% yield). MS (ESI): mass calculated for $C_{22}H_{24}N_6OS$, 420.17; m/z found, 421.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.72 (d, J = 7.8, 1H), 7.58 (d, J = 7.8, 1H), 7.44-7.28 (m, 5H), 7.25 (t, J = 8.1, 1H), 4.06 (s, 3H), 3.80 (d, J = 12.1, 1H), 3.66-3.35 (m, 4H), 3.28-3.17 (m, 2H), 3.16-3.08 (m, 2H), 2.33-2.23 (m, 2H), 2.22-2.07 (m, 2H).

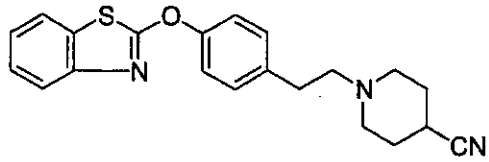
EXAMPLE 395



2-(4-{2-[4-(2-Methyl-2H-tetrazol-5-yl)-piperidin-1-yl]-ethyl}-phenoxy)-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 394. MS (ESI): mass calculated for $C_{22}H_{24}N_6OS$, 420.17; m/z found, 421.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.75 (d, J = 7.8, 1H), 7.60 (d, J = 7.8, 1H), 7.46-7.33 (m, 5H), 7.28 (t, J = 7.8, 1H), 4.31 (s, 3H), 3.79 (d, J = 13.4, 1H), 3.62-3.06 (m, 8H), 2.48-2.30 (m, 2H), 2.15-2.02 (m, 2H).

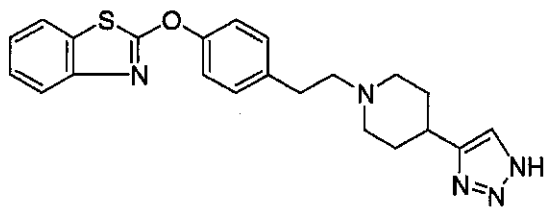
EXAMPLE 396



1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carbonitrile.

The title compound was prepared according to the procedure for EXAMPLE 262, using piperidine-4-carbonitrile. MS (ESI): mass calculated for $C_{21}H_{21}N_3OS$, 363.14; m/z found, 364.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.63 (d, J = 7.6, 1H), 7.55 (d, J = 7.6, 1H), 7.28 (t, J = 8.1, 1H), 7.20-7.12 (m, 5H), 2.71 (dd, J = 7.1, 3.3, 2H), 2.68-2.55 (m, 3H), 2.52 (dd, J = 7.1, 3.3, 2H), 2.37-2.25 (m, 2H), 1.91-1.73 (m, 2H).

EXAMPLE 397

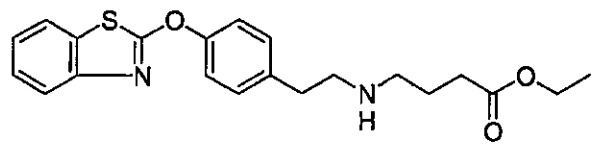


2-(4-{2-[4-(1H-[1,2,3]Triazol-4-yl)-piperidin-1-yl]-ethyl}-phenoxy)-benzothiazole.

To a solution of trimethylsilyldiazomethane (1.8 mL, 3.6 mmol) in diethyl ether (30 mL) at 0 °C under nitrogen was added dropwise n-butyllithium (2.5 M in hexane, 1.44 mL, 3.6 mmol) and the mixture was stirred at 0 °C for 20 min. To the resulting solution was added dropwise a solution of 1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carbonitrile (Example 396, 1.09 g, 3.0 mmol) in THF (10 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 3 h. The mixture was treated with sat. aq. NH_4Cl and extracted with CH_2Cl_2 (2 x 100 mL). The extracts were washed with H_2O (2 x 25 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as an off-white solid. The crude product was purified on SiO_2 (40 g; 0-10% CH_3OH/CH_2Cl_2) to give an off-white solid (768 mg, 54% yield). MS (ESI): mass calculated for $C_{22}H_{23}N_5OS$, 405.16; m/z found, 406.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$):

7.63 (d, J = 8.1, 1H), 7.56 (d, J = 8.1, 1H), 7.42 (s, 1H), 7.29 (t, J = 7.8, 1H), 7.23-7.14 (m, 5H), 4.67 (br s, 1H), 3.04 (d, J = 11.9, 2H), 2.84-2.70 (m, 3H), 2.63-2.56 (m, 2H), 2.16 (t, J = 11.1, 2H), 1.97 (d, J = 12.6, 2H), 1.82-1.70 (m, 2H).

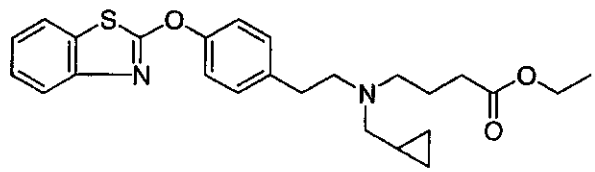
EXAMPLE 398



4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-butyric acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 378, step A using 4-amino-butyric acid ethyl ester. MS (ESI): mass calculated for $C_{21}H_{24}N_2O_3S$, 384.15; m/z found, 385.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.1, 1H), 7.66 (d, J = 8.1, 1H), 7.38 (t, J = 8.1, 1H), 7.31-7.22 (m, 5H), 6.67 (br s, 1H), 4.12 (dd, J = 7.3, 7.1, 2H), 2.95-2.80 (m, 2H), 2.69 (t, J = 6.8, 2H), 2.35 (t, J = 7.3, 2H), 2.29 (t, J = 7.3, 2H), 1.86-1.77 (m, 2H), 1.25 (t, J = 7.1, 3H).

EXAMPLE 399

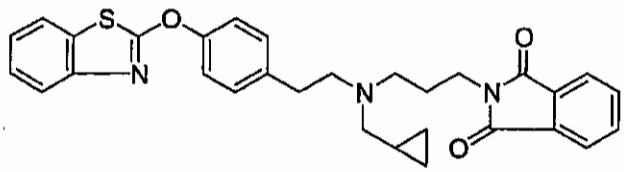


4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-butyric acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 378, step A using cyclopropyl-methylamine and EXAMPLE 379, step A using 4-bromo-butyric acid ethyl ester. MS (ESI): mass calculated for $C_{25}H_{30}N_2O_3S$, 438.20; m/z found, 439.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, J = 8.1, 1H), 7.63 (d, J = 8.1, 1H), 7.35 (t, J = 8.1, 1H), 7.27-7.20 (m, 5H), 6.67 (br s,

1H), 4.10 (dd, *J* = 7.1, 7.1, 2H), 2.83-2.71 (m, 4H), 2.60 (t, *J* = 7.1, 2H), 2.40 (t, *J* = 6.6, 2H), 2.31 (t, *J* = 7.3, 2H), 1.81-1.72 (m, 2H), 1.23 (t, *J* = 7.1, 3H), 0.88-0.79 (m, 1H), 0.52-0.45 (m, 2H), 0.13-0.07 (m, 2H).

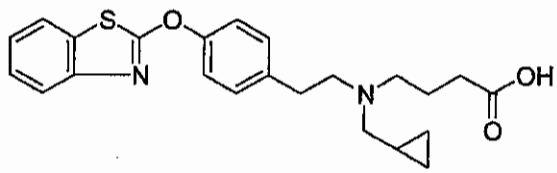
EXAMPLE 400



2-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-isoindole-1,3-dione.

The title compound was prepared according to the procedure for EXAMPLE 378, steps A using cyclopropyl-methylamine and EXAMPLE 379, step A using 2-(3-bromo-propyl)-isoindole-1,3-dione. MS (ESI): mass calculated for $C_{30}H_{29}N_3O_3S$, 511.19; m/z found, 512.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.84-7.77 (m, 2H), 7.72-7.63 (m, 3H), 7.60 (d, *J* = 7.8, 1H), 7.34 (t, *J* = 8.1, 1H), 7.27-7.18 (m, 5H), 3.71 (t, *J* = 7.1, 2H), 2.82-2.70 (m, 4H), 2.65 (t, *J* = 7.6, 2H), 2.39 (d, *J* = 6.6, 2H), 1.88-1.79 (m, 2H), 0.87-0.76 (m, 1H), 0.50-0.42 (m, 2H), 0.12-0.06 (m, 2H).

EXAMPLE 401

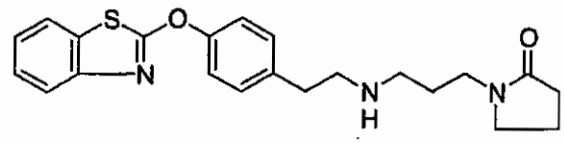


4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-butyric acid.

The title compound was prepared from EXAMPLE 399 followed by the procedure for EXAMPLE 379, step B. MS (ESI): mass calculated for $C_{23}H_{26}N_2O_3S$, 410.17; m/z found, 411.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.42 (d, *J* = 7.8, 1H), 7.31 (d, *J* = 7.8, 1H), 7.16-7.10 (m, 2H), 7.07 (t, *J* = 7.8,

1H), 7.04-7.00 (m, 2H), 6.96 (t, *J* = 7.8, 1H), 3.23-3.11 (m, 2H), 3.07 (t, *J* = 7.8, 2H), 2.91-2.77 (m, 4H), 2.19 (t, *J* = 7.1, 2H), 1.78-1.68 (m, 2H), 0.91-0.82 (m, 1H), 0.49-0.41 (m, 2H), 0.20-0.13 (m, 2H).

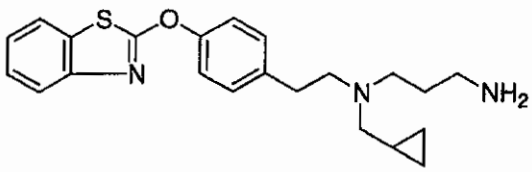
EXAMPLE 402



1-(3-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-propyl)-pyrrolidin-2-one.

The title compound was prepared according to the procedure for EXAMPLE 378, step A using 1-(3-aminio-propyl)-pyrrolidin-2-one. MS (ESI): mass calculated for $C_{22}H_{25}N_3O_2S$, 395.17; m/z found, 396.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.67 (d, *J* = 8.1, 1H), 7.60 (d, *J* = 8.1, 1H), 7.32 (t, *J* = 7.8, 1H), 7.28-7.15 (m, 5H), 5.61 (br s, 1H), 3.34-3.25 (m, 4H), 2.94-2.81 (m, 4H), 2.65 (t, *J* = 7.3, 2H), 2.32 (t, *J* = 7.8, 2H), 1.94 (t, *J* = 7.3, 2H), 1.79-1.69 (m, 2H).

EXAMPLE 403

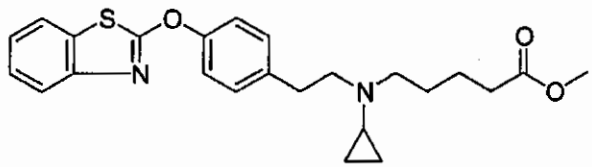


N-1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-N1-cyclopropylmethyl-propane-1,3-diamine.

To a solution of 2-[3-({2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-isoindole-1,3-dione (Example 400, 3.0 g, 5.86 mmol) in EtOH (12 mL) was added hydrazine (220 µL, 7.03 mmol). The reaction mixture was stirred at room temperature for 24 h. The mixture was dissolved in CH_2Cl_2 (200 mL), washed with saturated $NaHCO_3$ (2 x 20 ml), H_2O (1 x 20 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as a off-white solid. The crude product was purified on SiO_2

(330 g; 0-10% 2 M NH_3 in CH_3OH/CH_2Cl_2) to give a clear oil (2.13 g, 96% yield). MS (ESI): mass calculated for $C_{22}H_{27}N_3OS$, 381.2; m/z found, 382.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.68 (d, J = 8.1, 1H), 7.58 (d, J = 8.1, 1H), 7.31 (t, J = 8.1, 1H), 7.24-7.16 (m, 5H), 2.79-2.71 (m, 4H), 2.67 (t, J = 6.8, 2H), 2.59 (t, J = 6.8, 2H), 2.37 (d, J = 6.6, 2H), 2.07 (s, 2H), 1.62-1.52 (m, 2H), 0.87-0.77 (m, 1H), 0.50-0.44 (m, 2H), 0.12-0.06 (m, 2H).

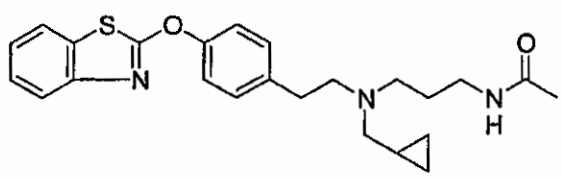
EXAMPLE 404



5-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-pentanoic acid methyl ester.

The title compound was prepared according to the procedure for EXAMPLE 379, step A using 5-bromo-pentanoic acid methyl ester. MS (ESI): mass calculated for $C_{24}H_{28}N_2O_3S$, 424.18; m/z found, 425.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.63 (d, J = 8.1, 1H), 7.36 (t, J = 8.1, 1H), 7.27-7.20 (m, 5H), 3.65 (s, 3H), 2.85-2.80 (m, 4H), 2.66 (t, J = 7.6, 2H), 2.33 (t, J = 7.6, 2H), 1.81-1.75 (m, 1H), 1.67-1.50 (m, 4H), 0.52-0.40 (m, 2H), 0.43-0.37 (m, 2H).

EXAMPLE 405

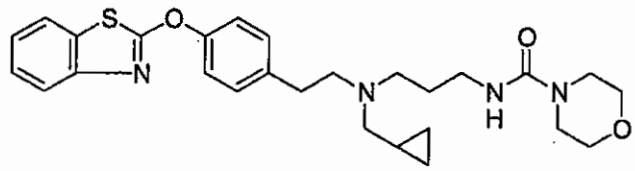


N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-acetamide.

To a solution of N-1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-N1-cyclopropylmethyl-propane-1,3-diamine (Example 403, 180 mg, 0.47 mmol) in

CH_2Cl_2 (10 mL) was added triethylamine (131 µL, 0.94 mmol), followed by acetic anhydride (76 µL, 0.71 mmol). The reaction mixture was stirred at room temperature for 24 h. The mixture was dissolved in CH_2Cl_2 (100 mL), washed with sat. $NaHCO_3$ (2 x 15 ml), H_2O (1 x 15 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as a off-white solid. The crude product was purified on SiO_2 (12 g; 0-10% CH_3OH/CH_2Cl_2) to give a white solid (154 mg, 77% yield). MS (ESI): mass calculated for $C_{24}H_{29}N_3OS$, 423.2; m/z found, 424.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 9.69 (br s, 1H), 7.67 (d, *J* = 8.1, 1H), 7.62 (d, *J* = 8.1, 1H), 7.33 (t, *J* = 8.1, 1H), 7.27-7.17 (m, 5H), 3.27 (dd, *J* = 6.6, 5.6, 2H), 2.96-2.89 (m, 2H), 2.87-2.81 (m, 2H), 2.78 (t, *J* = 6.8, 2H), 2.53 (d, *J* = 6.8, 2H), 1.88 (s, 3H), 1.76-1.67 (m, 2H), 0.94-0.83 (m, 1H), 0.60-0.53 (m, 2H), 0.21-0.15 (m, 2H).

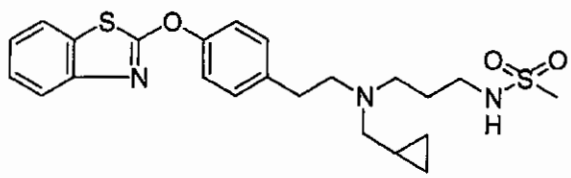
EXAMPLE 406



Morpholine-4-carboxylic acid [3-({2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-amide.

The title compound was prepared according to the procedure for EXAMPLE 405, using morpholine-4-carbonyl chloride. MS (ESI): mass calculated for $C_{28}H_{34}N_4O_3S$, 494.24; m/z found, 495.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.69 (t, *J* = 8.5, 2H), 7.41-7.23 (m, 6H), 6.85 (br s, 1H), 3.68-3.60 (m, 4H), 3.51-3.40 (m, 6H), 3.39-3.27 (m, 4H), 3.26-3.17 (m, 2H), 3.09-3.01 (m, 2H), 2.19-2.06 (m, 2H), 1.25-1.14 (m, 1H), 0.85-0.76 (m, 2H), 0.53-0.45 (m, 2H).

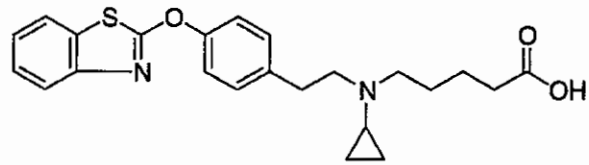
EXAMPLE 407



N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-methanesulfonamide.

The title compound was prepared according to the procedure for EXAMPLE 405, using methanesulfonyl chloride. MS (ESI): mass calculated for $C_{23}H_{29}N_3O_3S_2$, 459.17; m/z found, 460.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.67 (t, J = 8.6, 2H), 7.39-7.17 (m, 6H), 7.06 (br s, 1H), 3.43-3.09 (m, 8H), 3.07-2.98 (m, 2H), 2.96 (s, 3H), 2.20-2.07 (m, 2H), 1.23-1.11(m, 1H), 0.79-0.67 (m, 2H), 0.49-0.41 (m, 2H).

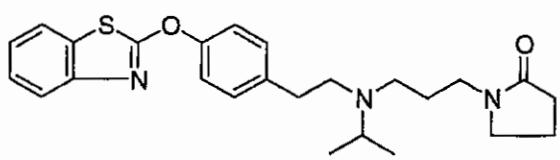
EXAMPLE 408



5-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-pentanoic acid.

The title compound was prepared from EXAMPLE 379 and the procedure for EXAMPLE 404, step B. MS (ESI): mass calculated for $C_{23}H_{26}N_2O_3S$, 410.17; m/z found, 411.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 12.39 (br s, 1H), 7.71 (d, J = 7.8, 1H), 7.62 (d, J = 7.8, 1H), 7.35 (t, J = 7.8, 1H), 7.31-7.20 (m, 5H), 3.04-2.90 (m, 4H), 2.82 (t, J = 7.8, 2H), 2.30 (t, J = 6.8, 2H), 1.98-1.91 (m, 1H), 1.72-1.54 (m, 4H), 0.83-0.76 (m, 2H), 0.63-0.55 (m, 2H).

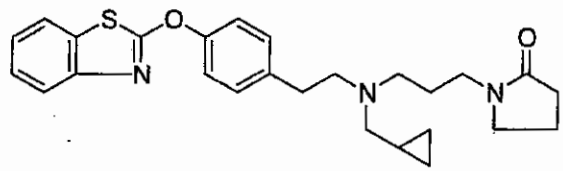
EXAMPLE 409



1-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-isopropyl-amino)-propyl]-pyrrolidin-2-one.

A mixture of 1-(3-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethylamino}-propyl)-pyrrolidin-2-one (Example 402, 500 mg, 1.26 mmol), acetone (185 µL, 2.52 mmol) in CH_2Cl_2 (25 mL) was stirred at room temperature for 1 h. To the resulting mixture was added $NaBH(OAc)_3$ (536 mg, 2.52 mmol). The mixture was stirred at room temperature for 16 h, filtered through diatomaceous earth, washed with CH_2Cl_2 (100 mL) and concentrated under reduced pressure to yield the crude product as a yellow oil. The crude product was purified on SiO_2 (40 g; 0-10% CH_3OH/CH_2Cl_2). The desired fractions were combined and concentrated under reduced pressure to give a clear oil which crystallized on standing (290 mg, 53% yield). MS (ESI): mass calculated for $C_{25}H_{31}N_3O_2S$, 437.21; m/z found, 438.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.3, 1H), 7.66 (d, J = 8.3, 1H), 7.38 (t, J = 8.3, 1H), 7.28-7.23 (m, 5H), 3.35 (t, J = 6.8, 2H), 3.27 (t, J = 7.3, 2H), 3.05-2.95 (m, 1H), 2.78-2.70 (m, 2H), 2.69-2.61 (m, 2H), 2.47 (t, J = 7.3, 2H), 2.37 (t, J = 8.1, 2H), 2.04-1.94 (m, 2H), 1.69-1.58 (m, 2H), 0.99 (d, J = 6.8, 6H).

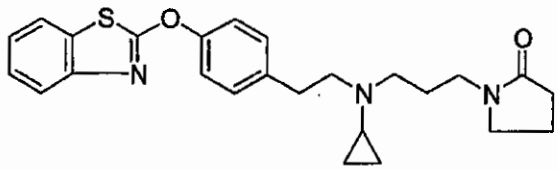
EXAMPLE 410



1-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-pyrrolidin-2-one.

The title compound was prepared according to the procedure for EXAMPLE 409, using cyclopropanecarbaldehyde. MS (ESI): mass calculated for $C_{26}H_{31}N_3O_2S$, 449.21; m/z found, 450.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.70 (d, J = 7.8, 1H), 7.64 (d, J = 8.1, 1H), 7.36 (t, J = 7.8, 1H), 7.32-7.21 (m, 5H), 3.38 (t, J = 7.1, 2H), 3.31 (t, J = 7.1, 2H), 3.09-3.02 (m, 2H), 2.95-2.83 (m, 4H), 2.72 (d, J = 7.1, 2H), 2.37 (t, J = 7.8, 2H), 2.05-1.95 (m, 2H), 1.92-1.82 (m, 2H), 1.02-0.91 (m, 1H), 0.66-0.59 (m, 2H), 0.29-0.23 (m, 2H).

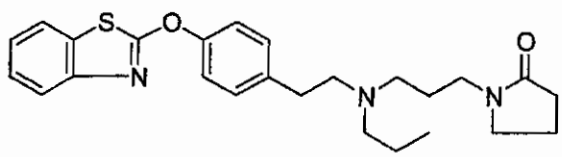
EXAMPLE 411



1-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-pyrrolidin-2-one.

To a solution of 1-(3-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethylamino}-propyl)-pyrrolidin-2-one (Example 402, 500 mg, 1.26 mmol) in EtOH (20 mL) was added acetic acid (716 µL, 1.26 mmol), molecular sieves (500 mg, 3A), (1-ethoxy-cyclopropoxy)-trimethyl-silane (1.51 mL, 7.58 mmol) and sodium cyanoboronhydride (357 mg, 5.69 mmol). The reaction mixture was heated at reflux for 16 h, cooled and filtered through diatomaceous earth, washed with CH_2Cl_2 (100 mL) and concentrated under reduced pressure to yield the crude product as a clear oil. The crude product was purified on SiO_2 (40 g; 0-10% CH_3OH/CH_2Cl_2). The desired fractions were combined and concentrated under reduced pressure to give a white solid (434 mg, 66% yield).
MS (ESI): mass calculated for $C_{25}H_{29}N_3O_2S$, 435.2; m/z found, 436.4 $[M+H]^+$.
^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 7.8, 1H), 7.64 (d, J = 7.8, 1H), 7.36 (t, J = 7.8, 1H), 7.28-7.19 (m, 5H), 3.36 (t, J = 7.1, 2H), 3.28 (t, J = 7.1, 2H), 2.87-2.80 (m, 4H), 2.67 (t, J = 7.3, 2H), 2.37 (t, J = 7.8, 2H), 2.03-1.94 (m, 2H), 1.82-1.70 (m, 3H), 0.53-0.47 (m, 2H), 0.43-0.38 (m, 2H).

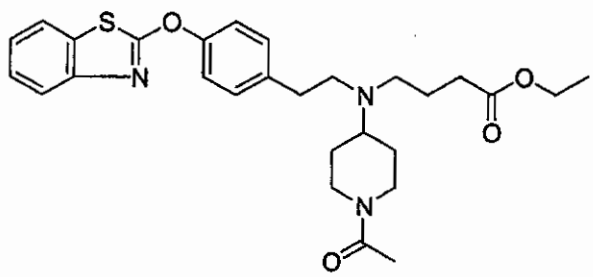
EXAMPLE 412



1-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-propyl-amino)-propyl]-pyrrolidin-2-one.

The title compound was prepared according to the procedure for EXAMPLE 409, using propionaldehyde. MS (ESI): mass calculated for $C_{25}H_{31}N_3O_2S$, 437.21; m/z found, 438.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.66 (d, J = 8.1, 1H), 7.38 (t, J = 8.1, 1H), 7.29-7.24 (m, 5H), 3.39 (t, J = 7.1, 2H), 3.30 (t, J = 7.1; 2H), 2.86-2.80 (m, 4H), 2.64 (t, J = 7.6, 2H), 2.58 (t, J = 7.6, 2H), 2.42-2.35 (m, 2H), 2.07-1.97 (m, 2H), 1.80-1.71 (m, 2H), 1.59-1.47 (m, 2H), 0.92 (d, J = 7.3, 3H).

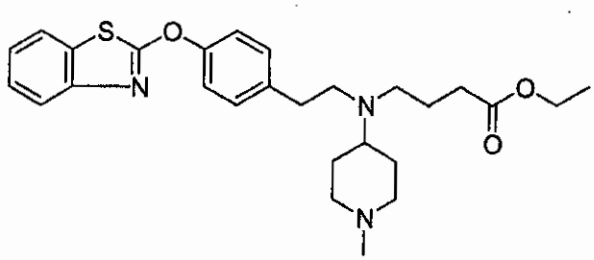
EXAMPLE 413



4-((1-Acetyl-piperidin-4-yl)-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-amino)-butyric acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 409, using 1-acetyl-piperidin-4-one. MS (ESI): mass calculated for $C_{28}H_{35}N_3O_4S$, 509.23; m/z found, 510.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.65 (d, J = 8.1, 1H), 7.38 (t, J = 8.1, 1H), 7.29-7.23 (m, 5H), 4.69 (d, J = 13.1, 1H), 4.13 (dd, J = 7.8, 6.8, 2H), 3.85 (d, J = 13.4, 1H), 3.09-2.98 (m, 2H), 2.79-2.74 (m, 4H), 2.60 (t, J = 6.8, 2H), 2.52-2.44 (m, 3H), 2.04 (s, 3H), 1.85-1.73 (m, 4H), 1.48-1.35 (m, 2H), 1.26 (t, J = 7.1, 3H).

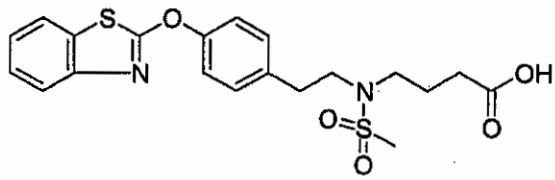
EXAMPLE 414



4-((1-Acetyl-piperidin-4-yl)-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-amino)-butyric acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 409, using 1-methyl-piperidin-4-one. MS (ESI): mass calculated for $C_{27}H_{35}N_3O_3S$, 481.2; m/z found, 482.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.65 (d, J = 8.1, 1H), 7.37 (t, J = 8.1, 1H), 7.28-7.19 (m, 5H), 4.12 (dd, J = 7.3, 7.1, 2H), 3.11 (d, J = 12.1, 2H), 2.75-2.69 (m, 4H), 2.58-2.50 (m, 3H), 2.38 (s, 3H), 2.29 (t, J = 7.1, 2H), 2.24-2.15 (m, 2H), 2.03-1.97 (m, 2H), 1.73 (t, J = 6.3, 4H), 1.25 (t, J = 7.1, 3H).

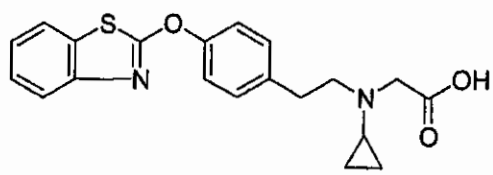
EXAMPLE 415



4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-methanesulfonyl-amino)-butyric acid.

The title compound was prepared from EXAMPLE 398 following the procedure for EXAMPLE 407 and EXAMPLE 379, step B. MS (ESI): mass calculated for $C_{20}H_{22}N_2O_5S_2$, 434.1; m/z found, 435.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.66 (d, J = 8.1, 1H), 7.38 (t, J = 8.1, 1H), 7.33-7.24 (m, 5H), 3.48 (t, J = 7.6, 2H), 3.20 (t, J = 7.6, 2H), 2.96 (t, J = 7.3, 2H), 2.77 (s, 3H), 2.37 (t, J = 6.6, 2H), 1.91-1.81 (m, 2H).

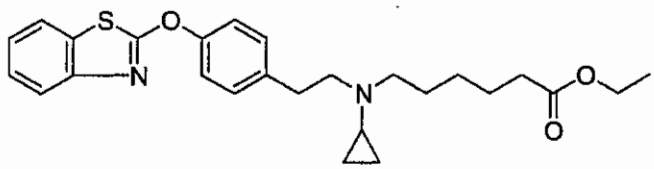
EXAMPLE 416



({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-acetic acid.

The title compound was prepared according to the procedure for EXAMPLE 379, step A and B using bromo-acetic acid methyl ester. MS (ESI): mass calculated for $C_{20}H_{20}N_2O_3S$, 368.12; m/z found, 369.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.70 (d, J = 8.1, 1H), 7.64 (d, J = 8.1, 1H), 7.37 (t, J = 8.1, 1H), 7.31-7.22 (m, 5H), 3.64 (s, 2H), 3.26 (dd, J = 7.6, 3.3, 2H), 2.98 (dd, J = 7.6, 3.3, 2H), 2.50-2.43 (m, 1H), 0.84-0.79 (m, 2H), 0.71-0.65 (m, 2H).

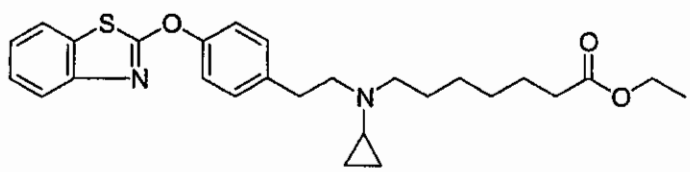
EXAMPLE 417



6-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-hexanoic acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 379, step A using 6-bromo-hexanoic acid ethyl ester. MS (ESI): mass calculated for $C_{26}H_{32}N_2O_3S$, 452.21; m/z found, 453.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.64 (d, J = 8.1, 1H), 7.36 (t, J = 8.1, 1H), 7.28-7.20 (m, 5H), 4.12 (dd, J = 7.3, 7.1, 2H), 2.87-2.81 (m, 4H), 2.65 (t, J = 7.8, 2H), 2.30 (t, J = 7.6, 2H), 1.81-1.74 (m, 1H), 1.69-1.60 (m, 2H), 1.59-1.50 (m, 2H), 1.37-1.27 (m, 2H), 1.24 (t, J = 7.1, 3H), 0.52-0.46 (m, 2H), 0.43-0.37 (m, 2H).

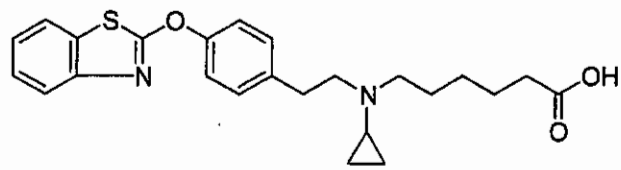
EXAMPLE 418



7-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-heptanoic acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 379, step A using 7-bromo-heptanoic acid ethyl ester. MS (ESI): mass calculated for $C_{27}H_{34}N_2O_3S$, 466.23; m/z found, 467.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, J = 8.1, 1H), 7.60 (d, J = 8.1, 1H), 7.34 (t, J = 8.1, 1H), 7.27-7.18 (m, 5H), 4.10 (dd, J = 7.1, 7.1, 2H), 2.86-2.79 (m, 4H), 2.63 (t, J = 7.6, 2H), 2.28 (t, J = 7.6, 2H), 1.80-1.74 (m, 1H), 1.67-1.58 (m, 2H), 1.57-1.47 (m, 2H), 1.38-1.25 (m, 4H), 1.23 (t, J = 7.1, 3H), 0.50-0.44 (m, 2H), 0.43-0.37 (m, 2H).

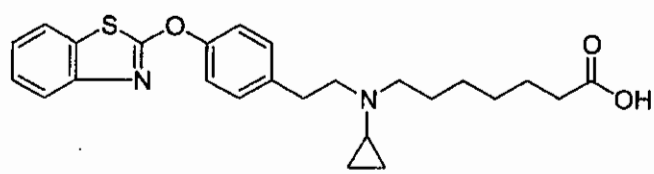
EXAMPLE 419



6-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-hexanoic acid.

The title compound was prepared from EXAMPLE 417 following the procedure for EXAMPLE 379, step B. MS (ESI): mass calculated for $C_{24}H_{28}N_2O_3S$, 424.18; m/z found, 425.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 11.17 (br s, 1H), 7.69 (d, J = 8.1, 1H), 7.65 (d, J = 8.1, 1H), 7.39-7.21 (m, 6H), 3.35-3.28 (m, 2H), 3.24-3.10 (m, 4H), 2.53-2.45 (m, 1H), 2.31 (t, J = 7.1, 2H), 1.92-1.81 (m, 2H), 1.70-1.61 (m, 2H), 1.44-1.34 (m, 4H), 0.91-0.83 (m, 2H).

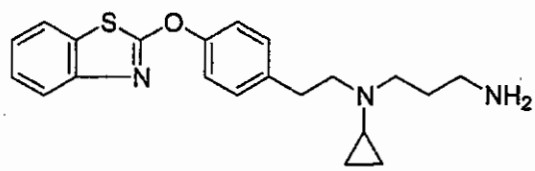
EXAMPLE 420



7-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-heptanoic acid.

The title compound was prepared from EXAMPLE 418 following the procedure for EXAMPLE 379, step B. MS (ESI): mass calculated for $C_{25}H_{30}N_2O_3S$, 438.2; m/z found, 439.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 12.57 (br s, 1H), 7.72 (d, J = 8.1, 1H), 7.64 (d, J = 8.1, 1H), 7.36 (t, J = 8.1, 1H), 7.31-7.20 (m, 5H), 3.02-2.90 (m, 4H), 2.78 (t, J = 7.8, 2H), 2.26 (t, J = 7.6, 2H), 1.97-1.90 (m, 1H), 1.67-1.56 (m, 4H), 1.41-1.26 (m, 4H), 0.80-0.73 (m, 2H), 0.62-0.55 (m, 2H).

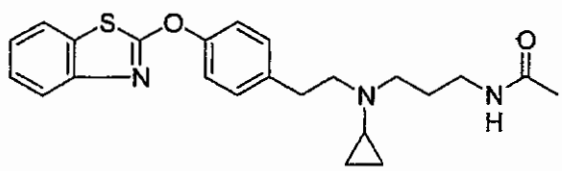
EXAMPLE 421



N-1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-N1-cyclopropyl-propane-1,3-diamine.

The title compound was prepared according to the procedures for EXAMPLE 378, step A using cyclopropylamine, EXAMPLE 379, step A using 2-(3-bromo-propyl)isoindole-1,3-dione and EXAMPLE 403. MS (ESI): mass calculated for $C_{21}H_{25}N_3OS$, 367.17; m/z found, 468.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 7.6, 1H), 7.65 (d, J = 7.8, 1H), 7.38 (t, J = 7.6, 1H), 7.29-7.23 (m, 5H), 2.89-2.82 (m, 4H), 2.71 (t, J = 7.1, 4H), 1.83-1.77 (m, 1H), 1.72-1.64 (m, 2H), 1.55 (br s, 2H), 0.54-0.48 (m, 2H), 0.44-0.39 (m, 2H).

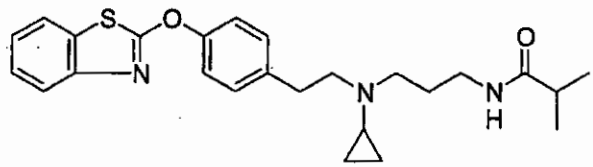
EXAMPLE 422



N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-acetamide.

The title compound was prepared from EXAMPLE 421 following the procedure for EXAMPLE 405. MS (ESI): mass calculated for $C_{23}H_{27}N_3O_2S$, 409.18; m/z found, 410.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, J = 8.1, 1H), 7.64 (d, J = 8.1, 1H), 7.36 (t, J = 8.0118, 1H), 7.28-7.21 (m, 5H), 6.77 (br s, 1H), 3.26 (dd, J = 6.1, 5.8, 2H), 2.89-2.83 (m, 4H), 2.75 (t, J = 6.8, 2H), 1.89 (s, 3H), 1.84-1.78 (m, 1H), 1.75-1.67 (m, 2H), 0.57-0.51 (m, 2H), 0.47-0.42 (m, 2H).

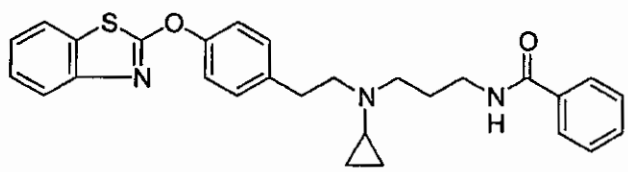
EXAMPLE 423



N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-isobutyramide.

The title compound was prepared according to the procedure for EXAMPLE 421, using isobutyryl chloride. MS (ESI): mass calculated for $C_{25}H_{31}N_3O_2S$, 437.21; m/z found, 438.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.66 (d, J = 8.1, 1H), 7.37 (t, J = 8.1, 1H), 7.30-7.23 (m, 5H), 6.54 (br s, 1H), 3.30 (dd, J = 6.1, 5.8, 2H), 2.90-2.83 (m, 4H), 2.77 (t, J = 6.3, 2H), 2.31-2.19 (m, 1H), 1.85-1.78 (m, 1H), 1.75-1.67 (m, 2H), 1.12 (d, J = 6.8, 6H), 0.58-0.52 (m, 2H), 0.45-0.40 (m, 2H).

EXAMPLE 424

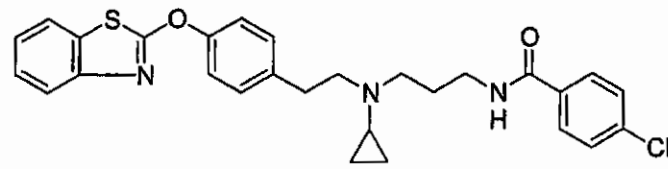


N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-benzamide.

The title compound was prepared according to the procedure for EXAMPLE 422, using benzoyl chloride. MS (ESI): mass calculated for $C_{28}H_{29}N_3O_2S$,

471.20; m/z found, 472.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.78-7.67 (m, 4H), 7.61 (d, *J* = 7.8, 1H), 7.44-7.39 (m, 1H), 7.38-7.31 (m, 3H), 7.25-7.13 (m, 5H), 3.50 (dd, *J* = 6.1, 5.6, 2H), 2.89-2.77 (m, 6H), 1.85-1.75 (m, 3H), 0.56-0.49 (m, 2H), 0.45-0.38 (m, 2H).

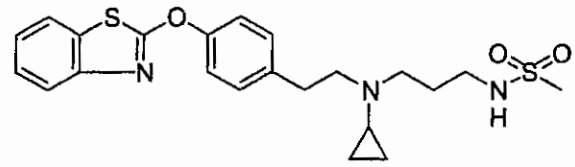
EXAMPLE 425



N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-4-chloro-benzamide.

The title compound was prepared according to the procedure for EXAMPLE 422, using 4-chloro-benzoyl chloride. MS (ESI): mass calculated for $C_{28}H_{28}ClN_3O_2S$, 505.16; m/z found, 506.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.80(t, *J* = 5.0, 1H), 7.68 (d, *J* = 7.6, 1H), 7.65-7.59 (m, 3H), 7.37-7.29 (m, 3H), 7.25-7.15 (m, 5H), 3.47 (dd, *J* = 6.1, 5.31, 2H), 2.89-2.77 (m, 6H), 1.84-1.75 (m, 3H), 0.57-0.51 (m, 2H), 0.42-0.36 (m, 2H).

EXAMPLE 426

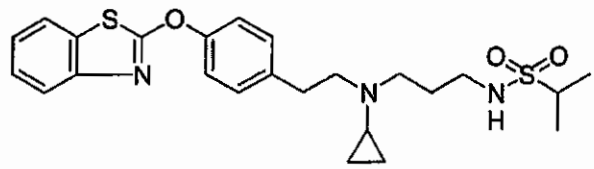


N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-methanesulfonamide.

The title compound was prepared according to the procedure for EXAMPLE 422, using methanesulfonyl chloride. MS (ESI): mass calculated for $C_{22}H_{27}N_3O_3S_2$, 445.15; m/z found, 446.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, *J* = 7.8, 1H), 7.64 (d, *J* = 7.8, 1H), 7.36 (t, *J* = 7.8, 1H), 7.28-7.21 (m,

5H), 6.03 (br s, 1H), 3.15 (t, *J* = 6.1, 2H), 2.88 (s, 3H), 2.87-2.82 (m, 4H), 2.78 (t, *J* = 6.1, 2H), 1.82-1.71 (m, 3H), 0.58-0.52 (m, 2H), 0.49-0.43 (m, 2H).

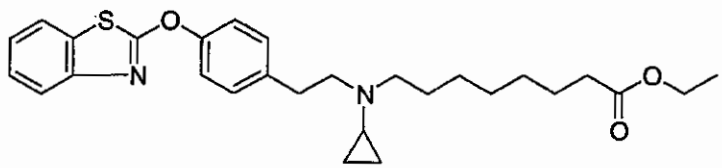
EXAMPLE 427



Propane-2-sulfonic acid [3-({2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-amide trifluoromethansulfonic acid salt.

The title compound was prepared according to the procedure for EXAMPLE 422, using propane-2-sulfonyl chloride. MS (ESI): mass calculated for $C_{24}H_{31}N_3O_3S_2$, 473.18; m/z found, 474.4 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.65 (d, *J* = 7.8, 1H), 7.53 (d, *J* = 8.1, 1H), 7.39-7.16 (m, 6H), 3.44 (t, *J* = 8.3, 2H), 3.37 (t, *J* = 8.3, 2H), 3.24-3.19 (m, 2H), 3.16-3.06 (m, 4H), 2.87-2.78 (m, 1H), 2.07-1.94 (m, 2H), 1.67 (d, *J* = 4.04, 3H), 1.23 (d, *J* = 6.1, 3H), 1.07-1.00 (m, 2H), 0.98-0.91 (m, 2H).

EXAMPLE 428

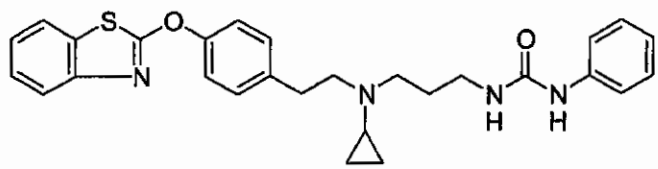


8-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-octanoic acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 379, step A, using 8-bromo-octanoic acid ethyl ester. MS (ESI): mass calculated for $C_{28}H_{36}N_2O_3S$, 480.24; m/z found, 481.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, *J* = 8.1, 1H), 7.63 (d, *J* = 8.1, 1H), 7.36 (t, *J* = 8.1, 1H), 7.27-7.20 (m, 5H), 4.11 (dd, *J* = 7.3, 7.1, 2H), 2.87-2.81 (m, 4H), 2.64 (t, *J* = 7.3, 2H), 2.28 (t, *J* = 7.1, 2H), 1.82-1.75 (m, 1H), 1.66-1.58 (m, 2H), 1.56-1.47

(m, 2H), 1.36-1.27 (m, 6H), 1.24 (t, J = 7.1, 3H), 0.51-0.45 (m, 2H), 0.43-0.38 (m, 2H).

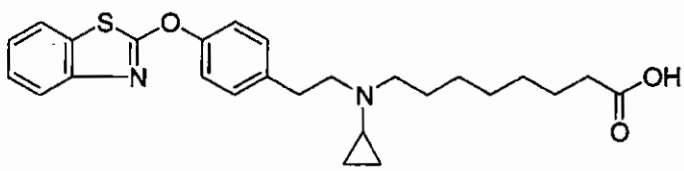
EXAMPLE 429



1-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-3-phenyl-urea.

The title compound was prepared according to the procedure for EXAMPLE 422, using phenyl isocyanate. MS (ESI): mass calculated for $C_{28}H_{30}N_4O_2S$, 486.21; m/z found, 487.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.61 (d, J = 8.1, 1H), 7.57 (d, J = 8.1, 1H), 7.28 (t, J = 8.1, 1H), 7.20-7.09 (m, 10H), 6.89 (t, J = 7.3, 1H), 5.64 (br s, 1H), 3.16-3.09 (m, 2H), 2.70-2.64 (m, 4H), 2.57 (t, J = 7.1, 2H), 1.67-1.60 (m, 1H), 1.60-1.52 (m, 2H), 0.39-0.33 (m, 2H), 0.25-0.20 (m, 2H).

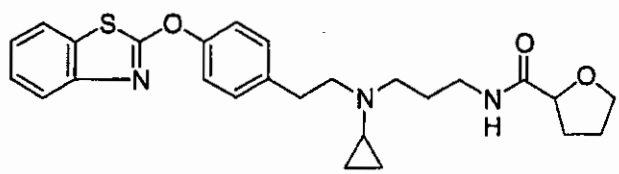
EXAMPLE 430



8-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-octanoic acid.

The title compound was prepared from EXAMPLE 428 following the procedure for EXAMPLE 379, step B. MS (ESI): mass calculated for $C_{26}H_{32}N_2O_3S$, 452.21; m/z found, 453.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 12.76 (br s, 1H), 7.72 (d, J = 7.6, 1H), 7.63 (d, J = 7.8, 1H), 7.36 (t, J = 7.6, 1H), 7.30-7.21 (m, 5H), 3.01-2.88 (m, 4H), 2.77 (t, J = 8.1, 2H), 2.27 (t, J = 7.8, 2H), 1.96-1.88 (m, 1H), 1.66-1.54 (m, 4H), 1.38-1.23 (m, 6H), 0.77-0.70 (m, 2H), 0.61-0.54 (m, 2H).

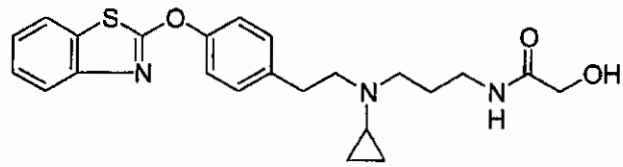
EXAMPLE 431



Tetrahydro-furan-2-carboxylic acid [3-({2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-amide.

To a solution of N-1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-N1-cyclopropyl-propane-1,3-diamine (Example 421, 330 mg, 0.9 mmol) in CH_2Cl_2 (18 mL) was added 2-tetrahydrofuroic acid (129 µL, 1.35 mmol) and Si-carbodiimide (1.05 mmol/g, 1.71 g, 1.8 mmol). The reaction mixture was stirred at room temperature overnight, filtered and concentrated. The crude product was purified on SiO_2 (40 g; 0-10% CH_3OH/CH_2Cl_2) to give a white solid (267 mg, 64% yield). MS (ESI): mass calculated for $C_{26}H_{31}N_3O_3S$, 465.21; m/z found, 466.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.64 (d, J = 8.1, 1H), 7.36 (t, J = 8.1, 1H), 7.32 (br s, 1H), 7.29-7.21 (m, 5H), 4.32 (dd, J = 6.1, 2.3, 1H), 3.93-3.81 (m, 2H), 3.41-3.31 (m, 1H), 3.30-3.21 (m, 1H), 2.90-2.80 (m, 4H), 2.75 (t, J = 6.8, 2H), 2.32-2.21 (m, 1H), 2.08-1.97 (m, 1H), 1.92-1.77 (m, 3H), 1.76-1.67 (m, 2H), 0.56-0.49 (m, 2H), 0.48-0.41 (m, 2H).

EXAMPLE 432

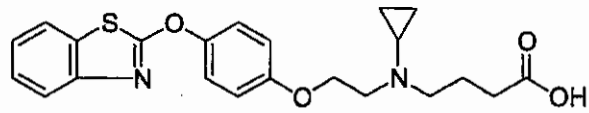


N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-2-hydroxy-acetamide.

The title compound was prepared according to the procedure for EXAMPLE 431 using gycolic acid. MS (ESI): mass calculated for $C_{23}H_{27}N_3O_3S$, 425.18; m/z found, 426.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73-7.63 (m, 2H), 7.44

(br s, 1H), 7.40-7.33 (m, 1H), 7.29-7.18 (m, 5H), 4.21 (s, 1H), 3.91 (s, 2H), 3.37-3.28 (m, 2H), 2.90-2.82 (m, 4H), 2.75 (t, *J* = 6.1, 2H), 1.85-1.78 (m, 1H), 1.77-1.70 (m, 2H), 0.58-0.38 (m, 4H).

EXAMPLE 433



4-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropyl-amino)-butyric acid.

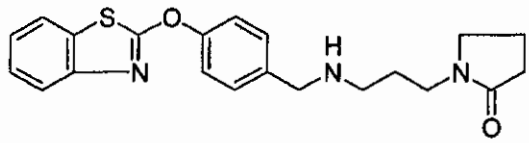
A. {2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropyl-amine. To a stirring solution of 2-[4-(2-bromo-ethoxy)-phenoxy]-benzothiazole (EXAMPLE 9, 1.1 g, 3.14 mmol) in CH_3CN (31 mL) was added cyclopropylamine (1.09 mL, 15.7 mmol) and *N,N*-diisopropylethylamine (1.1 mL, 6.28 mmol). The mixture was heated to 60 °C for 16 h, cooled to room temperature, and then dissolved in CH_2Cl_2 (100 mL). The solution was washed with H_2O (2 x 20 mL), dried, and concentrated. The resultant oil purified on SiO_2 (40 g, 0–15% CH_3OH/CH_2Cl_2) to give a clear oil (999 mg, 98% yield). MS (ESI): mass calculated for $C_{18}H_{18}N_2O_2S$, 326.11; m/z found, 327.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, *J* = 8.1, 1H), 7.59 (d, *J* = 8.1, 1H), 7.33 (t, *J* = 8.1, 1H), 7.27-7.17 (m, 3H), 6.95-6.89 (m, 2H), 4.03 (t, *J* = 5.3, 2H), 3.06 (t, *J* = 5.3, 2H), 2.20-2.14 (m, 1H), 2.02 (bs, 1H), 0.47-0.41 (m, 2H), 0.39-0.34 (m, 2H).

B. 4-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropyl-amino)-butyric acid ethyl ester. To a stirring solution of {2-[4-(benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropyl-amine (950 mg, 2.91 mmol) in CH_3CN (29 mL) was added 4-bromo-butyric acid ethyl ester (625 µL, 4.37 mmol) and *N,N*-diisopropylethylamine (1.0 mL, 5.82 mmol). The mixture was heated to 60 °C for 16 h, cooled to room temperature, and then dissolved in CH_2Cl_2 (100 mL). The solution was washed with H_2O (2 x 20 mL), dried, and concentrated. The resultant oil was purified on SiO_2 (40 g, 0–50% EtOAc/Hexanes) to give a colorless oil (1.0 g, 78% yield). MS (ESI): mass calculated for $C_{24}H_{28}N_2O_4S$, 440.18; m/z found, 441.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, *J* = 8.1, 1H), 7.61 (d, *J* = 8.1, 1H), 7.34 (t, *J* = 8.1, 1H), 7.28-7.18 (m, 3H), 6.95-6.90 (m,

2H), 4.14-4.04 (m, 4H), 3.00 (t, *J* = 6.3, 2H), 2.71 (t, *J* = 7.1, 2H), 2.31 (t, *J* = 7.1, 2H), 1.90-1.80 (m, 3H), 1.23 (t, *J* = 7.1, 3H), 0.51-0.44 (m, 2H), 0.43-0.38 (m, 2H).

C. 4-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropyl-amino)-butyric acid. To a solution of 4-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropyl-amino)-butyric acid ethyl ester (970 mg, 2.2 mmol) in 3:1 THF/CH_3OH (80 mL), was added lithium hydroxide (211 mg, 8.8 mmol) in water (20 mL). This solution was stirred at room temperature for 16 h and then adjusted the pH to 7 using 1 N aqueous HCl. Extracted the mixture with CH_2Cl_2 (2 x 100 mL). The combined organic phase was concentrated under reduced pressure. The resultant oil was purified on SiO_2 (40 g, 0–10% CH_3OH/CH_2Cl_2) to give a white solid (877 mg, 97% yield). MS (ESI): mass calculated for $C_{22}H_{24}N_2O_4S$, 412.15; m/z found, 413.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 11.44 (br s, 1H), 7.68 (d, *J* = 8.1, 1H), 7.62 (d, *J* = 8.1, 1H), 7.35 (t, *J* = 8.1, 1H), 7.27-7.20 (m, 3H), 7.01-6.95 (m, 2H), 4.44 (t, *J* = 5.0, 2H), 3.56 (t, *J* = 5.005, 2H), 3.32 (t, *J* = 8.1, 2H), 2.67-2.60 (m, 1H), 2.46 (t, *J* = 6.8, 2H), 2.18-2.09 (m, 2H), 1.32-1.25 (m, 2H), 0.88-0.81 (m, 2H).

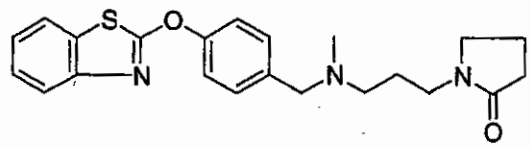
EXAMPLE 434



1-{3-[4-(Benzothiazol-2-yloxy)-benzylamino]-propyl}-pyrrolidin-2-one.

The title compound was prepared according to the procedure for EXAMPLE 251, step B using 1-(3-amino-propyl)-pyrrolidine-2-one. MS (ESI): mass calculated for $C_{21}H_{23}N_3O_2S$, 381.15; m/z found, 382.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, *J* = 8.1, 1H), 7.64 (d, *J* = 8.1, 1H), 7.45-7.41 (m, 2H), 7.36 (t, *J* = 8.1, 1H), 7.32-7.28 (m, 2H), 7.24 (t, *J* = 8.1, 1H), 3.81 (s, 2H), 3.38-3.27 (m, 5H), 3.63 (t, *J* = 6.8, 2H), 3.35 (t, *J* = 7.6, 2H), 2.02-1.93 (m, 2H), 1.82-1.73 (m, 2H).

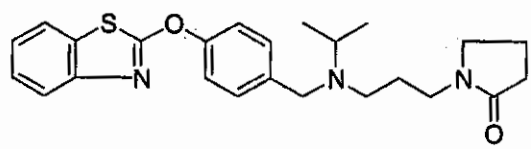
EXAMPLE 435



1-(3-{[4-(Benzothiazol-2-yloxy)-benzyl]-methyl-amino}-propyl)-pyrrolidin-2-one.

The title compound was prepared according to the procedure for EXAMPLE 409 using formaldehyde. MS (ESI): mass calculated for $C_{22}H_{25}N_3O_2S$, 395.17; m/z found, 396.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, J = 8.1, 1H), 7.64 (d, J = 8.1, 1H), 7.43-7.27 (m, 5H), 7.24 (t, J = 8.1, 1H), 3.54 (s, 2H), 3.32 (dd, J = 7.1, 7.1, 4H), 2.43 (t, J = 7.1, 2H), 2.34 (t, J = 7.1, 2H), 2.23 (s, 3H), 2.00-1.91 (m, 2H), 1.80-1.70 (m, 2H).

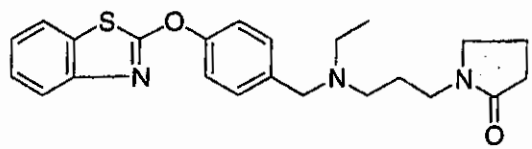
EXAMPLE 436



1-(3-{[4-(Benzothiazol-2-yloxy)-benzyl]-isopropyl-amino}-propyl)-pyrrolidin-2-one.

The title compound was prepared according to the procedure for EXAMPLE 409 using acetone. MS (ESI): mass calculated for $C_{24}H_{29}N_3O_2S$, 423.20; m/z found, 424.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.65 (d, J = 8.1, 1H), 7.45-7.40 (m, 2H), 7.37 (t, J = 7.8, 1H), 7.30-7.21 (m, 3H), 3.55 (s, 2H), 3.29-3.20 (m, 4H), 3.01-2.90 (m, 1H), 2.42 (t, J = 7.1, 2H), 2.32 (t, J = 7.8, 2H), 1.97-1.83 (m, 2H), 1.63-1.53 (m, 2H), 1.02 (d, J = 6.6, 6H).

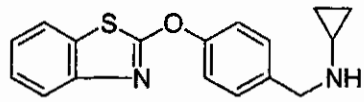
EXAMPLE 437



1-(3-{[4-(Benzothiazol-2-yloxy)-benzyl]-ethyl-amino}-propyl)-pyrrolidin-2-one.

The title compound was prepared according to the procedure for EXAMPLE 409 using acetaldehyde. MS (ESI): mass calculated for $C_{23}H_{27}N_3O_2S$, 409.18; m/z found, 410.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.66 (d, J = 8.1, 1H), 7.43-7.34 (m, 3H), 7.32-7.23 (m, 3H), 3.56 (s, 2H), 3.30 (dd, J = 7.1, 7.1, 4H), 2.53 (dd, J = 7.1, 7.1, 2H), 2.45 (t, J = 7.1, 2H), 2.34 (t, J = 7.8, 2H), 2.00-1.91 (m, 2H), 1.73-1.64 (m, 2H), 1.04 (t, J = 7.1, 3H).

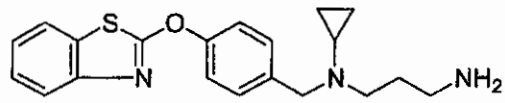
EXAMPLE 438



[4-(Benzothiazol-2-yloxy)-benzyl]-cyclopropyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 251, step B using cyclopropylamine. MS (ESI): mass calculated for $C_{17}H_{16}N_2OS$, 296.10; m/z found, 297.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.63 (d, J = 8.1, 1H), 7.40-7.33 (m, 3H), 7.32-7.27 (m, 2H), 7.24 (t, J = 8.1, 1H), 3.85 (s, 2H), 2.19-2.12 (m, 1H), 1.86 (br s, 1H), 0.48-0.35 (m, 4H).

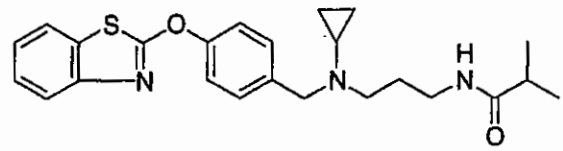
EXAMPLE 439



N-1-[4-(Benzothiazol-2-yloxy)-benzyl]-N1-cyclopropyl-propane-1,3-diamine.

The title compound was prepared according to the procedure for EXAMPLE 421 using compound from EXAMPLE 438. MS (ESI): mass calculated for $C_{20}H_{23}N_3OS$, 353.16; m/z found, 354.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.1, 1H), 7.65 (d, J = 8.1, 1H), 7.41-7.32 (m, 3H), 7.30-7.23 (m, 3H), 3.75 (s, 2H), 2.67 (t, J = 7.1, 2H), 2.58 (t, J = 7.1, 2H), 1.80-1.73 (m, 1H), 1.72-1.64 (m, 2H), 1.19 (br s, 2H), 0.52-0.46 (m, 2H), 0.42-0.36 (m, 2H).

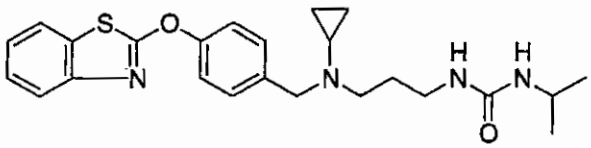
EXAMPLE 440



N-(3-{[4-(Benzothiazol-2-yloxy)-benzyl]-cyclopropyl-amino}-propyl)-isobutyramide.

The title compound was prepared according to the procedure for EXAMPLE 422 using isobutyryl chloride. MS (ESI): mass calculated for $C_{24}H_{29}N_3O_2S$, 423.20; m/z found, 424.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.65 (d, J = 8.1, 1H), 7.40-7.22 (m, 6H), 6.26 (br s, 1H), 3.73 (s, 2H), 3.23 (dd, J = 6.3, 5.8, 2H), 2.61 (t, J = 6.6, 2H), 2.29-2.18 (m, 1H), 1.79-1.68 (m, 3H), 1.09 (d, J = 6.8, 6H), 0.54-0.47 (m, 2H), 0.43-0.37 (m, 2H).

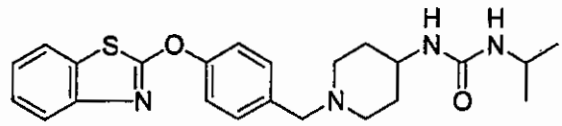
EXAMPLE 441



1-(3-{[4-(Benzothiazol-2-yloxy)-benzyl]-cyclopropyl-amino}-propyl)-3-isopropyl-urea.

The title compound was prepared according to the procedure for EXAMPLE 422 using isopropyl isocyanate. MS (ESI): mass calculated for $C_{24}H_{30}N_4O_2S$, 438.21; m/z found, 439.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.69 (d, J = 8.1, 1H), 7.63 (d, J = 8.1, 1H), 7.38-7.29 (m, 3H), 7.27-7.20 (m, 3H), 5.44 (br s, 1H), 5.15 (d, J = 7.8, 1H), 3.87-3.76 (m, 1H), 3.70 (s, 2H), 3.12 (dd, J = 6.3, 6.1, 2H), 2.56 (t, J = 7.1, 2H), 1.76-1.67 (m, 3H), 1.07 (d, J = 6.3, 6H), 0.49-0.42 (m, 2H), 0.40-0.34 (m, 2H).

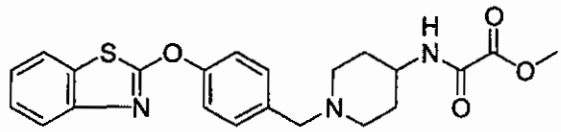
EXAMPLE 442



1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-3-isopropyl-urea.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using isopropyl isocyanate. MS (ESI): mass calculated for $C_{23}H_{28}N_4O_2S$, 424.19; m/z found, 425.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.1, 1H), 7.67 (d, J = 8.1, 1H), 7.41-7.35 (m, 3H), 7.32-7.24 (m, 3H), 4.77 (dd, J = 8.1, 7.8, 1H), 3.88-3.78 (m, 1H), 3.66-3.55 (m, 1H), 3.51 (s, 2H), 2.82 (d, J = 11.6, 2H), 2.13 (t, J = 10.9, 2H), 1.94 (d, J = 11.9, 2H), 1.69 (br s, 1H), 1.48-1.36 (m, 2H), 1.14 (d, J = 6.6, 6H).

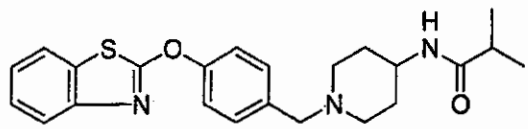
EXAMPLE 443



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-oxalamic acid methyl ester.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using chloro-oxo-acetic acid methyl ester. MS (ESI): mass calculated for $C_{22}H_{23}N_3O_4S$, 425.14; m/z found, 426.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.78 (d, J = 8.1, 1H), 7.64 (d, J = 8.1, 1H), 7.55-7.50 (m, 2H), 7.44-7.36 (m, 3H), 7.31 (t, J = 8.1, 1H), 3.84 (s, 2H), 3.81-3.72 (m, 1H), 3.41 (s, 3H), 3.11 (d, J = 10.9, 2H), 2.59-2.47 (m, 2H), 2.00-1.91 (m, 2H), 1.79-1.66 (m, 2H).

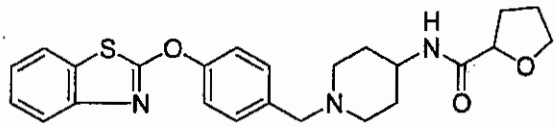
EXAMPLE 444



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-isobutyramide.

The title compound was prepared according to the procedure for EXAMPLE 253 using isobutyryl chloride. MS (ESI): mass calculated for $C_{23}H_{27}N_3O_2S$, 409.18; m/z found, 410.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.84 (d, J = 8.6, 2H), 7.69 (t, J = 7.8, 2H), 7.44 (d, J = 8.6, 2H), 7.41-7.33 (m, 2H), 7.27 (t, J = 8.1, 1H), 4.33 (s, 2H), 4.16-4.00 (m, 1H), 3.57-3.42 (m, 2H), 3.31-3.16 (m, 2H), 2.58-2.45 (m, 1H), 2.31-2.07 (m, 4H), 1.10 (d, J = 6.8, 6H).

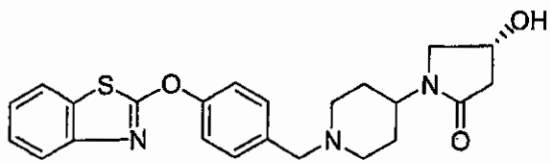
EXAMPLE 445



Tetrahydro-furan-2-carboxylic acid {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-amide.

The title compound was prepared from EXAMPLE 253, step D following the procedure for EXAMPLE 431. MS (ESI): mass calculated for $C_{24}H_{27}N_3O_3S$, 437.18; m/z found, 438.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 11.03 (br s, 1H), 7.73 (d, J = 7.8, 1H), 7.67 (d, J = 7.8, 1H), 7.46-7.42 (m, 2H), 7.41-7.32 (m, 3H), 7.27 (d, J = 7.8, 1H), 4.31 (t, J = 8.34, 1H), 3.98-3.89 (m, 1H), 3.84 (s, 2H), 3.19 (d, J = 11.6, 2H), 2.43 (t, J = 10.4, 2H), 2.34-2.21 (m, 2H), 2.08-1.69 (m, 8H).

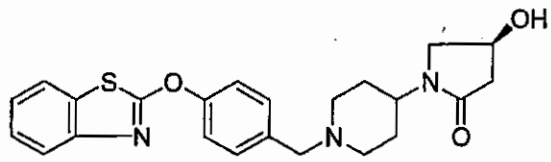
EXAMPLE 446



1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-4-hydroxy-pyrrolidin-2-one.

The title compound was prepared from EXAMPLE 253, step D following the procedure for EXAMPLE 254, step D. MS (ESI): mass calculated for $C_{23}H_{25}N_3O_3S$, 423.16; m/z found, 424.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.80 (d, J = 8.1, 1H), 7.68-7.62 (m, 3H), 7.53-7.49 (m, 2H), 7.42 (t, J = 8.1, 1H), 7.32 (t, J = 8.3, 1H), 4.44 (t, J = 6.3, 1H), 4.38 (s, 2H), 4.25-4.15 (m, 1H), 3.68-3.57 (m, 3H), 3.33-3.13 (m, 3H), 2.71 (dd, J = 10.9, 6.3, 1H), 2.28 (t, J = 17.7, 1H), 2.13-2.02 (m, 2H), 2.01-1.92 (m, 2H).

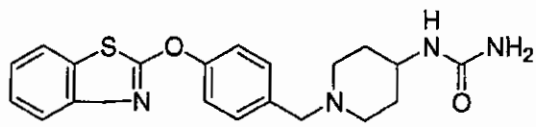
EXAMPLE 447



1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-4-hydroxy-pyrrolidin-2-one.

The title compound was prepared from EXAMPLE 253, step D following the procedure for EXAMPLE 254, step D. MS (ESI): mass calculated for $C_{23}H_{25}N_3O_3S$, 423.16; m/z found, 424.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.80 (d, J = 8.1, 1H), 7.68-7.62 (m, 3H), 7.53-7.49 (m, 2H), 7.42 (t, J = 8.1, 1H), 7.32 (t, J = 8.3, 1H), 4.44 (t, J = 6.3, 1H), 4.38 (s, 2H), 4.25-4.15 (m, 1H), 3.68-3.57 (m, 3H), 3.33-3.13 (m, 3H), 2.71 (dd, J = 10.9, 6.3, 1H), 2.28 (t, J = 17.7, 1H), 2.13-2.02 (m, 2H), 2.01-1.92 (m, 2H).

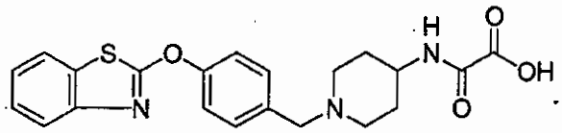
EXAMPLE 448



{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-urea.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using trimethylsilyl isocyanate. MS (ESI): mass calculated for $C_{20}H_{22}N_4O_2S$, 382.15; m/z found, 383.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, J = 7.8, 1H), 7.63 (d, J = 7.8, 1H), 7.40-7.33 (m, 3H), 7.30-7.21 (m, 3H), 5.82 (d, J = 7.8, 1H), 5.10 (d, J = 4.6, 1H), 3.84 (s, 1H), 3.56 (br s, 1H), 3.49 (s, 2H), 2.81 (d, J = 11.6, 2H), 2.12 (t, J = 11.1, 2H), 1.90 (d, J = 11.9, 2H), 1.51-1.39 (m, 2H).

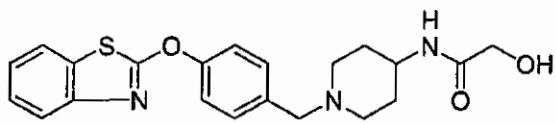
EXAMPLE 449



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-oxalamic acid.

The title compound was prepared from EXAMPLE 443 following the procedure for EXAMPLE 433, step C. MS (ESI): mass calculated for $C_{21}H_{21}N_3O_4S$, 411.13; m/z found, 412.3 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD): 7.78 (d, J = 8.1, 1H), 7.64 (d, J = 8.1, 1H), 7.55-7.50 (m, 2H), 7.44-7.36 (m, 3H), 7.31 (t, J = 8.1, 1H), 3.84 (s, 2H), 3.81-3.72 (m, 1H), 3.11 (d, J = 10.9, 2H), 2.59-2.47 (m, 2H), 2.00-1.91 (m, 2H), 1.79-1.66 (m, 2H).

EXAMPLE 450

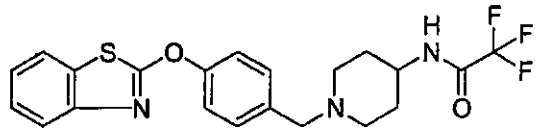


N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-2-hydroxy-acetamide.

The title compound was prepared according to the procedure for EXAMPLE 431 using glycolic acid. MS (ESI): mass calculated for $C_{21}H_{23}N_3O_3S$, 397.15; m/z found, 398.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, J = 7.8, 1H), 7.65 (d, J = 8.1, 1H), 7.40-7.35 (m, 3H), 7.31-7.23 (m, 3H), 6.83 (d, J = 8.1,

1H), 5.33, (br s, 1H), 3.99 (s, 2H), 3.87-3.75 (m, 1H), 3.50 (s, 2H), 2.85 (d, *J* = 11.4, 2H), 2.14 (t, *J* = 10.9, 2H), 1.92 (d, *J* = 12.6, 2H), 1.56-1.43 (m, 2H).

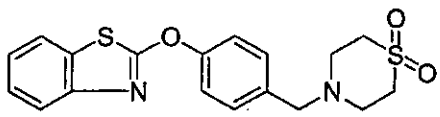
EXAMPLE 451



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-2,2,2-trifluoro-acetamide.

The title compound was prepared according to the procedure for EXAMPLE 431 using trifluoroacetic acid. MS (ESI): mass calculated for $C_{21}H_{20}F_3N_3O_2S$, 435.12; m/z found, 436.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, *J* = 8.3, 2H), 7.54 (d, *J* = 8.6, 2H), 7.47 (d, *J* = 8.8, 2H), 7.41 (t, *J* = 8.3, 1H), 7.34-7.28 (m, 1H), 4.24 (s, 2H), 4.15-4.02 (m, 1H), 3.59 (d, *J* = 12.1, 2H), 3.40, (br s, 1H), 2.87 (t, *J* = 11.9, 2H), 2.22-2.02 (m, 4H).

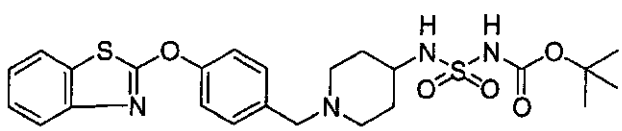
EXAMPLE 452



2-[4-(1,1-Dioxo-1l6-thiomorpholin-4-ylmethyl)-phenoxy]-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 251 using thiomorpholine -1,1-dioxide. MS (ESI): mass calculated for $C_{18}H_{18}N_2O_3S_2$, 374.08; m/z found, 375.2 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, *J* = 8.1, 1H), 7.67 (d, *J* = 8.1, 1H), 7.42-7.31 (m, 5H), 7.27 (t, *J* = 7.8, 1H), 3.66 (s, 2H), 3.03 (d, *J* = 26.3, 8H).

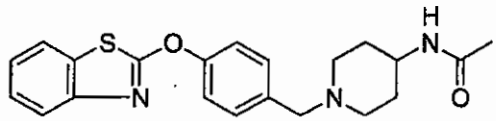
EXAMPLE 453



N-{1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-amino sulfonyl}-carbamic acid tert-butyl ester

The title compound was prepared according to the procedure for EXAMPLE 253 using carbamic acid, N-(sulfonyl chloride) tert butyl ester. MS (ESI): mass calculated for $C_{24}H_{30}N_4O_5S_2$, 518.17; m/z found, 519.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.2, 1H), 7.67 (d, J = 8.2, 1H), 7.42-7.35 (m, 3H), 7.34-7.24 (m, 3H), 5.18 (br s, 1H), 3.55 (s, 2H), 3.39-3.29 (m, 1H), 2.83 (d, J = 11.7, 2H), 2.31-2.18 (m, 2H), 1.98 (d, J = 11.7, 2H), 1.72-1.59 (m, 2H), 1.47 (s, 9H).

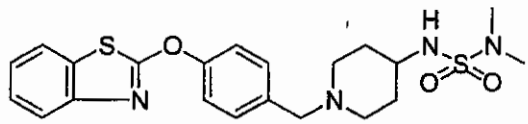
EXAMPLE 454



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-acetamide.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using acetyl chloride. MS (ESI): mass calculated for $C_{21}H_{23}N_3O_2S$, 381.15; m/z found, 382.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 7.8, 1H), 7.67 (d, J = 8.1, 1H), 7.43-7.36 (m, 3H), 7.33-7.24 (m, 3H), 5.65 (br s, 1H), 3.87-3.76 (m, 1H), 3.54 (s, 2H), 2.86 (d, J = 12.1, 2H), 2.17 (t, J = 11.4, 2H), 1.97 (s, 3H), 1.93 (d, J = 11.9, 2H), 1.56-1.44 (m, 2H).

EXAMPLE 455

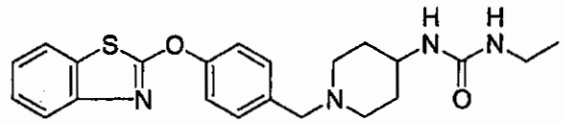


N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-N,N-dimethylsulfamide

The title compound was prepared according to the procedure for EXAMPLE 253, step C using N,N-dimethyl-sulfamoyl chloride. MS (ESI): mass calculated

for $C_{21}H_{26}N_4O_3S_2$, 446.14; m/z found, 447.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.1, 1H), 7.66 (d, J = 8.1, 1H), 7.41-7.35 (m, 3H), 7.32-7.23 (m, 3H), 4.37 (d, J = 7.8, 1H), 3.49 (s, 2H), 3.28-3.17 (m, 1H), 2.81 (d, J = 10.9, 2H), 2.78 (s, 6H), 2.11 (t, J = 11.1, 2H), 1.98 (d, J = 10.9, 2H), 1.61-1.50 (m, 2H).

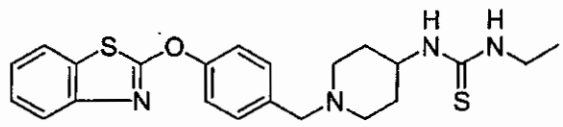
EXAMPLE 456



1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-3-ethyl-urea.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using ethyl isocyanate. MS (ESI): mass calculated for $C_{22}H_{26}N_4O_2S$, 410.18; m/z found, 411.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.66 (d, J = 8.1, 1H), 7.42-7.34 (m, 3H), 7.32-7.23 (m, 3H), 4.54 (br s, 1H), 4.45 (d, J = 7.6, 1H), 3.67-3.55 (m, 1H), 3.50 (s, 2H), 3.23-3.14 (m, 2H), 2.80 (d, J = 11.9, 2H), 2.13 (t, J = 11.4, 2H), 1.93 (d, J = 12.6, 2H), 1.48-1.36 (m, 2H), 1.12 (t, J = 7.3, 3H).

EXAMPLE 457

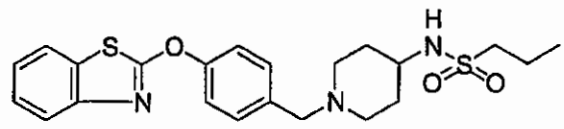


1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-3-ethyl-thiourea.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using ethyl isothiocyanate. MS (ESI): mass calculated for $C_{22}H_{26}N_4OS_2$, 426.15; m/z found, 427.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, J = 7.8, 1H), 7.67 (d, J = 8.1, 1H), 7.41-7.34 (m, 3H), 7.32-7.24 (m, 3H), 6.03 (br s, 1H), 5.74 (br s, 1H), 4.20-4.00 (m, 1H), 3.51 (s, 2H), 3.47-3.35

(m, 2H), 2.82 (d, *J* = 11.6, 2H), 2.05 (t, *J* = 11.1, 2H), 2.05 (d, *J* = 11.9, 2H), 1.57-1.45 (m, 2H), 1.21 (t, *J* = 7.3, 3H).

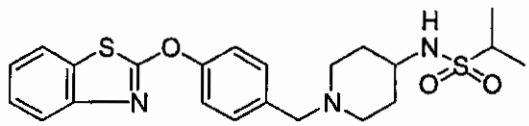
EXAMPLE 458



Propane-1-sulfonic acid {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-amide.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using 1-propanesulfonyl chloride. MS (ESI): mass calculated for $C_{22}H_{27}N_3O_3S_2$, 445.15; m/z found, 446.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, *J* = 8.1, 1H), 7.65 (d, *J* = 8.1, 1H), 7.40-7.34 (m, 3H), 7.32-7.22 (m, 3H), 4.85 (d, *J* = 8.1, 1H), 3.48 (s, 2H), 3.36-3.24 (m, 1H), 3.02-2.94 (m, 2H), 2.81 (d, *J* = 11.9, 2H), 2.11 (t, *J* = 10.6, 2H), 1.95 (d, *J* = 12.6, 2H), 1.89-1.78 (m, 2H), 1.65-1.54 (m, 2H), 1.04 (t, *J* = 7.3, 3H).

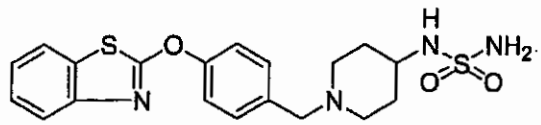
EXAMPLE 459



Propane-2-sulfonic acid {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-amide.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using 2-propanesulfonyl chloride. MS (ESI): mass calculated for $C_{22}H_{27}N_3O_3S_2$, 445.15; m/z found, 446.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, *J* = 8.1, 1H), 7.66 (d, *J* = 8.1, 1H), 7.41-7.35 (m, 3H), 7.32-7.24 (m, 3H), 3.79 (d, *J* = 5.6, 1H), 3.51 (s, 2H), 3.38-3.27 (m, 1H), 2.89-2.78 (m, 2H), 2.19-1.94 (m, 5H), 1.76 (d, *J* = 30.8, 6H), 1.69-1.55 (m, 2H).

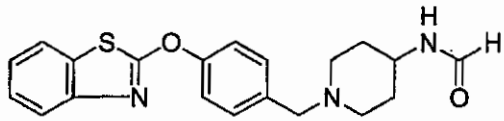
EXAMPLE 460



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-sulfamide

The title compound was prepared from EXAMPLE 453 following the procedure for EXAMPLE 253, step B. MS (ESI): mass calculated for $C_{19}H_{22}N_4O_3S_2$, 418.11; m/z found, 419.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 10.68 (br s, 1H), 7.60 (d, J = 8.3, 1H), 7.56 (d, J = 8.3, 1H), 7.48-7.38 (m, 2H), 7.32-7.24 (m, 3H), 7.18 (t, J = 7.8, 1H), 6.24 (br s, 2H), 4.10 (s, 2H), 3.80-3.66 (m, 1H), 3.57-3.10 (m, 2H), 3.04-2.61 (m, 2H), 2.41-1.61 (m, 4H).

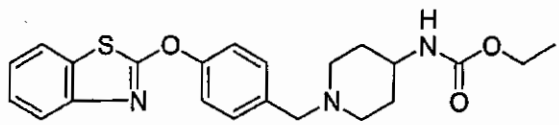
EXAMPLE 461



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-formamide.

The title compound was prepared according to the procedure for EXAMPLE 431, formic acid. MS (ESI): mass calculated for $C_{20}H_{21}N_3O_2S$, 367.14; m/z found, 368.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 12.28 (br s, 1H), 7.73 (d, J = 7.8, 1H), 7.68 (d, J = 7.8, 1H), 7.47-7.24 (m, 6H), 6.33 (d, J = 7.3, 1H), 4.05-3.94 (m, 1H), 3.80 (s, 2H), 3.14 (d, J = 11.6, 2H), 2.41 (t, J = 11.9, 2H), 1.99 (d, J = 13.1, 2H), 1.83-1.70 (m, 2H).

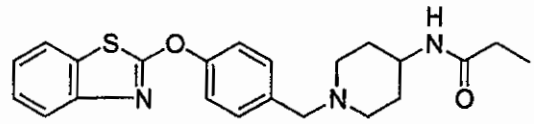
EXAMPLE 462



{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-carbamic acid ethyl ester.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using ethyl chloroformate. MS (ESI): mass calculated for $C_{22}H_{25}N_3O_3S$, 411.16; m/z found, 412.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.1, 1H), 7.66 (d, J = 8.1, 1H), 7.41-7.34 (m, 3H), 7.32-7.22 (m, 3H), 4.62 (br s, 1H), 4.10 (dd, J = 7.3, 6.8, 2H), 3.59-3.51 (m, 1H), 3.49 (s, 2H), 2.80 (d, J = 11.6, 2H), 2.12 (t, J = 11.6, 2H), 1.93 (d, J = 12.1, 2H), 1.51-1.39 (m, 2H), 1.23 (t, J = 7.1, 3H).

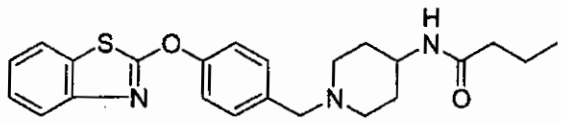
EXAMPLE 463



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-propionamide.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using propionyl chloride. MS (ESI): mass calculated for $C_{22}H_{25}N_3O_2S$, 395.17; m/z found, 396.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.65 (d, J = 8.1, 1H), 7.41-7.34 (m, 3H), 7.32-7.22 (m, 3H), 5.61 (d, J = 8.1, 1H), 3.87-3.76 (m, 1H), 3.49 (s, 2H), 2.82 (d, J = 11.9, 2H), 2.22-2.07 (m, 4H), 1.90 (d, J = 13.1, 2H), 1.51-1.39 (m, 2H), 1.14 (t, J = 7.6, 3H).

EXAMPLE 464

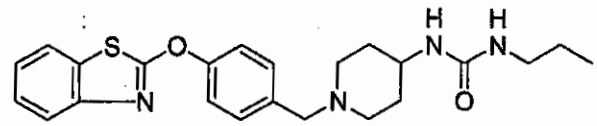


N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-butyramide.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using butyryl chloride. MS (ESI): mass calculated for $C_{23}H_{27}N_3O_2S$, 409.18; m/z found, 410.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.65 (d, J = 8.1, 1H), 7.40-7.35 (m, 3H), 7.31-7.23 (m, 3H), 5.64 (d, J = 8.1, 1H), 3.87-3.77 (m, 1H), 3.49 (s, 2H), 2.81 (d, J = 11.6,

2H), 2.16-2.07 (m, 4H), 1.91 (d, *J* = 12.9, 2H), 1.71-1.60 (m, 2H), 1.51-1.39 (m, 2H), 0.93 (t, *J* = 7.3, 3H).

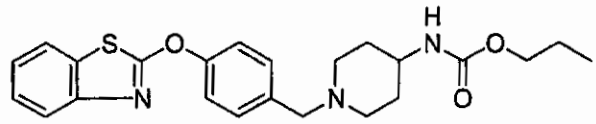
EXAMPLE 465



1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-3-propyl-urea.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using propyl isocyanate. MS (ESI): mass calculated for $C_{23}H_{28}N_4O_2S$, 424.19; m/z found, 425.5 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.70 (d, *J* = 8.1, 1H), 7.63 (d, *J* = 8.1, 1H), 7.39-7.33 (m, 3H), 7.28-7.21 (m, 3H), 5.54 (br s, 1H), 5.37 (d, *J* = 8.1, 1H), 3.66-3.56 (m, 1H), 3.48 (s, 2H), 3.11 (dd, *J* = 7.1, 6.8, 2H), 2.80 (d, *J* = 11.1, 2H), 2.11 (t, *J* = 11.1, 2H), 1.91 (d, *J* = 11.1, 2H), 1.54-1.38 (m, 4H), 0.91 (t, *J* = 7.3, 3H).

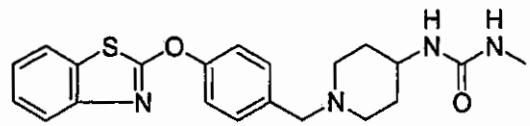
EXAMPLE 466



{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-carbamic acid propyl ester.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using propyl chloroformate. MS (ESI): mass calculated for $C_{23}H_{27}N_3O_3S$, 425.18; m/z found, 426.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, *J* = 8.1, 1H), 7.63 (d, *J* = 8.1, 1H), 7.39-7.33 (m, 3H), 7.31-7.21 (m, 3H), 4.83 (d, *J* = 7.6, 1H), 4.00 (t, *J* = 6.6, 2H), 3.58-3.49 (m, 1H), 3.47 (s, 2H), 2.79 (d, *J* = 11.6, 2H), 2.10 (t, *J* = 10.9, 2H), 1.91 (d, *J* = 11.1, 2H), 1.67-1.56 (m, 2H), 1.52-1.40 (m, 2H), 0.92 (t, *J* = 7.6, 3H).

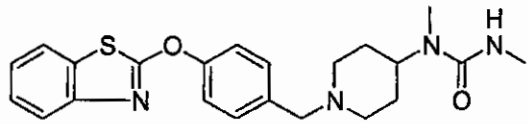
EXAMPLE 467



1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-3-methyl-urea.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using methyl isocyanate. MS (ESI): mass calculated for $C_{21}H_{24}N_4O_2S$, 396.16; m/z found, 397.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, J = 8.1, 1H), 7.65 (d, J = 8.1, 1H), 7.45-7.34 (m, 3H), 7.33-7.22 (m, 3H), 5.71 (br s, 2H), 3.69-3.59 (m, 1H), 3.56 (s, 2H), 2.87 (d, J = 11.9, 2H), 2.73 (d, J = 4.8, 3H), 2.21 (t, J = 10.1, 2H), 1.93 (d, J = 10.4, 2H), 1.58-1.45 (m, 2H).

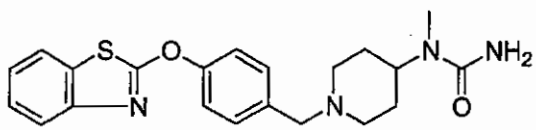
EXAMPLE 469



1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-1,3-dimethyl-urea.

The title compound was prepared according to the procedure for EXAMPLE 255, step C using methyl isocyanate. MS (ESI): mass calculated for $C_{22}H_{26}N_4O_2S$, 410.18; m/z found, 411.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.65 (d, J = 8.1, 1H), 7.41-7.34 (m, 3H), 7.31-7.22 (m, 3H), 4.63 (dd, J = 4.6, 4.6, 1H), 4.21-4.11 (m, 1H), 3.49 (s, 2H), 2.93 (d, J = 11.9, 2H), 2.79 (d, J = 4.8, 3H), 2.71 (s, 3H), 2.08 (t, J = 11.9, 2H), 1.76-1.64 (m, 2H), 1.63-1.54 (m, 2H).

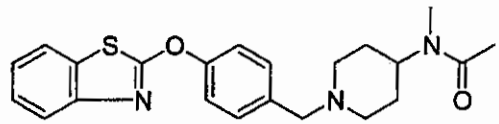
EXAMPLE 470



1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-1-methyl-urea.

The title compound was prepared according to the procedure for EXAMPLE 255, step C using trimethylsilyl isocyanate. MS (ESI): mass calculated for $C_{21}H_{24}N_4O_2S$, 396.16; m/z found, 397.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.65 (d, J = 8.1, 1H), 7.42-7.34 (m, 3H), 7.32-7.21 (m, 3H), 4.93 (s, 2H), 4.16-4.03 (m, 1H), 3.50 (s, 2H), 2.94 (d, J = 11.4, 2H), 2.76 (s, 3H), 2.09 (t, J = 11.4, 2H), 1.79-1.66 (m, 2H), 1.65-1.56 (m, 2H).

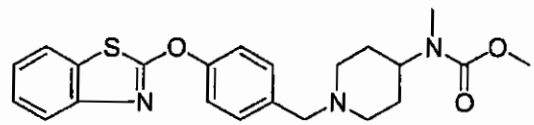
EXAMPLE 471



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-N-methyl-acetamide.

The title compound was prepared according to the procedure for EXAMPLE 255, step C using acetyl chloride. MS (ESI): mass calculated for $C_{22}H_{25}N_3O_2S$, 395.17; m/z found, 396.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.65 (d, J = 8.1, 1H), 7.41-7.34 (m, 3H), 7.31-7.22 (m, 3H), 4.55-4.44 (m, 1H), 3.49 (s, 2H), 3.01-2.90 (m, 2H), 2.84 (s, 3H), 2.15-2.09 (m, 2H), 2.07 (s, 3H), 1.77-1.65 (m, 2H), 1.64-1.53 (m, 2H).

EXAMPLE 472

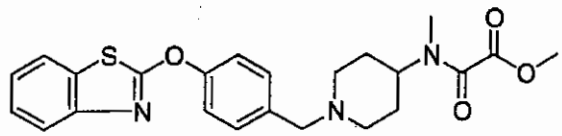


{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-methyl-carbamic acid methyl ester.

The title compound was prepared according to the procedure for EXAMPLE 255, step C using methyl chloroformate. MS (ESI): mass calculated for $C_{21}H_{25}N_3O_3S$, 411.16; m/z found, 412.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$):

7.73 (d, J = 8.1, 1H), 7.66 (d, J = 8.1, 1H), 7.42-7.35 (m, 3H), 7.33-7.24 (m, 3H), 4.16-3.96 (m, 1H), 3.69 (s, 3H), 3.51 (s, 2H), 2.95 (d, J = 11.4, 2H), 2.78 (s, 3H), 2.08 (t, J = 10.9, 2H), 1.82-1.69 (m, 2H), 1.65-1.57 (m, 2H).

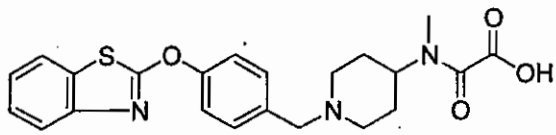
EXAMPLE 473



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-N-methyl-oxalamic acid methyl ester.

The title compound was prepared according to the procedure for EXAMPLE 255, step C using chloro-oxo-acetic acid methyl ester. MS (ESI): mass calculated for $C_{23}H_{25}N_3O_4S$, 439.16; m/z found, 440.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.73 (d, J = 8.1, 1H), 7.66 (d, J = 8.1, 1H), 7.41-7.34 (m, 3H), 7.33-7.23 (m, 3H), 4.41-4.32 (m, 1H), 3.87 (s, 3H), 3.51 (s, 2H), 2.97 (d, J = 11.9, 2H), 2.88 (s, 3H), 2.13 (t, J = 11.9, 2H), 1.95-1.83 (m, 2H), 1.72-1.62 (m, 2H).

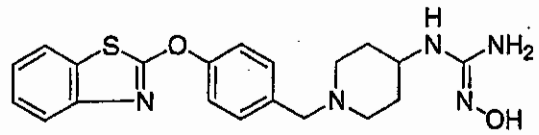
EXAMPLE 474



N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-N-methyl-oxalamic acid.

The title compound was prepared from EXAMPLE 473 following the procedure for EXAMPLE 433, step C. MS (ESI): mass calculated for $C_{22}H_{23}N_3O_4S$, 425.14; m/z found, 426.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.68 (d, J = 8.1, 1H), 7.59 (d, J = 8.1, 1H), 7.37-7.28 (m, 3H), 7.27-7.16 (m, 3H), 4.27-4.16 (m, 1H), 3.43 (s, 2H), 2.93 (d, J = 11.897, 2H), 2.75 (s, 3H), 2.01 (t, J = 11.9, 2H), 1.82-1.65 (m, 2H), 1.58-1.47 (m, 2H).

EXAMPLE 475

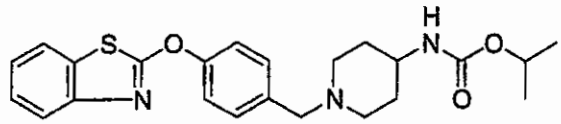


Guanidine, N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-N'-hydroxy

A. 1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl-cyanamide. To a suspension of 1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylamine (339 mg, 1.0 mmol) in CH_3OH (2.0 mL) was added sodium acetate (180 mg, 2.2 mmol) at room temperature. The suspension became a clear solution. Cooled the solution to 0 °C. Cyanogen bromide (159 mg, 1.5 mmol) in CH_3OH (0.7 mL) was added dropwise. The reaction mixture was stirred at 5 °C for 2 h and then at ambient temperature overnight. The mixture was filtered through a frit fnnel and the filtrate was absorbed onto silica gel (40 g) and purified (0–10% CH_3OH/CH_2Cl_2) to give an unstable oil (123 mg, 34% yield). MS (ESI): mass calculated for $C_{20}H_{20}N_4OS$, 364.14; m/z found, 365.3 $[M+H]^+$.

B. Guanidine, N-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-N'-hydroxy. To a solution of 1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl-cyanamide (123 mg, 0.34 mmol) in DMF (2 mL) was added hydroxylamine hydrochloride (41.5 mg, 0.60 mmol), followed by sodium carbonate (119 mg, 1.12 mmol) in small portions. The reaction mixture was stirred at room temerature for 2 h and partitioned between EtOAc (20 mL) and H_2O (20 mL). The organic phase was washed with brine, dried and concentrated under reduced pressure to yield the crude product as a pale solid. The crude product was purified on SiO_2 (12 g; 0-10% CH_3OH/CH_2Cl_2) to give a white soid (117 mg, 86% yield). MS (ESI): mass calculated for $C_{20}H_{23}N_5O_4S$, 397.16; m/z found, 398.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, J = 8.1, 1H), 7.63 (d, J = 8.1, 1H), 7.38-7.32 (m, 3H), 7.28-7.21 (m, 3H), 4.69 (br s, 2H), 3.46 (s, 2H), 3.27-3.16 (m, 1H), 2.78 (d, J = 10.9, 2H), 2.04 (t, J = 11.1, 2H), 1.92 (d, J = 11.1, 2H), 1.51-1.38 (m, 2H).

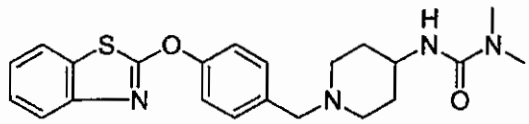
EXAMPLE 476



{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-carbamic acid isopropyl ester.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using isopropyl isocyanate. MS (ESI): mass calculated for $C_{23}H_{27}N_3O_3S$, 425.18; m/z found, 426.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.63 (d, J = 8.1, 1H), 7.38-7.33 (m, 3H), 7.31-7.21 (m, 3H), 4.95-4.85 (m, 1H), 4.75 (d, J = 7.1, 1H), 3.58-3.49 (m, 1H), 3.47 (s, 2H), 2.79 (d, J = 11.6, 2H), 2.09 (t, J = 11.4, 2H), 1.91 (d, J = 11.9, 2H), 1.50-1.39 (m, 2H), 1.21 (d, J = 6.5, 6H).

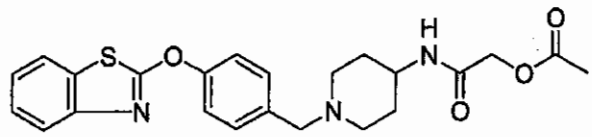
EXAMPLE 477



3-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-1,1-dimethyl-urea.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using N,N-dimethylcarbamoyl chloride. MS (ESI): mass calculated for $C_{22}H_{26}N_4O_2S$, 410.18; m/z found, 411.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.71 (d, J = 8.1, 1H), 7.64 (d, J = 8.1, 1H), 7.39-7.33 (m, 3H), 7.30-7.21 (m, 3H), 4.41 (d, J = 7.8, 1H), 3.73-3.62 (m, 1H), 3.48 (s, 2H), 2.87 (s, 6H), 2.81 (d, J = 11.6, 2H), 2.11 (t, J = 11.9, 2H), 1.93 (d, J = 11.6, 2H), 1.50-1.38 (m, 2H).

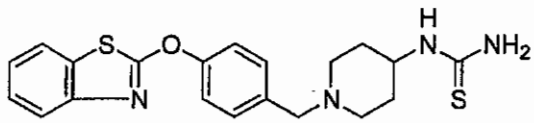
EXAMPLE 478



Acetic acid {1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-ylcarbamoyl}-methyl ester.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using acetic acid chlorocarbonyl methyl ester. MS (ESI): mass calculated for $C_{23}H_{25}N_3O_4S$, 439.16; m/z found, 440.4 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 7.8, 1H), 7.65 (d, J = 8.1, 1H), 7.40-7.35 (m, 3H), 7.32-7.23 (m, 3H), 6.11 (d, J = 8.3, 1H), 4.53, (s, 2H), 3.93-3.82 (m, 1H), 3.50 (s, 2H), 2.83 (d, J = 11.9, 2H), 2.15 (s, 3H), 2.14 (t, J = 11.9, 2H), 1.93 (d, J = 12.1, 2H), 1.56-1.45 (m, 2H).

EXAMPLE 479



{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-thiourea.

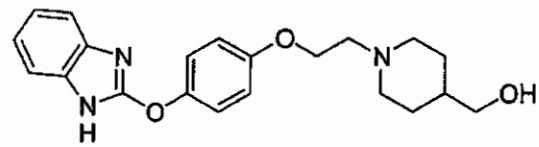
A. 1-{1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-3-benzoyl-thiourea.

The title compound was prepared according to the procedure for EXAMPLE 253, step C using benzoyl isocyanate. MS (ESI): mass calculated for $C_{27}H_{26}N_4O2S_2$, 502.15; m/z found, 503.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 10.80 (d, J = 8.1, 1H), 9.06 (s, 1H), 7.81 (d, J = 8.3, 2H), 7.72 (d, J = 8.3, 1H), 7.65 (d, J = 7.8, 1H), 7.59 (t, J = 7.6, 1H), 7.50-7.45 (m, 2H), 7.42-7.34 (m, 3H), 7.33-7.22 (m, 3H), 4.40-4.29 (m, 1H), 3.53 (s, 2H), 2.80 (d, J = 11.1, 2H), 2.26 (t, J = 10.1, 2H), 2.12 (d, J = 11.9, 2H), 1.76-1.64 (m, 2H).

B. {1-[4-(Benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-thiourea. To 1-{1-[4-(benzothiazol-2-yloxy)-benzyl]-piperidin-4-yl}-3-benzoyl-thiourea (300 mg, 0.60 mmol) was added 10% aqueous sodium hydroxide (10 mL). The reaction mixture was heated at reflux for 1 h. The resulting white suspension was

cooled to room temperature and extracted with 10% CH_3OH/CH_2Cl_2 (3 x 50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude product as an off-white solid. The crude product was purified on SiO_2 (40 g; 0-10% CH_3OH/CH_2Cl_2) to give the title compound as a white solid (219 mg, 92% yield). MS (ESI): mass calculated for $C_{20}H_{22}N_4OS_2$, 398.12; m/z found, 399.3 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.72 (d, J = 8.1, 1H), 7.68 (d, J = 8.1, 1H), 7.42-7.36 (m, 3H), 7.34-7.26 (m, 3H), 6.09 (m, 1H), 4.29-4.02 (m, 1H), 3.57 (s, 2H), 2.88 (d, J = 11.1, 2H), 2.29 (s, 2H), 2.20 (t, J = 11.1, 2H), 2.04 (d, J = 10.1, 2H), 1.60-1.45 (m, 2H).

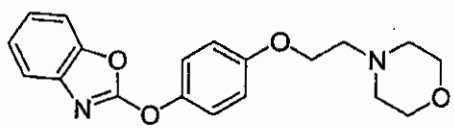
EXAMPLE 480



(1-{2-[4-(1H-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-methanol.

The title compound was prepared according to the procedure for EXAMPLE 37, using piperidin-4-yl-methanol. MS (ESI): mass calculated for $C_{21}H_{25}N_3O_3$, 367.19; m/z found, 368.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO-d_6): 12.24 (s, 1H), 7.32 (s, 2H), 7.27 (d, J = 8.9, 2H), 7.08 (s, 2H), 7.00 (d, J = 8.9, 2H), 4.41 (s, 1H), 4.09 (s, 2H), 3.24 (s, 2H), 2.92 (d, J = 11.1, 2H), 2.68 (s, 2H), 1.98 (t, J = 11.6, 2H), 1.62 (d, J = 11.6, 2H), 1.24 (br s, 1H), 1.11 (d, J = 9.2, 2H).

EXAMPLE 481

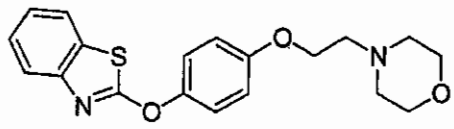


2-[4-(2-Morpholin-4-yl-ethoxy)-phenoxy]-benzooxazole.

The title compound was prepared according to the procedure for EXAMPLE 11, using 4-(2-chloro-ethyl)-morpholine. MS (ESI): mass calculated for $C_{19}H_{20}N_2O_4$, 340.14; m/z found, 341.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$):

7.51 (d, *J* = 7.1, 1H), 7.42 (d, *J* = 7.2, 1H), 7.36-7.30 (m, 2H), 7.29-7.20 (m, 2H), 7.03-6.95 (m, 2H), 4.14 (t, *J* = 5.7, 2H), 3.80-3.72 (m, 4H), 2.83 (t, *J* = 5.7, 2H), 2.60 (t, *J* = 4.6, 4H).

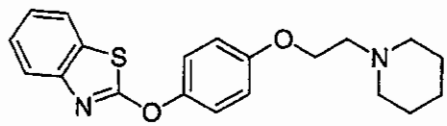
EXAMPLE 482



2-[4-(2-Morpholin-4-yl-ethoxy)-phenoxy]-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 12, using 4-(2-chloro-ethyl)-morpholine and 2-chloro-benzothiazole. MS (ESI): mass calculated for $C_{19}H_{20}N_2O_3S$, 35; m/z found, 341.1 $[M+H]^+$. ^1H 6.12 NMR (400 MHz, $CDCl_3$): 7.74 (d, *J* = 7.6, 1H), 7.66 (d, *J* = 7.3, 1H), 7.39 (t, *J* = 7.3, 1H), 7.31-7.20 (m, 3H), 7.00-6.93 (m, 2H), 4.14 (t, *J* = 5.7, 2H), 3.80-3.72 (m, 4H), 2.83 (t, *J* = 5.7, 2H), 2.60 (t, *J* = 4.6, 4H).

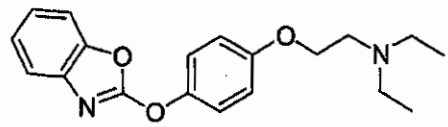
EXAMPLE 483



2-[4-(2-Piperidin-1-yl-ethoxy)-phenoxy]-benzothiazole.

The title compound was prepared according to the procedure for EXAMPLE 12, using 4-(2-chloro-ethyl)-piperidine and 2-chloro-benzothiazole. MS (ESI): mass calculated for $C_{20}H_{22}N_2O_2S$, 354.14; m/z found, 355.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.74 (d, *J* = 8.1, 1H), 7.65 (d, *J* = 8.0, 1H), 7.39 (t, *J* = 7.3, 1H), 7.30-7.22 (m, 3H), 7.00-6.92 (m, 2H), 4.13 (t, *J* = 6.0, 2H), 2.81 (t, *J* = 6.0, 2H), 2.58-2.48 (br s, 4H), 1.68-1.58 (m, 4H), 1.52-1.42 (m, 2H).

EXAMPLE 484



{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-diethyl-amine.

The title compound was prepared according to the procedure for EXAMPLE 11, using (2-chloro-ethyl)-diethyl-amine. MS (ESI): mass calculated for $C_{19}H_{22}N_2O_3$, 326.16; m/z found, 327.1 $[M+H]^+$. ^1H NMR (400 MHz, $CDCl_3$): 7.51 (d, J = 7.6, 1H), 7.42 (d, J = 7.2, 1H), 7.36-7.29 (m, 2H), 7.28-7.19 (m, 2H), 7.02-6.94 (m, 2H), 4.07 (t, J = 6.3, 2H), 2.90 (t, J = 6.3, 2H), 2.65 (q, J = 7.2, 4H), 1.09 (t, J = 7.1, 6H).

Assay Methods

Assay results providd herein are illustrative results of the assays that were performed for compounds of this invention.

Recombinant Human LTA4 Hydrolase Assay for LTA4 Hydrolase Inhibitor Activity

Compounds of the present invention were tested for LTA4 hydrolase inhibitor activity against recombinant human LTA4 hydrolase (rhLTA4H). Vectors were prepared and used to express rhLTA4H essentially as follows: LTA4 hydrolase encoding DNA was amplified by polymerase chain reaction (PCR) using a human placental cDNA library as a template. Oligonucleotide primers for the PCR reaction were based on the 5'-end, and the complement of the 3'-end, of the published nucleotide sequence for the coding region of the human LTA4 hydrolase gene (C.D. Funk et al., Proc. Natl. Acad. Sci. USA 1987, 84:6677–6681). The amplified 1.9 kb DNA fragment encoding LTA4 hydrolase was isolated and cloned into the pFastBac1 vector (Invitrogen). Recombinant baculovirus was generated as described by the manufacturer, and used to infect Spodoptera frugiperda (Sf-9) cells. Recombinant LTA4 hydrolase enzyme was purified from the infected Sf-9 cells essentially as described by J.K. Gierse et al. (Protein Expression and Purification 1993, 4:358–366). The purified enzyme solution was adjusted to contain 0.29 mg/mL

LTA4 hydrolase, 50 mM Tris (pH 8.0), 150 mM NaCl, 5 mM dithiothreitol, 50% glycerol, and EDTA-free Complete protease inhibitor cocktail (Roche). The specific activity of the enzyme was about 3.8 µmol/min/mg.

LTA4 substrate was prepared from the methyl ester of LTA4 (Cayman Chemical) by treatment with 67 equiv of NaOH under nitrogen at room temperature for 40 min. The LTA4 substrate in its free acid form was kept frozen at –80 °C until needed. Each compound was diluted to different concentrations in assay buffer (0.1 M potassium phosphate (pH 7.4), 5 mg/mL fatty acid free BSA) containing 10% DMSO. A 25-uL aliquot of each compound dilution was incubated for 10 min at room temperature with an equal volume of assay buffer containing 36 ng of recombinant human LTA4H. The solution was then adjusted to 200 µL with assay buffer. LTA4 (free acid) was thawed and diluted in assay buffer to a concentration of 357 ng/mL, and 25 µL (9 ng) of LTA4 substrate was added to the reaction mixture (total volume = 225 µL) at time zero. Each reaction was carried out at room temperature for 10 min. The reaction was stopped by diluting 10 µL of the reaction mixture with 200 µL of assay buffer. LTB4 was quantified in the diluted sample by a commercially available enzyme-linked immunoassay (Cayman Chemical Co.), as recommended by the manufacturer. Positive controls, under essentially identical conditions but without addition of an inhibitor compound, and negative controls, containing all assay components except enzyme, were routinely run in each experiment. IC_{50} values were determined by fitting the activity data at different compound concentrations to a 4-parameter equation using the Grafit program (Erithacus software).

The IC_{50} values presented in the tables below should be expected to fall within the typical three-fold variability of assays of this type. The values presented here are, in general, an average of one to three determinations.

Table 1

Example	IC_{50} (nM)	Example	IC_{50} (nM)	Example	IC_{50} (nM)
11	6	**45**	15	**94**	1

13	2	**46**	17	**135**	92
14	9	**59**	5	**136**	25
27	7	**77**	10	**271**	2
36	14	**78**	3	**481**	55
44	8	**92**	1	**484**	19

Table 2

Example	IC_{50} (nM)	Example	IC_{50} (nM)	Example	IC_{50} (nM)
12	100	**176**	12	**298**	15
15	22	**180**	2	**302**	60
18	6	**183**	18	**325**	12
22	7	**192**	3	**328**	22
23	1	**195**	58	**331**	13
25	4	**202**	4	**334**	100
31	17	**206**	4	**336**	24
80	23	**207**	16	**353**	7
81	5	**211**	9	**357**	45
102	3	**214**	18	**358**	11
104	14	**224**	14	**359**	48
109	21	**225**	25	**360**	33
110	40	**250**	26	**361**	8
143	64	**251**	16	**363**	4
146	43	**255**	1	**366**	39
147	33	**259**	14	**380**	6
150	1	**261**	33	**389**	2
153	8	**262**	4	**419**	4
155	9	**263**	5	**437**	21
156	7	**265**	112	**446**	8
157	1	**270**	16	**447**	28
161	1	**274**	29	**450**	7

163	9	**285**	76	**454**	4
167	37	**287**	28	**462**	27
168	27	**288**	4	**471**	19
169	32	**296**	33	**479**	7
172	27	**294**	6	**483**	45

Table 3

Example	IC_{50} (nM)	Example	IC_{50} (nM)
37	10	**134**	110
123	4	**230**	36
127	29	**231**	18
132	139	**485**	39
133	111		

LTB4 Production by Calcium Ionophore-Stimulated Murine Blood for LTA4H Inhibitor Activity

CD-1 mice were sacrificed, and blood was collected in heparin-containing syringes by cardiac puncture. The blood was diluted 1:15 with RPMI-1640 medium, and 200-µL aliquots of the diluted blood were added to wells of a 96-well microtiter plate. LTA4H inhibitor test compounds were prepared at different concentrations in RPMI-1640 medium containing 1% DMSO, and 20 µL of each test solution was added to a well containing diluted whole blood (final DMSO concentration of 0.1%). After the microtiter plate contents were incubated for 15 min at 37 °C in a humidified incubator, calcium ionophore A23187 (Sigma Chemical Co., St. Louis, Mo.) was added to each sample well (final concentration = 20 ng/mL). The incubation was continued under the same conditions for an additional 10 min to allow LTB4 formation. The reaction was terminated by centrifugation (833 x g, 10 min at 4 °C), and supernatants were analyzed for LTB4 by a commercially available enzyme-linked immunoassay (Cayman Chemical Co.) according to the manufacturer's

instructions. Positive controls, under essentially identical conditions but without addition of an inhibitor compound, and negative unstimulated controls, containing all assay components except calcium ionophore, were routinely run in each experiment. IC_{50} values were determined by fitting the activity data at different compound concentrations to a 4-parameter equation using the Grafit program (Erithacus software).

Table 4

Example	IC_{50} (nM)	Example	IC_{50} (nM)	Example	IC_{50} (nM)
11	44	**27**	143	**94**	72
13	41	**44**	23	**481**	264
14	89	**46**	29	**484**	11

Table 5

Example	IC_{50} (nM)	Example	IC_{50} (nM)	Example	IC_{50} (nM)
15	251	**250**	99	**328**	143
18	162	**198**	39	**331**	85
22	123	**206**	43	**334**	453
23	93	**207**	81	**336**	153
81	41	**251**	159	**359**	446
102	55	**259**	49	**360**	246
104	520	**261**	81	**380**	17
109	189	**263**	49	**437**	105
150	52	**274**	331	**446**	131
155	127	**288**	57	**447**	240
156	2000	**296**	133	**462**	144
161	100	**298**	69	**483**	161
180	15	**302**	212		

Table 6

Example	IC_{50} (nM)	Example	IC_{50} (nM)
127	376	**133**	290
132	347	**134**	436

Murine arachidonic acid-induced inflammation model

LTA4H inhibitor compounds of the present invention were dissolved in 20% cyclodextran/H_2O at a concentration of 3 mg/mL. The solutions were administered by oral gavage to female Balb/c mice weighing approximately 20 grams each (0.2 mL per mouse, 30 mg of LTA4H inhibitor compound per kg). Sixty minutes after being administered an LTA4 inhibitor, each mouse received topical application of 20 µL of arachidonic acid (100 mg/mL in acetone) to the left ear and 20 µL of acetone only to the right ear. After 3 h, the mice were sacrificed, blood was withdrawn in heparinized syringes, and 8 mm ear biopsies were taken. Ear biopsies were weighed to determine edema and then frozen at –80 °C until needed for determination of neutrophil influx.

One hundred-microliter aliquots of heparinized blood were added to wells of a microtiter plate, along with equal volumes of RPMI-1640 medium, and calcium ionophore A23187 was added to each sample well (final concentration = 20 ng/µL). The microtiter plate contents were incubated for 10 min at 37 °C in a humidified incubator. The reaction was terminated by centrifugation (833 x g, 10 min at 4 °C). Supernatants were analyzed for LTB4 by a commercially available enzyme-linked immunoassay (Cayman Chemical Co.) in accordance with the manufacturer's instructions. The percent inhibition of ex vivo stimulated LTB4 production (% Inh. LTB4) was determined by comparison to animals treated identically except that the solution admininstered by oral gavage was devoid of inhibitor compound.

Neutrophil influx was quantified by measuring the activity of myeloperoxidase (MPO), a neutrophil-specific enzyme. The ear biopsies were homogenized in 0.5 mL extraction buffer (0.3 M sucrose, 0.22% (w/v)

hexadecyl trimethyl ammonium bromide (CTAB), and 2.5 mM citrate prepared from 0.5 M citrate stock solution (pH 5.0)). Debris was removed by centrifugation at 14000 x g for 10 min. Aliquots of 10 µL of the resulting supernatant were added to wells of a microtiter plate, along with 90-µL aliquots of dilution buffer (10 mM citrate, 0.22% CTAB), followed by addition of 20 µL TMB liquid substrate system (Sigma Chemical Co.) to each sample well. The microtiter plate contents were held at room temperature for 1 h. The reaction was stopped by addition of 100 µL 1 M H_2SO_4 to each sample well, and the myeloperoxidase activity in each sample was determined from the absorbance at 405 nm. The background value from the right ear, treated only with acetone, was subtracted from that for the left ear, treated with arachidonic acid in acetone, for each animal. The percent inhibition of neutrophil influx (% Inh. MPO) by compounds of the invention was determined by comparison to animals treated identically, except that the solution administered by oral gavage was devoid of inhibitor compound.

Table 7

Example	% Inh. LTB4	% Inh. MPO
11	83	95
14	81	56
27	50	72

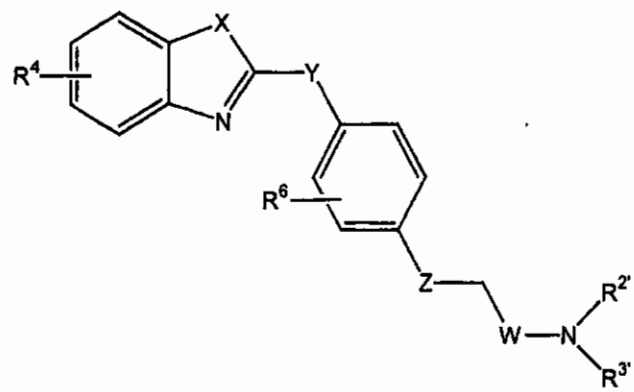
Table 8

Example	% Inh. LTB4	% Inh. MPO	Example	% Inh. LTB4	% Inh. MPO
15	32	29	**251**	79	66
18	78	83	**259**	95	74
22	79	79	**263**	0	19
23	67	84	**274**	93	87
81	78	83	**325**	76	67
109	51	44	**336**	67	0

150	81	91	**360**	87	88
155	96	93	**361**	86	90
180	87	87	**446**	64	43
250	80	94	**447**	90	48
206	67	76	**471**	90	89
250	80	94			

Having described the invention in specific detail and exemplified the manner in which it may be carried into practice, it will be apparent to those skilled in the art that innumerable variations, applications, modifications, and extensions of the basic principles involved may be made without departing from its spirit or scope. It is to be understood that the foregoing is merely exemplary and the present invention is not to be limited to the specific form or arrangements of parts herein described and shown.

1. A compound of formula (II):



(II)

or an enantiomer, diasteromer, racemic, tautomer, hydrate, solvate, or a pharmaceutically acceptable salt, ester, or amide thereof,
wherein
X is selected from the group consisting of NR^5, O, and S, with R^5 being one of H and CH_3;
Y is selected from the group consisting of CH_2, and O;
Z is selected from the group consisting of O and bond;
W is selected from the group consisting of CH_2 and CHR^1-CH_2, with R^1 being one of H and OH, wherein the R^1-attached carbon member in said CHR^1-CH_2 is not directly attached to the nitrogen member to which said W is attached;
R^4 is selected from the group consisting of H, OCH_3, Cl, F, Br, I, OH, NH_2, CN, CF_3 and CH_3;
R^6 is H or F; and
$R^{2'}$ is defined as R^2 and $R^{3'}$ is defined as R^3, as follows:
R^2 and R^3 are each independently selected from the group consisting of

A) H, C_{1-7}alkyl, C_{3-7}alkenyl, wherein the carbon in said alkenyl that is attached to the nitrogen member has only single bonds, C_{3-7}alkynyl, wherein the carbon in said alkynyl that is attached to the nitrogen member has only single bonds, C_{3-7}cycloalkyl optionally benzofused, C_{5-7}cycloalkenyl, -C_{3-7}cycloalkylC_{1-7}alkyl, -C_{1-7}alkylC_{3-7}cycloalkyl and phenyl, wherein each of the substituents A) is independently substituted with 0, 1, or 2 R^Q, and each of said R^Q is a substituent at a carbon member that is at least one carbon member removed from the nitrogen member;
B) a substituent $HetR^a$;
C) -C_{1-7}alkyl$C(O)R^X$, optionally substituted with CH_2R^{Ar} or $CH_2R^{Ar'}$;
D) -C_{2-5}alkyl$C(O)R^X$, wherein two valence allowed carbon members in the C_{2-5}alkyl of said -C_{2-5}alkyl$C(O)R^X$ are part of a saturated C_{3-6}carbocycle;
E) -C_{2-5}alkylOH wherein two valence allowed carbon members in the C_{2-5}alkyl of said -C_{2-5}alkylOH are part of a saturated C_{3-6}carbocycle;
F) -C_{0-4}alkylphenyl, wherein the phenyl in said -C_{0-4}alkylphenyl is fused at two adjacent carbon members in said phenyl to R^f, or is benzofused;

G) -C_{0-4}alkylAr^6, where Ar^6 is a 6-membered heteroaryl having a carbon member point of attachment and having one or two –N= heteroatom members, and benzofused;

H) -C_{0-4}alkylAr^5, where Ar^5 is a 5-membered heteroaryl, having one heteroatom member selected from the group consisting of O, S, and >NR^Y, and having 0 or 1 –N= additional heteroatom member, optionally containing two carbonyl groups, and optionally benzofused;

I) -C_{1-4}alkylAr$^{5'}$, where Ar$^{5'}$ is a 5-membered heteroaryl containing 3 or 4 nitrogen members, optionally substituted with R^Y, and having a valence allowed site as a point of attachment;

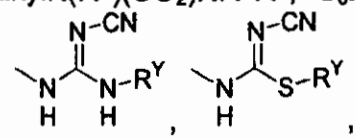
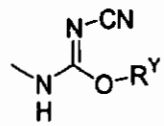
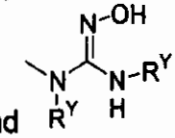
J) -C_{0-4}alkylAr$^{6-6}$, where Ar$^{6-6}$ is a C_{0-4}alkyl-attached phenyl fused at valence allowed sites to a 6-membered heteroaryl, wherein said 6-membered heteroaryl has one or two –N= heteroatom members;

K) -C_{0-4}alkylAr$^{6-5}$, where Ar$^{6-5}$ is a C_{0-4}alkyl-attached phenyl fused at valence allowed sites to a 5-membered heteroaryl, said 5-membered heteroaryl having one heteroatom member selected from the group consisting of O, S, and >NR^Y, and said 5-membered heteroaryl having 0 or 1 additional heteroatom member which is –N=; and

L) one of 2-(4-ethyl-phenoxy)-benzothiazole, 2-(4-ethyl-phenoxy)-benzooxazole, and 2-(4-ethyl-phenoxy)-1*H*-benzoimidazole;

M) SO_2C_{1-4}alkyl;

alternatively R^2 and R^3 are taken together with the nitrogen to which they are attached to form a heterocyclic ring that contains at least one heteroatom member that is said attachment nitrogen, said heterocyclic ring being selected from the group consisting of

a 4-7 membered heterocyclic ring HetR^b, said 4-7 membered heterocyclic ring HetR^b having one heteroatom member that is said attachment nitrogen, and being substituted with 0, 1, or 2 substituents at the same or at different substitution members, said substituents being selected from the group consisting of -R^Y, -CN, -C(O)R^Y, -C_{0-4}alkylCO$_2$R^Y, -C_{0-4}alkylC(O)CO$_2$R^Y, -C_{0-4}alkylOR^Y, -C_{0-4}alkylC(O)NR^{Y}R^Z, -C_{0-4}alkylNR^{Y}C(O)R^Z, -C(O)NR^{Z}OR^Y, -C_{0-4}alkylNR^{Y}C(O)CH$_2$OR^Y, -C_{0-4}alkylNR^{Y}C(O)CH$_2$C(O)R^Y, -C_{0-4}alkylNR^{Y}CO$_2$R^Y, -C_{0-4}alkylNR^{Y}C(O)NR^{Y}R^Z, -C_{0-4}alkylNR^{Y}C(S)NR^{Y}R^Z, -NR^{Y}C(O)CO$_2$R^Y,-NR^{Y}R^Z, -C_{0-4}alkylNR^{W}SO$_2$R^Y,1,3-dihydro-indol-2-one-1-yl, 1,3-dihydro-benzoimidazol-2-one-1-yl, tetrazol-5-yl, 1-R^Y-1*H*-tetrazol-5-yl, R^Y-triazolyl, 2-R^Y-2*H*-tetrazol-5-yl, pyrrolidine-2-thion-1-yl, piperidine-2-thion-1-yl, -C_{0-4}alkylC(O)N(R^Y)(SO$_2$R^Y), -C_{0-4}alkylN(R^Y)(SO$_2$)NR^{Y}R^Y, -C_{0-4}alkylN(R^Y)(SO$_2$)NR^{Y}CO$_2$R^Y, halo,  , ,  , and  ;

ii) a 5-7 membered heterocyclic ring $HetR^c$, said 5-7 heterocyclic ring $HetR^c$ having one additional heteroatom member separated from said attachment nitrogen by at least one carbon members, said additional heteroatom member being selected from the group consisting of O, $S(=O)_{0-2}$, and $>NR^M$, said 5-7 membered heterocyclic ring $HetR^c$ having 0 or 1 carbonyl members, and being substituted with 0, 1, or 2 substituents at the same or at different carbon substitution members, said substituents being selected from the group consisting of $-C(O)R^Y$, $-CO_2R^Y$ $-C_{3-4}alkylCO_2R^Y$ and R^Z;

iii) one of imidazolidin-1-yl, 2-imidazolin-1-yl, pyrazol-1-yl, imidazol-1-yl, 2*H*-tetrazol-2-yl, 1*H*-tetrazol-1-yl, pyrrol-1-yl, 2-pyrrolin-1-yl, and 3-pyrrolin-1-yl, wherein each of said 2*H*-tetrazol-2-yl and 1*H*-tetrazol-1-yl is substituted at the carbon member with 0 or 1 of $-C_{0-4}alkylR^Z$, $-C_{0-4}alkylSR^Y$, $-C_{0-4}alkylCO_2R^Y$, and substituent $HetR^a$; and

iv) one of 1,2,3,4-tetrahydro-quinolin-1-yl, 1,2,3,4-tetrahydro-isoquinolin-2-yl, indol-1-yl, isoindol-2-yl, indolin-1-yl, benzimidazol-1-yl, 2,8-diaza-spiro[4.5]decan-1-one-8-yl, 4-{[(2-tert-butoxycarbonylamino-cyclobutanecarbonyl)-amino]-methyl}-piperidin-1-yl, 4-{[(2-amino-cyclobutanecarbonyl)-amino]-methyl}-piperidin-1-yl, 3,9-diaza-spiro[5.5]undecane-3-carboxylic acid-9-yl tert-butyl ester, 4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-8-yl, and 4-oxo-1,3,8-triaza-spiro[4.5]dec-8-yl;

wherein

substituent $HetR^a$ is a 4-7 membered heterocyclic ring having a carbon member point of attachment and containing a member $>NR^M$ as a heteroatom member, and said heteroatom member being separated from said carbon member point of attachment by at least 1 additional carbon member;

R^K is selected from the group consisting of H, $-C_{1-4}alkyl$, $-C_{0-4}alkylR^{Ar}$ each optionally substituted with 1, 2, or 3 substituents R^N

R^L is selected from the group consisting of $-CO_2R^S$ and $-C(O)NR^SR^{S'}$;

R^M is selected from the group consisting of R^Z, indol-7-yl, $-SO_2R^Y$, $-C_{3-4}alkylCO_2R^Y$, $-CO_2R^Y$, $-C(O)NR^ZOR^Y$, $-C(O)R^Y$, $-C(O)C_{1-4}alkylOR^Y$, $-C_{0-4}alkylC(O)NR^SR^{S'}$, $C_{0-4}alkylC(O)CO_2R^Y$, 1,3-dihydro-indol-2-one-1-yl, 1,3-dihydro-benzoimidazol-2-one-1-yl, tetrazol-5-yl, 1-R^Y-1*H*-tetrazol-5-yl, R^Y-triazolyl, 2-R^Y-2*H*-tetrazol-5-yl and $-C_{0-4}alkylC(O)N(R^Y)(SO_2R^Y)$, each optionally substituted with 1, 2 or 3 substituents R^N;

R^N is selected from the group consisting of OCH_3, Cl, F, Br, I, OH, NH_2, CN, CF_3, CH_3, $OC(O)CH_3$, and NO_2;

R^P is selected from the group consisting of R^Y, $-C_{2-4}alkylOR^Y$, R^{Ar}, $-C_{1-2}alkylCO_2R^Y$, $-C_{1-2}alkylCONR^SR^{S'}$, indol-7-yl, and $-SO_2C_{1-4}alkyl$;

R^Q is selected from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, trichloromethyl, -CN, $-C_{1-4}alkyl$, $-C_{0-4}alkylR^{Ar}$, $-C_{0-4}alkylR^{Ar'}$, $-C_{0-4}alkylOR^Y$, $-C_{0-4}alkylCO_2R^Y$, $-C_{0-4}alkylNR^YR^Z$, $-C_{0-4}alkylNR^YCOR^Y$, $-C_{0-4}alkylNR^YCONR^YR^Z$, $-C_{0-4}alkylNR^YSO_2R^Y$, and $-C_{0-4}alkylSR^Y$;

R^S and $R^{S'}$ are independently selected from the group consisting of H, -C_{1-4}alkyl, and -C_{0-4}alkylphenyl; alternatively, R^S and $R^{S'}$ are taken together with the nitrogen member to which said R^S and $R^{S'}$ are attached to form a 4-7 membered heterocyclic ring having 0 or 1 additional heteroatom member selected from the group consisting of O, S, and >NR^Y, provided that said additional heteroatom member is separated by at least two carbon members from said nitrogen member to which said R^S and $R^{S'}$ are attached, and provided that where R^Y is C_{0-4}alkylR^{Ar}, then R^{Ar} is not substituted with R^L;

R^W is selected from the group consisting of R^Y, and -C_{3-7}cycloalkyl;

R^X is selected from the group consisting of -OR^Y, -NR^YR^Z, -C_{1-4}alkyl, and -C_{0-4}alkylR^{Ar};

R^Y is selected from the group consisting of H, -C_{1-4}alkyl, -C_{0-4}alkylR^{Ar} and -C_{0-4}alkyl$R^{Ar'}$, each optionally substituted with 1, 2, or 3 substituents R^N;

R^Z is selected from the group consisting of R^Y, -C_{2-4}alkylOR^Y, -C_{1-2}alkylCO_2R^Y, -C_{1-2}alkylC(O)$NR^SR^{S'}$, and -C_{2-4}alkyl$NR^SR^{S'}$;

when R^Y and R^Z are attached to a nitrogen member, R^Y and R^Z are selected as defined above, or R^Y and R^Z are taken together with the R^Y- and R^Z-attached nitrogen member to form a 4-7 membered heterocyclic ring $HetR^d$ having 0 or 1 additional heteroatom members selected from the group consisting of O, S, and >NR^M, said 4-7 membered heterocyclic ring $HetR^d$ having 0 or 1 carbonyl members, and said 4-7 membered heterocyclic ring $HetR^d$ having 0 or 1 valence allowed carbon members substituted with at least one of R^M, -CO_2H, and -C_{0-1}alkylOR^Y;

R^{Ar} is a moiety with a carbon member attachment point and said moiety is selected from the group consisting of phenyl, pyridyl, pyrimidyl, and pyrazinyl, wherein each valence allowed carbon member in each of said moieties is independently substituted with at least one of 0, 1, 2 or 3 R^N, and 0 or 1 R^L;

$R^{Ar'}$ is a 3-8 membered ring, having 0, 1 or 2 heteroatom members selected from the group consisting of O, S, N, and >NR^Y, having 0, 1, or 2 unsaturated bonds, having 0 or 1 carbonyl members, wherein each valence allowed member in each of said rings is independently substituted with 0, 1, or 2 R^K; and

R^f is a linear 3- to 5-membered hydrocarbon moiety having 0 or 1 unsaturated carbon-carbon bonds and having 0 or 1 carbonyl members;

provided that

(a) at least one of said $R^{2'}$ and $R^{3'}$ is not ethyl when one selection in the group consisting of selections (s1), (s2), (s3), and (s4), is satisfied, and each of said selections is specified as

(s1): R^4 is H, Z is O, W is CH_2, Y is CH_2, and X is S;

(s2): R^4 is H, Z is O, W is CH_2, Y is CH_2, and X is NH;

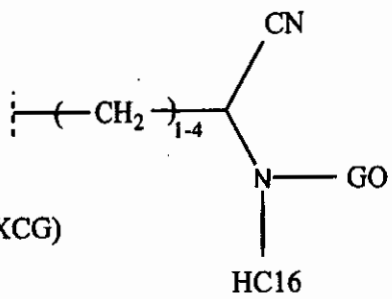
(s3): R^4 is H, Z is O, W is CH_2, Y is O, and X is S;

(s4): R^4 is 5-chloro, Z is O, W is CH_2, Y is CH_2, and X is S;

(b) further provided that when Z is bond, Y is CH_2, W is CHR^1-CH_2, R^1 is H, and one of $R^{2'}$ and $R^{3'}$ is 1*H*-imidazol-2-yl, then the other of $R^{2'}$ and $R^{3'}$ is selected from A1), B)-L), wherein B)-L) are as defined above for compound of formula (I), and A1) consists of H, C_{3-7}alkenyl, wherein the carbon in said C_{3-7}alkenyl that is attached to the nitrogen member has only single bonds, C_{3-7}alkynyl,

wherein the carbon in said alkynyl that is attached to the nitrogen member has only single bonds, C_{3-7}cycloalkyl optionally benzofused, C_{5-7}cycloalkenyl, -C_{3-7}cycloalkylC_{1-7}alkyl, -C_{1-7}alkylC_{3-7}cycloalkyl; and

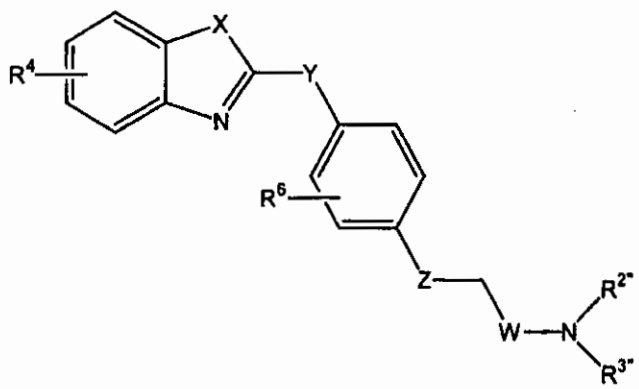
(c) further provided that when X is S, Y is O, Z is bond, and W is CH_2, then one of $R^{2'}$ and $R^{3'}$ is not XCG when the other is C_{1-6}alkyl, wherein XCG is the group



(XCG)

wherein HC16 is one of H, C_{1-6}alkyl, haloC_{1-6}alkyl, allyl, and C_{1-6}alkoxymethyl, and GO is a group attached by a carbon member that has a =O substituent forming an amido group with the nitrogen member to which said GO group is attached.

2. A compound of formula (III):



(III)

or an enantiomer, diasteromer, racemic, tautomer, hydrate, solvate, or a pharmaceutically acceptable salt, ester, or amide thereof,

wherein

X is selected from the group consisting of NR^5, O, and S, with R^5 being one of H and CH_3;

Y is selected from the group consisting of CH_2, and O;

Z is selected from the group consisting of O and bond;

W is selected from the group consisting of CH_2 and CHR^1-CH_2, with R^1 being one of H and OH, wherein the R^1-attached carbon member in said CHR^1-CH_2 is not directly attached to the nitrogen member to which said W is attached;

R^4 is selected from the group consisting of H, OCH_3, Cl, F, Br, I, OH, NH_2, CN, CF_3 and CH_3;

R^6 is H or F; and

$R^{2"}$ is defined as R^2 and $R^{3"}$ is defined as R^3, as follows:

R^2 and R^3 are each independently selected from the group consisting of

A) H, C_{1-7}alkyl, C_{3-7}alkenyl, wherein the carbon in said alkenyl that is attached to the nitrogen member has only single bonds, C_{3-7}alkynyl, wherein the carbon in said alkynyl that is attached to the nitrogen member has only single bonds, C_{3-7}cycloalkyl optionally benzofused, C_{5-7}cycloalkenyl, -C_{3-7}cycloalkylC_{1-7}alkyl, -C_{1-7}alkylC_{3-7}cycloalkyl and phenyl, wherein each of the substituents A) is independently substituted with 0, 1, or 2 R^Q, and each of said R^Q is a substituent at a carbon member that is at least one carbon member removed from the nitrogen member;

B) a substituent $HetR^a$;

C) -C_{1-7}alkyl$C(O)R^x$, optionally substituted with CH_2R^{Ar} or $CH_2R^{Ar'}$;

D) -C_{2-5}alkyl$C(O)R^x$, wherein two valence allowed carbon members in the C_{2-5}alkyl of said -C_{2-5}alkyl$C(O)R^x$ are part of a saturated C_{3-6}carbocycle;

E) -C_{2-5}alkylOH wherein two valence allowed carbon members in the C_{2-5}alkyl of said -C_{2-5}alkylOH are part of a saturated C_{3-6}carbocycle;

F) -C_{0-4}alkylphenyl, wherein the phenyl in said -C_{0-4}alkylphenyl is fused at two adjacent carbon members in said phenyl to R^f, or is benzofused;

G) -C_{0-4}alkylAr^6, where Ar^6 is a 6-membered heteroaryl having a carbon member point of attachment and having one or two –N= heteroatom members, and benzofused;

H) -C_{0-4}alkylAr^5, where Ar^5 is a 5-membered heteroaryl, having one heteroatom member selected from the group consisting of O, S, and $>NR^Y$, and having 0 or 1 –N= additional heteroatom member, optionally containing two carbonyl groups, and optionally benzofused;

I) -C_{1-4}alkyl$Ar^{5'}$, where $Ar^{5'}$ is a 5-membered heteroaryl containing 3 or 4 nitrogen members, optionally substituted with R^Y, and having a valence allowed site as a point of attachment;

J) -C_{0-4}alkylAr^{6-6}, where Ar^{6-6} is a C_{0-4}alkyl-attached phenyl fused at valence allowed sites to a 6-membered heteroaryl, wherein said 6-membered heteroaryl has one or two –N= heteroatom members;

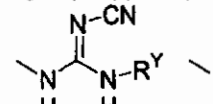
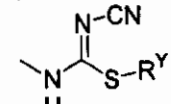
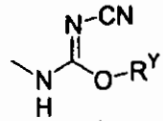
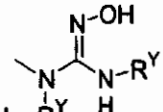
K) -C_{0-4}alkylAr^{6-5}, where Ar^{6-5} is a C_{0-4}alkyl-attached phenyl fused at valence allowed sites to a 5-membered heteroaryl, said 5-membered heteroaryl having one heteroatom member selected from the group consisting of O, S, and $>NR^Y$, and said 5-membered heteroaryl having 0 or 1 additional heteroatom member which is –N=; and

L) one of 2-(4-ethyl-phenoxy)-benzothiazole, 2-(4-ethyl-phenoxy)-benzooxazole, and 2-(4-ethyl-phenoxy)-1*H*-benzoimidazole;

M) SO_2C_{1-4}alkyl;

alternatively R^2 and R^3 are taken together with the nitrogen to which they are attached to form a heterocyclic ring that contains at least one heteroatom member that is said attachment nitrogen, said heterocyclic ring being selected from the group consisting of

i) a 4-7 membered heterocyclic ring $HetR^b$, said 4-7 membered heterocyclic ring $HetR^b$ having one heteroatom member that is said attachment nitrogen, and being substituted with 0, 1, or 2

substituents at the same or at different substitution members, said substituents being selected from the group consisting of $-R^Y$, -CN, $-C(O)R^Y$, $-C_{0-4}alkylCO_2R^Y$, $-C_{0-4}alkylC(O)CO_2R^Y$, $-C_{0-4}alkylOR^Y$, $-C_{0-4}alkylC(O)NR^YR^Z$, $-C_{0-4}alkylNR^YC(O)R^Z$, $-C(O)NR^ZOR^Y$, $-C_{0-4}alkylNR^YC(O)CH_2OR^Y$, $-C_{0-4}alkylNR^YC(O)CH_2C(O)R^Y$, $-C_{0-4}alkylNR^YCO_2R^Y$, $-C_{0-4}alkylNR^YC(O)NR^YR^Z$, $-C_{0-4}alkylNR^YC(S)NR^YR^Z$, $-NR^YC(O)CO_2R^Y$, $-NR^YR^Z$, $-C_{0-4}alkylNR^WSO_2R^Y$, 1,3-dihydro-indol-2-one-1-yl, 1,3-dihydro-benzoimidazol-2-one-1-yl, tetrazol-5-yl, 1-R^Y-1*H*-tetrazol-5-yl, R^Y-triazolyl, 2-R^Y-2*H*-tetrazol-5-yl, pyrrolidine-2-thion-1-yl, piperidine-2-thion-1-yl, $-C_{0-4}alkylC(O)N(R^Y)(SO_2R^Y)$, $-C_{0-4}alkylN(R^Y)(SO_2)NR^YR^Y$, $-C_{0-4}alkylN(R^Y)(SO_2)NR^YCO_2R^Y$, halo,  ,  ,  , and  ;

ii) a 5-7 membered heterocyclic ring $HetR^c$, said 5-7 heterocyclic ring $HetR^c$ having one additional heteroatom member separated from said attachment nitrogen by at least one carbon members, said additional heteroatom member being selected from the group consisting of O, $S(=O)_{0-2}$, and $>NR^M$, said 5-7 membered heterocyclic ring $HetR^c$ having 0 or 1 carbonyl members, and being substituted with 0, 1, or 2 substituents at the same or at different carbon substitution members, said substituents being selected from the group consisting of $-C(O)R^Y$, $-CO_2R^Y$ $-C_{3-4}alkylCO_2R^Y$ and R^Z;

iii) one of imidazolidin-1-yl, 2-imidazolin-1-yl, pyrazol-1-yl, imidazol-1-yl, 2*H*-tetrazol-2-yl, 1*H*-tetrazol-1-yl, pyrrol-1-yl, 2-pyrrolin-1-yl, and 3-pyrrolin-1-yl, wherein each of said 2*H*-tetrazol-2-yl and 1*H*-tetrazol-1-yl is substituted at the carbon member with 0 or 1 of $-C_{0-4}alkylR^Z$, $-C_{0-4}alkylSR^Y$, $-C_{0-4}alkylCO_2R^Y$, and substituent $HetR^a$; and

iv) one of 1,2,3,4-tetrahydro-quinolin-1-yl, 1,2,3,4-tetrahydro-isoquinolin-2-yl, indol-1-yl, isoindol-2-yl, indolin-1-yl, benzimidazol-1-yl, 2,8-diaza-spiro[4.5]decan-1-one-8-yl, 4-{[(2-tert-butoxycarbonylamino-cyclobutanecarbonyl)-amino]-methyl}-piperidin-1-yl, 4-{[(2-amino-cyclobutanecarbonyl)-amino]-methyl}-piperidin-1-yl, 3,9-diaza-spiro[5.5]undecane-3-carboxylic acid-9-yl tert-butyl ester, 4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-8-yl, and 4-oxo-1,3,8-triaza-spiro[4.5]dec-8-yl;

wherein

substituent $HetR^a$ is a 4-7 membered heterocyclic ring having a carbon member point of attachment and containing a member $>NR^M$ as a heteroatom member, and said heteroatom member being separated from

said carbon member point of attachment by at least 1 additional carbon member;

R^K is selected from the group consisting of H, -C_{1-4}alkyl, -C_{0-4}alkylR^{Ar} each optionally substituted with 1, 2, or 3 substituents R^N

R^L is selected from the group consisting of -CO_2R^S and -$C(O)NR^SR^{S'}$;

R^M is selected from the group consisting of R^Z, indol-7-yl, -SO_2R^Y, -C_{3-4}alkylCO_2R^Y, -CO_2R^Y, -$C(O)NR^ZOR^Y$, -$C(O)R^Y$, -$C(O)C_{1-4}$alkylOR^Y, -C_{0-4}alkyl$C(O)NR^SR^{S'}$, C_{0-4}alkyl$C(O)CO_2R^Y$, 1,3-dihydro-indol-2-one-1-yl, 1,3-dihydro-benzoimidazol-2-one-1-yl, tetrazol-5-yl, 1-R^Y-1*H*-tetrazol-5-yl, R^Y-triazolyl, 2-R^Y-2*H*-tetrazol-5-yl and -C_{0-4}alkyl$C(O)N(R^Y)(SO_2R^Y)$, each optionally substituted with 1, 2 or 3 substituents R^N;

R^N is selected from the group consisting of OCH_3, Cl, F, Br, I, OH, NH_2, CN, CF_3, CH_3, $OC(O)CH_3$, and NO_2;

R^P is selected from the group consisting of R^Y, -C_{2-4}alkylOR^Y, R^{Ar}, -C_{1-2}alkylCO_2R^Y, -C_{1-2}alkyl$CONR^SR^{S'}$, indol-7-yl, and -SO_2C_{1-4}alkyl;

R^Q is selected from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, trichloromethyl, -CN, -C_{1-4}alkyl, -C_{0-4}alkylR^{Ar}, -C_{0-4}alkyl$R^{Ar'}$, -C_{0-4}alkylOR^Y, -C_{0-4}alkylCO_2R^Y, -C_{0-4}alkylNR^YR^Z, -C_{0-4}alkylNR^YCOR^Y, -C_{0-4}alkyl$NR^YCONR^YR^Z$, -C_{0-4}alkyl$NR^YSO_2R^Y$, and -C_{0-4}alkylSR^Y;

R^S and $R^{S'}$ are independently selected from the group consisting of H, -C_{1-4}alkyl, and -C_{0-4}alkylphenyl; alternatively, R^S and $R^{S'}$ are taken together with the nitrogen member to which said R^S and $R^{S'}$ are attached to form a 4-7 membered heterocyclic ring having 0 or 1 additional heteroatom member selected from the group consisting of O, S, and $>NR^Y$, provided that said additional heteroatom member is separated by at least two carbon members from said nitrogen member to which said R^S and $R^{S'}$ are attached, and provided that where R^Y is C_{0-4}alkylR^{Ar}, then R^{Ar} is not substituted with R^L;

R^W is selected from the group consisting of R^Y, and -C_{3-7}cycloalkyl;

R^X is selected from the group consisting of -OR^Y, -NR^YR^Z, -C_{1-4}alkyl, and -C_{0-4}alkylR^{Ar};

R^Y is selected from the group consisting of H, -C_{1-4}alkyl, -C_{0-4}alkylR^{Ar} and -C_{0-4}alkyl$R^{Ar'}$, each optionally substituted with 1, 2, or 3 substituents R^N;

R^Z is selected from the group consisting of R^Y, -C_{2-4}alkylOR^Y, -C_{1-2}alkylCO_2R^Y, -C_{1-2}alkyl$C(O)NR^SR^{S'}$, and -C_{2-4}alkyl$NR^SR^{S'}$;

when R^Y and R^Z are attached to a nitrogen member, R^Y and R^Z are selected as defined above, or R^Y and R^Z are taken together with the R^Y- and R^Z-attached nitrogen member to form a 4-7 membered heterocyclic ring $HetR^d$ having 0 or 1 additional heteroatom members selected from the group consisting of O, S, and $>NR^M$, said 4-7 membered heterocyclic ring $HetR^d$ having 0 or 1 carbonyl members, and said 4-7 membered heterocyclic ring $HetR^d$ having 0 or 1 valence allowed carbon members substituted with at least one of R^M, -CO_2H, and -C_{0-1}alkylOR^Y;

R^{Ar} is a moiety with a carbon member attachment point and said moiety is selected from the group consisting of phenyl, pyridyl, pyrimidyl, and pyrazinyl, wherein each valence allowed carbon member in each of said moieties is independently substituted with at least one of 0, 1, 2 or 3 R^N, and 0 or 1 R^L;

$R^{Ar'}$ is a 3-8 membered ring, having 0, 1 or 2 heteroatom members selected from the group consisting of O, S, N, and $>NR^Y$, having 0, 1, or 2 unsaturated bonds, having 0 or 1 carbonyl members, wherein each valence allowed member in each of said rings is independently substituted with 0, 1, or 2 R^K; and

R^f is a linear 3- to 5-membered hydrocarbon moiety having 0 or 1 unsaturated carbon-carbon bonds and having 0 or 1 carbonyl members;

provided that

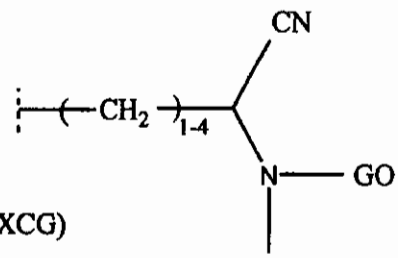
(a) said $R^{2''}$ and $R^{3''}$ further satisfy one of the following:

(e1): at least one of said $R^{2''}$ and $R^{3''}$ is not C_{1-5}alkyl , when Z is O and X is S;

(e2): none of $R^{2''}$ and $R^{3''}$ is C_{1-4}alkylC(O)R^X, with R^X being one of C_{1-4}alkyl, OH, -OC_{1-4}alkyl, -OC_{0-4}alkylR^{Ar}, or $-NR^YR^Y$, when Y is O, Z is bond, and $R^{2''}$ is different from $R^{3''}$; and

(e3): none of $R^{2''}$ and $R^{3''}$ is -C_{1-6}alkylCN, when Y is O, Z is bond, and $R^{2''}$ is different from $R^{3''}$; and

(b) further provided that when X is S, Y is O, Z is bond, and W is CH_2, then one of $R^{2''}$ and $R^{3''}$ is not XCG when the other is C_{1-6}alkyl, wherein XCG is the group



(XCG)

wherein HC16 is one of H, C_{1-6}alkyl, haloC_{1-6}alkyl, allyl, and C_{1-6}alkoxymethyl, and GO is a group attached by a carbon member that has a =O substituent forming an amido group with the nitrogen member to which said GO group is attached.

3. A compound as claimed in claim 1 wherein said R^4 is H.

4. A compound as claimed in claim 2 wherein said R^4 is H.

5. A compound as claimed in claim 1, wherein said R^2 and R^3 are each independently selected from

(i) the group consisting of A), B), C), D), E), and I) when R^2 and R^3 are selected from different groups; or

(ii) group A); or

(iii) group B); or

(iv) group C); or

(v) group D); or

(vi) group E); or

(vii) group I),

as defined in claim 1.

6. A compound as claimed in claim 2, wherein said R^2 and R^3 are each independently selected from

(i) the group consisting of A), B), C), D), E), and I) when R^2 and R^3 are selected from different groups; or

(ii) group A); or

(iii) group B); or

(iv) group C); or

(v) group D); or

(vi) group E); or

(vii) group I),

as defined in claim 2.

7. A compound as claimed in claim 1 wherein said R^2 and R^3 are taken together with the nitrogen to which they are attached to form a heterocyclic ring that contains at least one heteroatom member that is said attachment nitrogen, said heterocyclic ring being selected from any one of

(a) the group consisting of i) and ii) when R^2 and R^3 are selected from different groups;

(b) the group i), and

(c) the group ii)

as defined in claim 1.

8. A compound as claimed in claim 2 wherein said R^2 and R^3 are taken together with the nitrogen to which they are attached to form a heterocyclic ring that contains at least one heteroatom member that is said attachment nitrogen, said heterocyclic ring being selected from any one of

(d) the group consisting of i) and ii) when R^2 and R^3 are selected from different groups;

(e) the group i), and

(f) the group ii)

as defined in claim 2.

9. A compound as claimed in claim 1, wherein said compound of formula (II) is one of:

2-[4-(2-Piperidin-1-yl-ethoxy)-phenoxy]-benzooxazole;
(1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]ethyl}-piperidin-4-yl)-methanol;
1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-ol;
{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-dibutyl-amine;
(1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidin-2-yl)-methanol;
1-{3-[4-(Benzooxazol-2-yloxy)-phenoxy]-propyl}-4-phenyl-piperidin-4-ol;
1-{3-[4-(Benzooxazol-2-yloxy)-phenoxy]-propyl}-4-benzyl-piperidin-4-ol;
2-[4-(2-Piperidin-1-yl-ethyl)-phenoxy]-benzooxazole;
{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-cyclohexyl-ethyl-amine;
1-{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-piperidin-4-ol;
1-{3-[4-(Benzooxazol-2-yloxy)-phenoxy]-2-hydroxy-propyl}-4-phenyl-piperidin-4-ol;
1-[2-(4-Benzooxazol-2-ylmethyl-phenoxy)-ethyl]-piperidine-4-carboxylic acid ethyl ester;
2-[4-(2-Pyrrolidin-1-yl-ethoxy)-phenoxy]-benzooxazole;
{3-[4-(Benzooxazol-2-yloxy)-phenoxy]-propyl}-dimethyl-amine;
{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-dimethyl-amine; and
2-[4-(2-Azepan-1-yl-ethoxy)-phenoxy]-benzooxazole.

10. A compound as in claim 1, wherein said compound of formula (II) is one of:

1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidin-4-ol;
{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-cyclohexyl-ethyl-amine;
2-{4-[2-(2-Ethyl-piperidin-1-yl)-ethoxy]-phenoxy}-benzooxazole;
1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidine-4-carbonitrile;
1-(1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidin-4-yl)-ethanone;
2-{4-[2-(4-Methyl-piperidin-1-yl)-ethoxy]-phenoxy}-benzooxazole;

1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-(4-chloro-phenyl)-piperidin-4-ol;
1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-(4-bromo-phenyl)-piperidin-4-ol;
1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-(4-chloro-3-trifluoromethyl-phenyl)-piperidin-4-ol;
1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-4-benzyl-piperidin-4-ol;
{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-cyclohexyl-methyl-amine; and
{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-cyclopropylmethyl-propyl-amine.

11. A compound as in claim 1, wherein said compound of formula (II) is one of:

{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-butyl-ethyl-amine;
2-({2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-benzyl-amino)-ethanol;
2-{4-[2-(4-Benzyl-piperidin-1-yl)-ethoxy]-phenoxy}-benzooxazole;
(1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidin-3-yl)-methanol;
2-({2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-propyl-amino)-ethanol;
2-[4-(2-Azetidin-1-yl-ethoxy)-phenoxy]-benzooxazole;
N-(1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-2-phenyl-acetamide;
1-{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-piperidine-3-carboxylic acid ethyl ester;
2-{4-[3-(4-Phenyl-piperidin-1-yl)-propoxy]-phenoxy}-benzooxazole;
1-{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-4-phenyl-piperidin-4-ol;
{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-cyclohexyl-ethyl-amine;
2-[4-(2-Pyrrolidin-1-yl-ethyl)-phenoxy]-benzooxazole; and
2-[4-(2-Azepan-1-yl-ethyl)-phenoxy]-benzooxazole.

12. A compound as in claim 1, wherein said compound of formula (II) is one of:

{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-propyl-amine;
{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-dibutyl-amine;
1-{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ol;
1-{2-[4-(Benzooxazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid methyl ester;
1-{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-4-phenyl-piperidin-4-ol;
2-[4-(3-Piperidin-1-yl-propyl)-phenoxy]-benzooxazole;
{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-dibutyl-amine;

{3-[4-(Benzooxazol-2-yloxy)-phenyl]-propyl}-cyclopropylmethyl-propyl-amine;
1-[4-(Benzooxazol-2-yloxy)-phenoxy]-3-pyrrolidin-1-yl-propan-2-ol;
1-[2-(4-Benzooxazol-2-ylmethyl-phenoxy)-ethyl]-4-phenyl-piperidin-4-ol;
1-[2-(4-Benzooxazol-2-ylmethyl-phenoxy)-ethyl]-piperidine-4-carboxylic acid amide
2-[4-(2-Morpholin-4-yl-ethoxy)-phenoxy]-benzooxazole; and
{2-[4-(Benzooxazol-2-yloxy)-phenoxy]-ethyl}-diethyl-amine.

13. A compound as in claim 1, wherein said compound of formula (II) is one of:

{2-[4-(6-Chloro-benzothiazol-2-yloxy)-phenoxy]-ethyl}-diethyl-amine;
1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-ol;
1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carboxylic acid ethyl ester;
1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carboxylic acid;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-pyrrolidin-1-yl-methanone;
3-[(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carbonyl)-amino]-propionic acid ethyl ester;
1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carboxylic acid amide;
1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-pyrrolidin-2-one;
1'-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-[1,4']bipiperidinyl-2-one;
8-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-2,8-diaza-spiro[4.5]decan-1-one;
2-[4-(3-Pyrrolidin-1-yl-propoxy)-phenoxy]-benzothiazole;
{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclohexyl-ethyl-amine;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-3-carboxylic acid amide;
1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-3-methyl-1,3-dihydro-benzoimidazol-2-one;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid methyl ester;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-(4-methyl-piperazin-1-yl)-methanone;
1-[2-(4-Benzothiazol-2-ylmethyl-phenoxy)-ethyl]-piperidine-4-carboxylic acid methyl ester;
3-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropyl-amino)-propionic acid;
{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-dimethyl-amine;
2-[4-(2-Pyrrolidin-1-yl-ethoxy)-phenoxy]-benzothiazole;
{3-[4-(Benzothiazol-2-yloxy)-phenoxy]-propyl}-dimethyl-amine;

2-[4-(2-Azepan-1-yl-ethoxy)-phenoxy]-benzothiazole;
2-[4-(2-Azepan-1-yl-ethoxy)-phenoxy]-6-methoxy-benzothiazole;
1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidin-4-ol;
{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclohexyl-ethyl-amine;
1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-(4-chloro-phenyl)-piperidin-4-ol;
{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-dibutyl-amine;
1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-(4-bromo-phenyl)-piperidin-4-ol;
1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-(4-chloro-3-trifluoromethyl-phenyl)-piperidin-4-ol;
1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-benzyl-piperidin-4-ol;
1'-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-[1,4']bipiperidine;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-methanol;
N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-2-phenyl-acetamide;
2-(4-{2-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-yl]-ethoxy}-phenoxy)-benzothiazole;
2-(4-{2-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-yl]-ethyl}-phenoxy)-benzothiazole;
1-{3-[4-(Benzothiazol-2-yloxy)-phenoxy]-propyl}-4-phenyl-piperidin-4-ol;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-4-phenyl-piperidin-4-ol;
2-[4-(2-Pyrrolidin-1-yl-ethyl)-phenoxy]-benzothiazole;
2-[4-(2-Azepan-1-yl-ethyl)-phenoxy]-benzothiazole;
{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-propyl-amine;
{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-dibutyl-amine;
2-[4-(2-Piperidin-1-yl-ethyl)-phenoxy]-benzothiazole;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ol;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid amide;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-3-carboxylic acid ethyl ester;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-4-phenyl-piperidine-4-carboxylic acid ethyl ester;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-acetic acid ethyl ester;
1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-1,3-dihydro-indol-2-one;
1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-pyrrolidin-2-one;
N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-2-phenyl-acetamide;

8-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-2,8-diaza-spiro[4.5]decan-1-one;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-3-ol;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid ethyl ester;
1'-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-[1,4']bipiperidine;
2-{4-[2-(4-Methyl-piperazin-1-yl)-ethyl]-phenoxy}-benzothiazole;
2-(4-{2-[4-(1-Benzyl-1*H*-tetrazol-5-yl)-piperidin-1-yl]-ethoxy}-phenoxy)-benzothiazole;
4-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carbonyl)-piperazine-1-carboxylic acid *tert*-butyl ester;
1-[2-(4-Benzothiazol-2-ylmethyl-phenoxy)-ethyl]-piperidine-4-carboxylic acid amide;
1-{1-[2-(4-Benzothiazol-2-ylmethyl-phenoxy)-ethyl]-piperidin-4-yl}-pyrrolidin-2-one;
1-[4-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carbonyl)-piperazin-1-yl]-ethanone;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid;
1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-pyrrolidine-2-thione;
2-(4-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperazin-1-yl)-ethanol;
2-(4-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperazin-1-yl)-1-pyrrolidin-1-yl-ethanone;
2-(4-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperazin-1-yl)-1-morpholin-4-yl-ethanone;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-3-carboxylic acid;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-2-carboxylic acid;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-3-yl)-acetic acid;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-acetic acid ethyl ester;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-carbamic acid tert-butyl ester;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-acetic acid;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-3-yl)-methanol;
({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclohexyl-amino)-acetic acid methyl ester;
(4-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperazin-1-yl)-acetic acid;
1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester;
1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-5-oxo-pyrrolidine-2-carboxylic acid;

4-(4-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperazin-1-yl)-phenol;
N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-4-chloro-*N*-cyclopropyl-benzene sulfonamide;
3-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropylmethyl-amino)-propionic acid;
3-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-isopropyl-amino)-propionic acid;
1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-ylamine;
3-[{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-(1-methyl-piperidin-4-yl)-amino]-propionic acid;
3-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-benzyl-amino)-propionic acid;
3-((1-Acetyl-piperidin-4-yl)-{2-[4-(benzothiazol-2-yloxy)-phenoxy]-ethyl}-amino)-propionic acid;
4-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-1H-tetrazol-5-yl)-piperidine-1-carboxylic acid tert-butyl ester;
3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propionic acid;
3-((1-Acetyl-piperidin-4-yl)-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-amino)-propionic acid;
3-[{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-(1-methyl-piperidin-4-yl)-amino]-propionic acid;
3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propionic acid;
3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-isopropyl-amino)-propionic acid;
2-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-1-pyrrolidin-1-yl-ethanone;
(*R*)-1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-3-carboxylic acid;
1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one;
2-(4-{2-[4-(6-Methyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-phenoxy)-benzothiazole;
2-{4-[2-(4-Ethanesulfonyl-piperazin-1-yl)-ethyl]-phenoxy}-benzothiazole;
2-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-1-morpholin-4-yl-ethanone;
3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-methyl-amino)-propionic acid;
3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopentyl-amino)-propionic acid;
3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclobutyl-amino)-propionic acid;
3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-benzyl-amino)-propionic acid;

(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-(4-hydroxymethyl-piperidin-1-yl)-methanone;
{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amine;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-methanone;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-methanone;
2-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-ethanol;
3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propan-1-ol;
4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-butyric acid;
3-[(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carbonyl)-amino]-propionic acid;
4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-butyronitrile;
3-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-propionic acid;
[(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carbonyl)-methyl-amino]-acetic acid;
3-(4-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperazin-1-yl)-phenol;
2-(4-{2-[4-(4-Methoxy-phenyl)-piperazin-1-yl]-ethoxy}-phenoxy)-benzothiazole;
2-{4-[2-(5-Piperidin-4-yl-tetrazol-1-yl)-ethoxy]-phenoxy}-benzothiazole;
(*S*)-1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one;
{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amine;
2-[({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-methyl]-cyclopropanecarboxylic acid ethyl ester;
4-(4-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperazine-1-carbonyl)-benzoic acid ethyl ester;
2-[({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-methyl]-cyclopropanecarboxylic acid;
1-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propan-2-ol;
3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-1,1,1-trifluoro-propan-2-ol;
3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propionamide;
3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propane-1,2-diol;
2-{4-[2-(5-Phenyl-tetrazol-2-yl)-ethoxy]-phenoxy}-benzothiazole;
2-{4-[2-(5-Phenyl-tetrazol-1-yl)-ethoxy]-phenoxy}-benzothiazole;
N-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-*N*-cyclopropyl-2-(2H-tetrazol-5-yl)-acetamide;

(S)-3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-2-methyl-propan-1-ol;
(*R*)-3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-2-methyl-propan-1-ol;
2-{4-[2-(5-Methylsulfanyl-tetrazol-2-yl)-ethoxy]-phenoxy}-benzothiazole;
2-{4-[2-(5-Methylsulfanyl-tetrazol-1-yl)-ethoxy]-phenoxy}-benzothiazole;
2-[4-(2-Tetrazol-2-yl-ethoxy)-phenoxy]-benzothiazole;
2-[4-(2-Tetrazol-1-yl-ethoxy)-phenoxy]-benzothiazole;
(1*R*,2*R*)-2-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-cyclohexanecarboxylic acid;
(1*S*,2*R*)-2-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-cyclohexanecarboxylic acid;
(1*R*,2*R*)-2-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-cyclohexanol;
(1*S*,2*R*)-2-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-cyclohexanol;
4-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-butyric acid;
(*R*) 1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one;
2-(4-{2-[4-(1H-Tetrazol-5-yl)-piperidin-1-yl]-ethyl}-phenoxy)-benzothiazole;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-2-yl)-methanol;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-1H-tetrazol-5-yl)-acetic acid ethyl ester;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-1H-tetrazol-5-yl)-acetic acid ethyl ester;
2-{4-[2-(5-Piperidin-4-yl-tetrazol-2-yl)-ethoxy]-phenoxy}-benzothiazole hydrochloride;
7-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-4-spiro-[3-phthalide]-piperidine;
1-{3-[4-(Benzothiazol-2-yloxy)-phenyl]-propyl}-piperidine-4-carboxylic acid ethyl ester;
2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamine hydrochloride;
2-(4-{2-[4-(1H-Tetrazol-5-yl)-piperidin-1-yl]-ethoxy}-phenoxy)-benzothiazole;
Cis-4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-cyclohexanecarboxylic acid trifluoromethanesulfonate salt;
(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(tetrahydro-furan-2-yl)-methanone;
Propane-2-sulfonic acid (1-{2-[4-(benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carbonyl)-amide;
(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-oxo-acetic acid methyl ester;
N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carbonyl)-benzenesulfonamide trifluoromethanesulfonate salt;

N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carbonyl)-methanesulfonamide trifluoromethanesulfonate salt;
(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-oxo-acetic acid trifluoromethanesulfonate salt;
(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-morpholin-4-yl-methanone;
1-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-2-thiophen-2-yl-ethanone;
(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-pyridin-3-yl-methanone;
(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-cyclopropyl-methanone;
1-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-2-methoxy-ethanone;
1-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-2,2,2-trifluoro-ethanone;
4-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazine-1-carbonyl)-benzoic acid;
(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-pyridin-4-yl-methanone;
(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(5-methyl-pyrazin-2-yl)-methanone;
(*R*)-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(tetrahydro-furan-2-yl)-methanone;
(*S*)-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(tetrahydro-furan-2-yl)-methanone;
(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-(tetrahydro-furan-3-yl)-methanone;
1-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-2-hydroxy-ethanone;
2-[2-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-2-oxo-ethyl]-cyclopentanone;
3-(4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperazin-1-yl)-propionic acid trifluoromethanesufonate salt;
3-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-oxazolidin-2-one;
4-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-morpholin-3-one;
4-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-morpholin-3-one;
3-(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-oxazolidin-2-one;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid benzyloxy-amide;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-acetic acid;
(*R*)-1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one;

1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid hydroxyamide;--
(*S*)-1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-4-hydroxy-pyrrolidin-2-one;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-carbamic acid tert-butyl ester;
2-{4-[2-(4-Fluoro-piperidin-1-yl)-ethyl]-phenoxy}-benzothiazole;
2-{4-[2-(4,4-Difluoro-piperidin-1-yl)-ethyl]-phenoxy}-benzothiazole;
(*R*)-1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-pyrrolidin-3-ol;
N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-formamide;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-urea;
1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-3-cyano-2-phenyl-isourea;
1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-3-cyano-2-methyl-isothiourea;
N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-methanesulfonamide;
1-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-3-cyano-2-methyl-guanidine;
8-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one;
8-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-1,3,8-triaza-spiro[4.5]decane-2,4-dione;
(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-methyl-carbamic acid tert-butyl ester;
N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-N-methyl-acetamide;
N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-N-methyl-methanesulfonamide;
Acetic acid [(1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-methyl-carbamoyl]-methyl ester;
N-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-N-acetamide;
Acetic acid (1-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ylcarbamoyl)-methyl ester;
2-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-methyl-amino)-3-(1H-imidazol-2-yl)-propionic acid;
2-(4-{2-[4-(3-Nitro-pyridin-2-yl)-[1,4]diazepan-1-yl]-ethyl}-phenoxy)-benzothiazole;
[(1-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-piperidine-4-carbonyl)-methyl-amino]-acetic acid ethyl ester;
1'-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-[1,4']bipiperidinyl-4-carboxylic acid ethyl ester;
1'-{2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-[1,4']bipiperidinyl-4-carboxylic acid;
{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-ethyl-amine;

3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-2-methyl-propionic acid trifluoromethansulfonic acid salt;
2-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-ethanol;
2-[2-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-ethoxy]-ethanol;
3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propan-1-ol;
{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-(3-tetrazol-2-yl-propyl)-amine;
{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-(3-pyrrol-1-yl-propyl)-amine;
4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-butyronitrile;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid (2-cyano-ethyl)-amide;
{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-[3-(2H-tetrazol-5-yl)-propyl]-amine;
3-[5-(1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-yl)-tetrazol-1-yl]-propionitrile;
{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-[3-(2H-tetrazol-5-yl)-propyl]-amine;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid (2-hydroxy-1,1-dimethyl-ethyl)-amide;
{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-[3-(1H-[1,2,4]triazol-3-yl)-propyl]-amine;
{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-[3-(5-methyl-1H-[1,2,4]triazol-3-yl)-propyl]-amine;
{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-[3-(5-phenyl-1H-[1,2,4]triazol-3-yl)-propyl]-amine;
2-(4-{2-[4-(1-Methyl-1H-tetrazol-5-yl)-piperidin-1-yl]-ethyl}-phenoxy)-benzothiazole;
2-(4-{2-[4-(2-Methyl-2H-tetrazol-5-yl)-piperidin-1-yl]-ethyl}-phenoxy)-benzothiazole;
1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carbonitrile;
2-(4-{2-[4-(1H-[1,2,3]Triazol-4-yl)-piperidin-1-yl]-ethyl}-phenoxy)-benzothiazole;
4-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-butyric acid ethyl ester;
4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-butyric acid ethyl ester;
2-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-isoindole-1,3-dione;
4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-butyric acid;
1-(3-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethylamino}-propyl)-pyrrolidin-2-one;

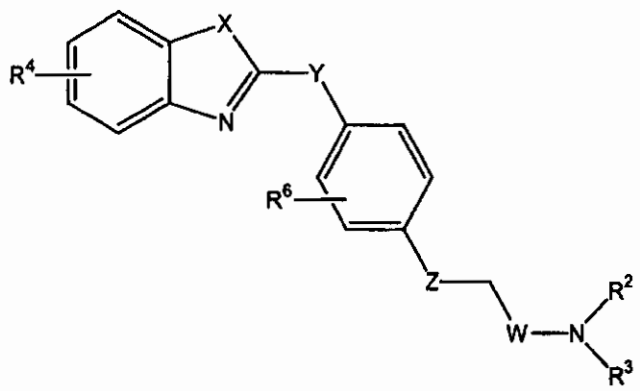
N-1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-N1-cyclopropylmethyl-propane-1,3-diamine;
5-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-pentanoic acid methyl ester;
N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-acetamide;
Morpholine-4-carboxylic acid [3-({2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-amide;
N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-methanesulfonamide
5-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-pentanoic acid;
1-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-isopropyl-amino)-propyl]-pyrrolidin-2-one;
1-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-amino)-propyl]-pyrrolidin-2-one;
1-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-pyrrolidin-2-one;
1-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-propyl-amino)-propyl]-pyrrolidin-2-one;
4-((1-Acetyl-piperidin-4-yl)-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-amino)-butyric acid ethyl ester;
4-((1-Acetyl-piperidin-4-yl)-{2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-amino)-butyric acid ethyl ester;
4-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-methanesulfonyl-amino)-butyric acid;
({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-acetic acid;
6-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-hexanoic acid ethyl ester;
7-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-heptanoic acid ethyl ester;
6-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-hexanoic acid;
7-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-heptanoic acid;
N-1-{2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-N1-cyclopropyl-propane-1,3-diamine;
N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-acetamide;
N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-isobutyramide;
N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-benzamide;
N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-4-chloro-benzamide;
N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-methanesulfonamide;

Propane-2-sulfonic acid [3-({2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-amide trifluoromethansulfonic acid salt;
8-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-octanoic acid ethyl ester;
1-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-3-phenyl-urea;
8-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-octanoic acid;
Tetrahydro-furan-2-carboxylic acid [3-({2-[4-(benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-amide;
N-[3-({2-[4-(Benzothiazol-2-yloxy)-phenyl]-ethyl}-cyclopropyl-amino)-propyl]-2-hydroxy-acetamide;
4-({2-[4-(Benzothiazol-2-yloxy)-phenoxy]-ethyl}-cyclopropyl-amino)-butyric acid;
2-[4-(2-Morpholin-4-yl-ethoxy)-phenoxy]-benzothiazole;
2-[4-(2-Piperidin-1-yl-ethoxy)-phenoxy]-benzothiazole.

14. A compound as in claim 1, wherein said compound of formula (II) is one of:
1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-4-phenyl-piperidin-4-ol;
{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-cyclopropylmethyl-propyl-amine;
Cyclohexyl-ethyl-{2-[4-(1-methyl-1*H*-benzoimidazol-2-yloxy)-phenyl]-ethyl}-amine;
1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-4-(4-bromo-phenyl)-piperidin-4-ol;
1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-4-(4-chloro-phenyl)-piperidin-4-ol;
1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-4-benzyl-piperidin-4-ol;
{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-cyclohexyl-ethyl-amine;
2-[4-(2-Pyrrolidin-1-yl-ethyl)-phenoxy]-1*H*-benzoimidazole;
2-[4-(2-Azepan-1-yl-ethyl)-phenoxy]-1*H*-benzoimidazole;
{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-dibutyl-amine;
1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-piperidin-4-ol;
1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenyl]-ethyl}-piperidine-4-carboxylic acid methyl ester;
{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-cyclohexyl-ethyl-amine;
2-{4-[2-(4-Methyl-piperidin-1-yl)-ethoxy]-phenoxy}-1*H*-benzoimidazole;
2-{4-[2-(2-Ethyl-piperidin-1-yl)-ethoxy]-phenoxy}-1*H*-benzoimidazole;
2-[4-(2-Piperidin-1-yl-ethoxy)-phenoxy]-1*H*-benzoimidazole;
1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-ol;
2-[4-(2-Azepan-1-yl-ethoxy)-phenoxy]-1*H*-benzoimidazole amide;

{3-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-propyl}-dimethyl-amine;
2-[4-(2-Pyrrolidin-1-yl-ethoxy)-phenoxy]-1*H*-benzoimidazole;
{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-diethyl-amine;
2-[4-(2-Morpholin-4-yl-ethoxy)-phenoxy]-1*H*-benzoimidazole;
2-[4-(2-Piperidin-1-yl-ethyl)-phenoxy]-1*H*-benzoimidazole;
1-(1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-pyrrolidin-2-one;
(1-{2-[4-(1H-Benzoimidazol-2-yloxy)-phenoxy]-ethyl}-piperidin-4-yl)-methanol; and
1-{2-[4-(1*H*-Benzoimidazol-2-yloxy)-phenoxy]-ethyl)-piperidine-4-carboxylic acid ethyl ester.

15. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of formula (I)



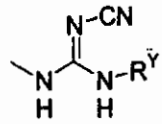
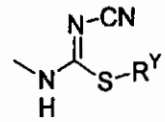
(I)

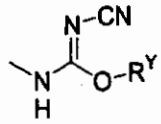
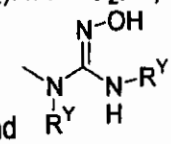
wherein
X is selected from the group consisting of NR^5, O, and S, with R^5 being one of H and CH_3;
Y is selected from the group consisting of CH_2, and O;
Z is selected from the group consisting of O and bond;
W is selected from the group consisting of CH_2 and CHR^1-CH_2, with R^1 being one of H and OH, wherein the R^1-attached carbon member in said CHR^1-CH_2 is not directly attached to the nitrogen member to which said W is attached;
R^4 is selected from the group consisting of H, OCH_3, Cl, F, Br, I, OH, NH_2, CN, CF_3 and CH_3;
R^6 is H or F; and
R^2 and R^3 are each independently selected from the group consisting of
A) H, C_{1-7}alkyl, C_{3-7}alkenyl, wherein the carbon in said alkenyl that is attached to the nitrogen member has only single bonds, C_{3-7}alkynyl, wherein the carbon in said alkynyl that is attached to the nitrogen member has only single bonds, C_{3-7}cycloalkyl optionally benzofused, C_{5-7}cycloalkenyl, -C_{3-7}cycloalkylC_{1-7}alkyl, -C_{1-7}alkylC_{3-7}cycloalkyl and phenyl, wherein each of the substituents A) is independently substituted with 0, 1, or 2 R^Q, and each of said R^Q is a substituent at a carbon member that is at least one carbon member removed from the nitrogen member;

B) a substituent $HetR^a$;
C) $-C_{1-7}alkylC(O)R^x$, optionally substituted with CH_2R^{Ar} or $CH_2R^{Ar'}$;
D) $-C_{2-5}alkylC(O)R^x$, wherein two valence allowed carbon members in the $C_{2-5}alkyl$ of said $-C_{2-5}alkylC(O)R^x$ are part of a saturated $C_{3-6}carbocycle$;
E) $-C_{2-5}alkylOH$ wherein two valence allowed carbon members in the $C_{2-5}alkyl$ of said $-C_{2-5}alkylOH$ are part of a saturated $C_{3-6}carbocycle$;
F) $-C_{0-4}alkylphenyl$, wherein the phenyl in said $-C_{0-4}alkylphenyl$ is fused at two adjacent carbon members in said phenyl to R^f, or is benzofused;
G) $-C_{0-4}alkylAr^6$, where Ar^6 is a 6-membered heteroaryl having a carbon member point of attachment and having one or two –N= heteroatom members, and benzofused;
H) $-C_{0-4}alkylAr^5$, where Ar^5 is a 5-membered heteroaryl, having one heteroatom member selected from the group consisting of O, S, and $>NR^Y$, and having 0 or 1 –N= additional heteroatom member, optionally containing two carbonyl groups, and optionally benzofused;
I) $-C_{1-4}alkylAr^{5'}$, where $Ar^{5'}$ is a 5-membered heteroaryl containing 3 or 4 nitrogen members, optionally substituted with R^Y, and having a valence allowed site as a point of attachment;
J) $-C_{0-4}alkylAr^{6-6}$, where Ar^{6-6} is a $C_{0-4}alkyl$-attached phenyl fused at valence allowed sites to a 6-membered heteroaryl, wherein said 6-membered heteroaryl has one or two –N= heteroatom members;
K) $-C_{0-4}alkylAr^{6-5}$, where Ar^{6-5} is a $C_{0-4}alkyl$-attached phenyl fused at valence allowed sites to a 5-membered heteroaryl, said 5-membered heteroaryl having one heteroatom member selected from the group consisting of O, S, and $>NR^Y$, and said 5-membered heteroaryl having 0 or 1 additional heteroatom member which is –N=; and
L) one of 2-(4-ethyl-phenoxy)-benzothiazole, 2-(4-ethyl-phenoxy)-benzooxazole, and 2-(4-ethyl-phenoxy)-1*H*-benzoimidazole;
M) $SO_2C_{1-4}alkyl$;

alternatively R^2 and R^3 are taken together with the nitrogen to which they are attached to form a heterocyclic ring that contains at least one heteroatom member that is said attachment nitrogen, said heterocyclic ring being selected from the group consisting of

a 4-7 membered heterocyclic ring $HetR^b$, said 4-7 membered heterocyclic ring $HetR^b$ having one heteroatom member that is said attachment nitrogen, and being substituted with 0, 1, or 2 substituents at the same or at different substitution members, said substituents being selected from the group consisting of $-R^Y$, -CN, $-C(O)R^Y$, $-C_{0-4}alkylCO_2R^Y$, $-C_{0-4}alkylC(O)CO_2R^Y$, $-C_{0-4}alkylOR^Y$, $-C_{0-4}alkylC(O)NR^YR^Z$, $-C_{0-4}alkylNR^YC(O)R^Z$, $-C(O)NR^ZOR^Y$, $-C_{0-4}alkylNR^YC(O)CH_2OR^Y$, $-C_{0-4}alkylNR^YC(O)CH_2C(O)R^Y$, $-C_{0-4}alkylNR^YCO_2R^Y$, $-C_{0-4}alkylNR^YC(O)NR^YR^Z$, $-C_{0-4}alkylNR^YC(S)NR^YR^Z$, $-NR^YC(O)CO_2R^Y$, $-NR^YR^Z$, $-C_{0-4}alkylNR^WSO_2R^Y$, 1,3-dihydro-indol-2-one-1-yl, 1,3-dihydro-benzoimidazol-2-one-1-yl, tetrazol-5-yl, 1-R^Y-1*H*-tetrazol-5-yl, R^Y-triazolyl, 2-R^Y-2*H*-tetrazol-5-yl, pyrrolidine-2-thion-1-yl, piperidine-2-thion-1-yl, $-C_{0-4}alkylC(O)N(R^Y)(SO_2R^Y)$, $-C_{0-4}alkylN(R^Y)(SO_2)NR^YR^Y$, $-C_{0-}$

$_4$alkylN(R^Y)(SO_2)$NR^YCO_2R^Y$, halo,  ,  ,

 , and  ;

ii) a 5-7 membered heterocyclic ring HetR^c, said 5-7 heterocyclic ring HetR^c having one additional heteroatom member separated from said attachment nitrogen by at least one carbon members, said additional heteroatom member being selected from the group consisting of O, $S(=O)_{0-2}$, and $>NR^M$, said 5-7 membered heterocyclic ring HetR^c having 0 or 1 carbonyl members, and being substituted with 0, 1, or 2 substituents at the same or at different carbon substitution members, said substituents being selected from the group consisting of $-C(O)R^Y$, $-CO_2R^Y$ $-C_{3-4}$alkylCO_2R^Y and R^Z;

iii) one of imidazolidin-1-yl, 2-imidazolin-1-yl, pyrazol-1-yl, imidazol-1-yl, 2*H*-tetrazol-2-yl, 1*H*-tetrazol-1-yl, pyrrol-1-yl, 2-pyrrolin-1-yl, and 3-pyrrolin-1-yl, wherein each of said 2*H*-tetrazol-2-yl and 1*H*-tetrazol-1-yl is substituted at the carbon member with 0 or 1 of $-C_{0-4}$alkylR^Z, $-C_{0-4}$alkylSR^Y, $-C_{0-4}$alkylCO_2R^Y, and substituent HetR^a; and

iv) one of 1,2,3,4-tetrahydro-quinolin-1-yl, 1,2,3,4-tetrahydro-isoquinolin-2-yl, indol-1-yl, isoindol-2-yl, indolin-1-yl, benzimidazol-1-yl, 2,8-diaza-spiro[4.5]decan-1-one-8-yl, 4-{[(2-tert-butoxycarbonylamino-cyclobutanecarbonyl)-amino]-methyl}-piperidin-1-yl, 4-{[(2-amino-cyclobutanecarbonyl)-amino]-methyl}-piperidin-1-yl, 3,9-diaza-spiro[5.5]undecane-3-carboxylic acid-9-yl tert-butyl ester, 4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-8-yl, and 4-oxo-1,3,8-triaza-spiro[4.5]dec-8-yl;

wherein

substituent HetR^a is a 4-7 membered heterocyclic ring having a carbon member point of attachment and containing a member $>NR^M$ as a heteroatom member, and said heteroatom member being separated from said carbon member point of attachment by at least 1 additional carbon member;

R^K is selected from the group consisting of H, $-C_{1-4}$alkyl, $-C_{0-4}$alkylR^{Ar} each optionally substituted with 1, 2, or 3 substituents R^N

R^L is selected from the group consisting of $-CO_2R^S$ and $-C(O)NR^SR^{S'}$;

R^M is selected from the group consisting of R^Z, indol-7-yl, $-SO_2R^Y$, $-C_{3-4}$alkylCO_2R^Y, $-CO_2R^Y$, $-C(O)NR^ZOR^Y$, $-C(O)R^Y$, $-C(O)C_{1-4}$alkylOR^Y, $-C_{0-4}$alkyl$C(O)NR^SR^{S'}$, C_{0-4}alkyl$C(O)CO_2R^Y$, 1,3-dihydro-indol-2-one-1-yl, 1,3-dihydro-benzoimidazol-2-one-1-yl, tetrazol-5-yl, 1-R^Y-1*H*-tetrazol-5-yl, R^Y-triazolyl, 2-R^Y-2*H*-tetrazol-5-yl and $-C_{0-4}$alkyl$C(O)N(R^Y)(SO_2R^Y)$, each optionally substituted with 1, 2 or 3 substituents R^N;

R^N is selected from the group consisting of OCH_3, Cl, F, Br, I, OH, NH_2, CN, CF_3, CH_3, $OC(O)CH_3$, and NO_2;

R^P is selected from the group consisting of R^Y, $-C_{2-4}alkylOR^Y$, R^{Ar}, $-C_{1-2}alkylCO_2R^Y$, $-C_{1-2}alkylCONR^SR^{S'}$, indol-7-yl, and $-SO_2C_{1-4}alkyl$;
R^Q is selected from the group consisting of fluoro, chloro, bromo, iodo, trifluoromethyl, trichloromethyl, -CN, $-C_{1-4}alkyl$, $-C_{0-4}alkylR^{Ar}$, $-C_{0-4}alkylR^{Ar'}$, $-C_{0-4}alkylOR^Y$, $-C_{0-4}alkylCO_2R^Y$, $-C_{0-4}alkylNR^YR^Z$, $-C_{0-4}alkylNR^YCOR^Y$, $-C_{0-4}alkylNR^YCONR^YR^Z$, $-C_{0-4}alkylNR^YSO_2R^Y$, and $-C_{0-4}alkylSR^Y$;
R^S and $R^{S'}$ are independently selected from the group consisting of H, $-C_{1-4}alkyl$, and $-C_{0-4}alkylphenyl$; alternatively, R^S and $R^{S'}$ are taken together with the nitrogen member to which said R^S and $R^{S'}$ are attached to form a 4-7 membered heterocyclic ring having 0 or 1 additional heteroatom member selected from the group consisting of O, S, and $>NR^Y$, provided that said additional heteroatom member is separated by at least two carbon members from said nitrogen member to which said R^S and $R^{S'}$ are attached, and provided that where R^Y is $C_{0-4}alkylR^{Ar}$, then R^{Ar} is not substituted with R^L;
R^W is selected from the group consisting of R^Y, and $-C_{3-7}cycloalkyl$;
R^X is selected from the group consisting of $-OR^Y$, $-NR^YR^Z$, $-C_{1-4}alkyl$, and $-C_{0-4}alkylR^{Ar}$;
R^Y is selected from the group consisting of H, $-C_{1-4}alkyl$, $-C_{0-4}alkylR^{Ar}$ and $-C_{0-4}alkylR^{Ar'}$, each optionally substituted with 1, 2, or 3 substituents R^N;
R^Z is selected from the group consisting of R^Y, $-C_{2-4}alkylOR^Y$, $-C_{1-2}alkylCO_2R^Y$, $-C_{1-2}alkylC(O)NR^SR^{S'}$, and $-C_{2-4}alkylNR^SR^{S'}$;
when R^Y and R^Z are attached to a nitrogen member, R^Y and R^Z are selected as defined above, or R^Y and R^Z are taken together with the R^Y- and R^Z-attached nitrogen member to form a 4-7 membered heterocyclic ring $HetR^d$ having 0 or 1 additional heteroatom members selected from the group consisting of O, S, and $>NR^M$, said 4-7 membered heterocyclic ring $HetR^d$ having 0 or 1 carbonyl members, and said 4-7 membered heterocyclic ring $HetR^d$ having 0 or 1 valence allowed carbon members substituted with at least one of R^M, $-CO_2H$, and $-C_{0-1}alkylOR^Y$;
R^{Ar} is a moiety with a carbon member attachment point and said moiety is selected from the group consisting of phenyl, pyridyl, pyrimidyl, and pyrazinyl, wherein each valence allowed carbon member in each of said moieties is independently substituted with at least one of 0, 1, 2 or 3 R^N, and 0 or 1 R^L;
$R^{Ar'}$ is a 3-8 membered ring, having 0, 1 or 2 heteroatom members selected from the group consisting of O, S, N, and $>NR^Y$, having 0, 1, or 2 unsaturated bonds, having 0 or 1 carbonyl members, wherein each valence allowed member in each of said rings is independently substituted with 0, 1, or 2 R^K; and
R^f is a linear 3- to 5-membered hydrocarbon moiety having 0 or 1 unsaturated carbon-carbon bonds and having 0 or 1 carbonyl members;
or an enantiomer, diasteromer, racemic, tautomer, hydrate, solvate, or a pharmaceutically acceptable salt, ester, or amide thereof.

16. A pharmaceutical composition comprising at least one compound as claimed in any one of claims 1 - 14.

17. Use of a therapeutically effective amount of at least one LTA4H modulator selected from compounds of any one of claim 1, claim 2 or compounds of formula (I) as claimed in claim 12, in the manufacture of a medicament for the treatment or prevention of an LTA4H-mediated condition in a subject:

18. Use of at least one LTA4H modulator selected from compounds as claimed in any one of claim 1, claim 2 or compounds of formula (I) as claimed in claim 12 in the manufacture of a medicament for the treatment, prevention or inhibition of inflammation in a subject.

19. Use of an inhibitory amount of at least one LTA4H modulator selected from compounds as claimed in any one of claim 1, claim 2 or compounds of formula (I) as claimed in claim 12 in the manufacture of a medicament for the inhibition of LTA4H enzyme activity.

20. A use as claimed in claim 17 wherein said R^4 is H.

21. A use as claimed in claim 18 wherein said R^4 is H.

22. A use as claimed in laim 19 wherein said R^4 is H.

23. A use as claimed in claim 17, wherein said R^2 and R^3 are each independently selected from

(i) the group consisting of A), B), C), D), E), and I) when R^2 and R^3 are selected from different groups; or

(ii) group A); or

(iii) group B); or

(iv) group C); or

(v) group D); or

(vi) group E); or

(vii) group I),

as defined in claim 1, claim 2 or claim 12.

24. A use as claimed in claim 18, wherein said R^2 and R^3 are each independently selected from

(i) the group consisting of A), B), C), D), E), and I) when R^2 and R^3 are selected from different groups; or

(ii) group A); or

(iii) group B); or

(iv) group C); or

(v) group D); or

(vi) group E); or

(vii) group I),

as defined in claim 1, claim 2 or claim 12.

25. A use as claimed in claim 19, wherein said R^2 and R^3 are each independently selected from

(i) the group consisting of A), B), C), D), E), and I) when R^2 and R^3 are selected from different groups; or

(ii) group A); or

(iii) group B); or

(iv) group C); or

(v) group D); or

(vi) group E); or

(vii) group I),

as defined in claim 1, claim 2 or claim 12.

26. A use as claimed in claim 17, wherein said R^2 and R^3 are taken together with the nitrogen to which they are attached to form a heterocyclic ring that contains at least one heteroatom member that is said attachment nitrogen, said heterocyclic ring being selected from any one of

(g) the group consisting of i) and ii) when R^2 and R^3 are selected from different groups;

(h) the group i), and

(i) the group ii)

as defined in claim 1, claim 2 or claim 12.

27. A use as claimed in claim 18, wherein said R^2 and R^3 are taken together with the nitrogen to which they are attached to form a heterocyclic ring that

contains at least one heteroatom member that is said attachment nitrogen, said heterocyclic ring being selected from any one of

(j) the group consisting of i) and ii) when R^2 and R^3 are selected from different groups;

(k) the group i), and

(l) the group ii)

as defined in claim 1, claim 2 or claim 12.

28. A use as claimed in claim 19, wherein said R^2 and R^3 are taken together with the nitrogen to which they are attached to form a heterocyclic ring that contains at least one heteroatom member that is said attachment nitrogen, said heterocyclic ring being selected from any one of

(m)the group consisting of i) and ii) when R^2 and R^3 are selected from different groups;

(n) the group i), and

(o) the group ii)

as defined in claim 1, claim 2 or claim 12.

29. A use as claimed in any one of claims 17 - 28, wherein said LTA4H-mediated condition is inflammation due to at least one of asthma, chronic obstructed pulmonary disease, atherosclerosis, rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, and psoriasis.

30. A use as claimed in any one of claims 17 - 19, wherein said at least one LTA4H modulator is selected from the compounds as claimed in any one of claims 9 – 14.