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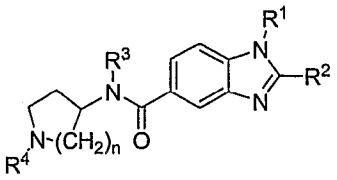
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(54) Title: BENZIMIDAZOLE ANTAGONISTS OF THE H-3 RECEPTOR



(I)

(57) Abstract: This invention is directed to a compound of formula (I), as defined herein, or a pharmaceutically acceptable salt thereof; a pharmaceutical composition containing a compound of formula (I), a process of preparation of a compound of formula (I), a method of treatment of a disorder or condition that may be treated by antagonizing histamine H3 receptors, the method comprising administering to a mammal in need of such treatment a compound of formula (I) as described above, and a method of treatment of a disorder or condition selected from the group consisting of depression, mood disorders, schizophrenia, anxiety disorders, Alzheimer's disease, attention-deficit hyperactivity disorder (ADHD), attention-deficit disorder (ADD), psychotic disorders, cognitive disorders, sleep disorders, obesity, dizziness, epilepsy, motion sickness, respiratory diseases, allergy, allergy-induced airway responses, allergic rhinitis, nasal congestion, allergic congestion, congestion, hypotension, cardiovascular disease, diseases of the G1 tract, hyper and hypo motility and acidic secretion of the gastro-intestinal tract, the method comprising administering to a mammal in need of such treatment a compound of formula (I) as described above.

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BENZIMIDAZOLE ANTAGONISTS OF THE H-3 RECEPTOR

Background of the Invention

This invention is directed to compounds of formula I described herein, to a pharmaceutical composition comprising such compounds, and to methods of treatment of disorders or conditions that may be treated by antagonizing histamine-3 (H3) receptors using such compounds.

Histamine is a well-known mediator in hypersensitive reactions (e.g. allergies, hay fever, and asthma) that are commonly treated with antagonists of histamine or "antihistamines." It has also been established that histamine receptors exist in at least two distinct types, referred to as H1 and H2 receptors.

A third histamine receptor (H3 receptor) is believed to play a role in neurotransmission in the central nervous system, where the H3 receptor is thought to be disposed presynaptically on histaminergic nerve endings (Nature, 302, S32- 837 (1983)). The existence of the H3 receptor has been confirmed by the development of selective H3 receptor agonists and antagonists (Nature, 327, 117-123 (1987)) and has subsequently been shown to regulate the release of the neurotransmitters in both the central nervous system and peripheral organs, particularly the lungs, cardiovascular system and gastrointestinal tract.

A number of diseases or conditions may be treated with histamine-3 receptor ligands wherein the H3 ligand may be an antagonist, agonist or partial agonist, see: (Imamura et al., Circ. Res., (1996) 78, 475-481); (Imamura et. al., Circ. Res., (1996) 78, 863-869); (Lin et al., Brain Res. (1990) 523, 325-330); (Monti et al., Neuropsychopharmacology (1996) 15, 31 35); (Sakai, et al., Life Sci. (1991) 48, 2397-2404); (Mazurkiewiez- Kwilecki and Nsonwah, Can. J. Physiol. Pharmacol. (1989) 67, 75-78); (Panula, P. et al., Neuroscience (1998) 44, 465-481); (Wada et al., Trends in Neuroscience (1991) 14,415); (Monti et al., Eur. J. Pharmacol. (1991) 205, 283); (Mazurkiewicz-Kwilecki and Nsonwah, Can. J. Physiol. Pharmacol. (1989) 67, 75-78); (Haas et al., Behav. Brain Res. (1995) 66, 41-44); (De Almeida and Izquierdo, Arch. Int. Pharmacodyn. (1986) 283, 193-198); (Kamei et al., Psychopharmacology (1990) 102, 312-318); (Kamei and Sakata, Japan. J. Pharmacol. (199 1) 57, 437-482); (Schwartz et al., Psychopharmacology; The fourth Generation of Progress, Bloom and Kupfer (eds.), Raven Press, New York, (1995) 3 97); (Shaywitz et al., Psychopharmacology (1984) 82, 73-77); (Dumery and Blozovski, Exp. Brain Res. (1987) 67, 61-69); (Tedford et al., J. Pharmacol. Exp. Ther. (1995) 275, 598-604); (Tedford et al., Soc. Neurosci. Abstr. (1996) 22, 22); (Yokoyama et al., Eur. J. Pharmacol. (1993) 234,129); (Yokoyama and Iinuma, CNS Drugs (1996) 5, 321); (Onodera et al., Prog. Neurobiol. (1994) 42, 685); (Leurs and Timmerman, Prog. Drug Res. (1992) 39,127); (The Histamine H3 Receptor, Leurs and Timmerman (ed.), Elsevier Science, Amsterdam, The Netherlands (1998); (Leurs et al., Trends in Pharm. Sci. (1998) 19, 177-183); (Phillips et al., Annual Reports in Medicinal Chemistry (1998) 33, 31-40);

(Matsubara et al., Eur. J. Pharmacol. (1992) 224, 145); (Rouleau et al., J. Pharmacol. Exp. Ther. (1997) 281, 1085); (Adam Szelag, "Role of histamine H3-receptors in the proliferation of neoplastic cells in vitro", Med. Sci. Monit., 4(5): 747- 755, (1998)); (Fitzsimons, C., H. Duran, F. Labombarda, B. Molinari and E. Rivera, "Histamine receptors signalling in epidermal tumor cell lines with H-ras gene alterations", Inflammation Res., 47 (Suppl. 1): S50-S51, (1998)); (R. Leurs, R.C. Vollinga and H. Timmerman, "The medicinal chemistry and therapeutic potentials of ligand of the histamine H3 receptor", Progress in Drug Research 45: 170-165, (1995)); (R. Levi and N.C.E. Smith, "Histamine H3-receptors: A new frontier in myocardial ischemia", J. Pharm. Exp. Ther., 292: 825-830, (2000)); (Hatta, E., K Yasuda and R. Levi, "Activation of histamine H3 receptors inhibits carrier-mediated norepinephrine release in a human model of protracted myocardial ischemia", J. Pharm. Exp. Ther., 283: 494-500, (1997); (H. Yokoyama and K. Iinuma, "Histamine and Seizures: Implications for the treatment of epilepsy", CNS Drugs, 5(5); 321-330, (1995)); (K. Hurukami, H. Yokoyama, K. Onodera, K. Iinuma and T. Watanabe, AQ-0 145, "A newly developed histamine H3 antagonist, decreased seizure susceptibility of electrically induced convulsions in mice", Meth. Find. Exp. Clin. Pharmacol., 17(C): 70-73, (1995); (Delaunois A., Gustin P., Garbarg M., and Ansay M., "Modulation of acetylcholine, capsaicin and substance P effects by histamine H3 receptors in isolated perfused rabbit lungs", European Journal of Pharmacology 277(2-3):243-50, (1995)); and (Dimitriadou, et al., "Functional relationship between mast cells and C- sensitive nerve fibres evidenced by histamine H3-receptor modulation in rat lung and spleen", *Clinical Science* 87(2):151-63, (1994). Such diseases or conditions include cardiovascular disorders such as acute myocardial infarction; memory processes, dementia and cognitive disorders such as Alzheimer's disease and attention-deficit hyperactivity disorder; neurological disorders such as Parkinson's disease, schizophrenia, depression, epilepsy, and seizures or convulsions; cancer such as cutaneous carcinoma, medullary thyroid carcinoma and melanoma; respiratory disorders such as asthma; sleep disorders such as narcolepsy; vestibular dysfunction such as Meniere's disease; gastrointestinal disorders, inflammation, migraine, motion sickness, obesity, pain, and septic shock.

H3 receptor antagonists have also been previously described in, for example, WO 03/050099, WO 02/0769252, WO 02/12224, and U.S. Patent Publication No. 2005/0171181 A1. The histamine H3 receptor (H3R) regulates the release of histamine and other neurotransmitters, including serotonin and acetylcholine. H3R is relatively neuron specific and inhibits the release of certain monoamines such as histamine. Selective antagonism of H3R receptors raises brain histamine levels and inhibits such activities as food consumption while minimizing non-specific peripheral consequences. Antagonists of the receptor increase synthesis and release of cerebral histamine and other monoamines. By this mechanism, they induce a prolonged wakefulness, improved cognitive function, reduction in food intake and

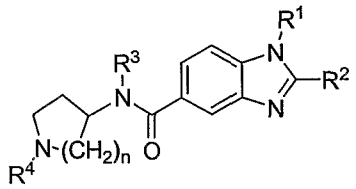
normalization of vestibular reflexes. Accordingly, the receptor is an important target for new therapeutics in Alzheimer disease, mood and attention adjustments, including attention deficit hyperactive disorder (ADHD), attention deficiet disorder (ADD), cognitive deficiencies, obesity, dizziness, schizophrenia, epilepsy, sleeping disorders, narcolepsy and motion sickness, and various forms of anxiety.

The majority of histamine H3 receptor antagonists to date resemble histamine in possessing an imidazole ring that may be substituted, as described, for example, in WO 96/38142. Non-imidazole neuroactive compounds such as beta histamines (Arrang, Eur. J. Pharm. 1985, 111:72-84) demonstrated some histamine H3 receptor activity but with poor potency. EP 978512 and EP 0982300A2 disclose non-imidazole alkyamines as histamine H3 receptor antagonists. WO 02/12224 (Ortho McNeil Pharmaceuticals) describes non-imidazole bicyclic derivatives as histamine H3 receptor ligands. Other receptor antagonists have been described in WO 02/32893 and WO 02/06233.

This invention is directed to histamine-3 (H3) receptor antagonists of the invention useful for treating the conditions listed in the preceding paragraphs. The compounds of this invention are highly selective for the H3 receptor (vs. other histamine receptors), and possess remarkable drug disposition properties (pharmacokinetics). In particular, the compounds of this invention selectively distinguish H3R from the other receptor subtypes H1R, H2R. In view of the increased level of interest in histamine H3 receptor agonists, inverse agonists and antagonists in the art, novel compounds, such as those directed to the invention herein, that interact with the histamine H3 receptor would be a highly desirable contribution to the art.

Summary of the Invention

This invention is directed to a compound of formula I,



or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-aryl, $(C_1\text{-}C_6)$alkyl-$(C_3\text{-}C_6)$cycloalkyl, and aryl optionally substituted with 1 to 4 substituents selected from the group consisting of halo, methoxy, CN, CO-NH$(C_1\text{-}C_6)$alkyl, and CO-N$((C_1\text{-}C_6)\text{alkyl})_2$;

R^2 is selected from the group consisting of $(C_3\text{-}C_6)$cycloalkyl, piperidine, morpholine, pyrrolidine, amino $(C_1\text{-}C_6)$alkyl, amino di-$(C_1\text{-}C_6)$alkyl, aminobenzyl, $(C_1\text{-}C_6)$alkylaryl, and $(C_1\text{-}C_6)$alkyl-$(C_1\text{-}C_6)$alkoxy; wherein R^2 may be optionally substituted with 1 to 3 substituents selected independently from hydroxyl, $(C_1\text{-}C_6)$alkyl, aryl, and heteroaryl;

R^3 is $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-$(C_1\text{-}C_6)$alkoxy, heteroaryl or $(C_1\text{-}C_6)$alkylaryl;

R^4 is $(C_1\text{-}C_6)$alkyl; and

n is 0, 1, 2, 3, or 4.

A preferred embodiment of the invention includes those compounds of formula I wherein R^1 is $(C_1\text{-}C_6)$alkyl, R^2 is $(C_3\text{-}C_6)$cycloalkyl, R^3 $(C_1\text{-}C_6)$alkyl, and n is 2.

The most preferred embodiment of the invention includes those compounds of formula I wherein R^1 is $(C_1\text{-}C_6)$alkyl, R^2 is pyrrolidine, R^3 is methyl, R^4 is ethyl, and n is 2.

Other preferred and exemplified embodiments of the present invention include the following compounds of formula I:

2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-(4-Hydroxy-cyclohexylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

1-Methyl-2-phenethylamino-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-Ethyl-1-phenyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

1-(2-Fluoro-phenyl)-2-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-(Benzyl-methyl-amino)-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-Ethyl-1-(4-methoxy-phenyl)-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-(2,2-Dimethyl-propylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-((R)-1,2-Dimethyl-propylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

1-Cyclopropylmethyl-2-((S)-2-methoxy-1-methyl-ethylamino)-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

1-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-Ethyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

[3-(Ethyl-methyl-amino)-pyrrolidin-1-yl]-[2-(3-hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazol-5-yl]-methanone,

[3-(Ethyl-methyl-amino)-pyrrolidin-1-yl]-(2-morpholin-4-yl-1-propyl-1H-benzoimidazol-5-yl)-methanone,

[1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazol-5-yl]-[3-(ethyl-methyl-amino)-pyrrolidin-1-yl]-methanone,

1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid (1-ethyl-piperidin-4-yl)-(2-methoxy-ethyl)-amide,

1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide,

2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide,

1-Cyclopropylmethyl-2-((S)-2-methoxy-1-methyl-ethylamino)-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide,

2-Cyclopentylamino-1-methyl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide,

2-(Cyclopropylmethyl-amino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-azepan-4-yl)-methyl-amide,

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide,

2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-azepan-4-yl)-methyl-amide,

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-azepan-4-yl)-methyl-amide,

2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-azepan-4-yl)-methyl-amide,

[3-(Methyl-propyl-amino)-pyrrolidin-1-yl]-(2-morpholin-4-yl-1-propyl-1H-benzoimidazol-5-yl)-methanone,

[2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazol-5-yl]-[3-(methyl-propyl-amino)-pyrrolidin-1-yl]-methanone,

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-(1-propyl-piperidin-4-yl)-amide,

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-propyl-piperidin-4-yl)-amide,

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid (4-methyl-1-propyl-piperidin-4-yl)-amide,

2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide,

2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide,

1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide,

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide,

2-Cyclopentylamino-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide,

1-Cyclopropylmethyl-2-((S)-2-methoxy-1-methyl-ethylamino)-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide,

2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide,

2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-isopropyl-piperidin-4-yl)-amide,

2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid (1-isopropyl-piperidin-4-yl)-methyl-amide,

2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-piperidin-4-yl)-methyl-amide,

2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-piperidin-4-yl)-pyridin-2-yl-amide,

2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid (1-isopropyl-piperidin-4-yl)-pyridin-2-yl-amide,

4-[(2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester, and

4-[(2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carbonyl)-methyl-amino]-piperidine-1-carboxylic acid tert-butyl ester.

This invention is also directed to pharmaceutical composition for treating a disorder or condition that may be treated by antagonizing histamine-3 receptors, the composition comprising a compound of formula I and optionally a pharmaceutically acceptable carrier.

This invention is also directed to a method of treatment of a disorder or condition that may be treated by antagonizing histamine-3 receptors, the method comprising administering to a mammal in need of such treatment a compound of formula I.

This invention is also directed to a method of treatment of a disorder or condition selected from the group consisting of depression, mood disorders, schizophrenia, anxiety disorders, cognitive disorders, Alzheimer's disease, attention-deficit disorder (ADD), attention-deficit hyperactivity disorder (ADHD), psychotic disorders, sleep disorders, obesity, dizziness, epilepsy, motion sickness, respiratory diseases, allergy, allergy- induced airway responses, allergic rhinitis, nasal congestion, allergic congestion, congestion, hypotension, cardiovascular disease, diseases of the GI tract, hyper and hypo motility and acidic secretion of the gastro- intestinal tract, the method comprising administering to a mammal in need of such treatment a compound of formula I.

This invention is also directed to a pharmaceutical composition for treating allergic rhinitis, nasal congestion or allergic congestion comprising: (a) an H3 receptor antagonist compound of formula I or a pharmaceutically acceptable salt thereof; (b) an H1 receptor antagonist or a pharmaceutically acceptable salt thereof; and (c) a pharmaceutically acceptable carrier; wherein the active ingredients (a) and (b) above are present in amounts that render the composition effective in treating allergy rhinitis, nasal congestion or allergic congestion.

This invention is also directed to a pharmaceutical composition for treating ADD, ADHD, depression, mood disorders, or cognitive disorders comprising: (a) an H3 receptor antagonist compound of Formula I or a pharmaceutically acceptable salt thereof; (b) a neurotransmitter re-uptake blocker or a pharmaceutically acceptable salt thereof; (c) a pharmaceutically acceptable carrier; wherein the active ingredients (a) and (b) above are present in amounts that render the composition effective in treating depression, mood disorders, and cognitive disorders.

In the general formula I according to the present invention, when a radical is mono- or poly-substituted, said substituent(s) can be located at any desired position(s), unless otherwise stated. Also, when a radical is polysubstituted, said substituents can be identical or different, unless otherwise stated.

The histamine-3 (H3) receptor antagonists of the invention are useful for treating, in particular, ADD, ADHD, obesity, anxiety disorders and respiratory diseases. Respiratory diseases that may be treated by the present invention include adult respiratory distress syndrome, acute respiratory distress syndrome, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis and chronic sinusitis.

The pharmaceutical composition and method of this invention may also be used for preventing a relapse in a disorder or condition described in the previous paragraphs. Preventing such relapse is accomplished by administering to a mammal in need of such prevention a compound of formula I as described above.

The disclosed compounds may also be used as part of a combination therapy, including their administration as separate entities or combined in a single delivery system, which employs an effective dose of a histamine H3 antagonist compound of general formula I and an effective dose of a histamine H1 antagonist, such as cetirizine (Zyrtec™), chlorpheniramine (Chlortrimeton™), loratidine (Claritin™), fexofenadine (Allegra™), or desloratadine (Clarinex™) for the treatment of allergic rhinitis, nasal congestion, and allergic congestion.

The disclosed compounds may also be used as part of a combination therapy, including their administration as separate entities or combined in a single delivery system, which employs an effective dose of a histamine H3 antagonist compound of general formula I and an effective dose of a neurotransmitter reuptake blocker. Examples of neurotransmitter reuptake blockers will include the serotonin-selective reuptake inhibitors (SSRI's) like sertraline (Zoloft™), fluoxetine (Prozac™), and paroxetine (Paxil™), or non-selective serotonin, dopamine or norepinephrine reuptake inhibitors for treating ADD, ADHD, depression, mood disorders, or cognitive disorders.

The compounds of the present invention may have optical centers and therefore may occur in different enantiomeric configurations. Formula I, as depicted above, includes all enantiomers, diastereomers, and other stereoisomers of the compounds depicted in structural formula I, as well as racemic and other mixtures thereof. Individual isomers can be obtained by known methods, such as optical resolution, optically selective reaction, or chromatographic separation in the preparation of the final product or its intermediate.

The present invention also includes isotopically labeled compounds, which are identical to those recited in formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the present invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine, chlorine, and iodine, such as ^{2}H, ^{3}H, ^{13}C, ^{11}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{15}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, ^{123}I, respectively. Compounds of the present invention and pharmaceutically acceptable salts of said compounds which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically labeled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly

preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Anxiety disorders include, for example, generalized anxiety disorder, panic disorder, PTSD, and social anxiety disorder. Mood adjustment disorders include, for example, depressed mood, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and depressed mood. Cognitive disorders include, for example, ADHD, attention-deficit disorder (ADD) or other attention adjustment or cognitive disorders due to general medical conditions. Psychotic disorders include, for example, schizoaffective disorders and schizophrenia; sleep disorders include, for example, narcolepsy and enuresis.

Examples of the disorders or conditions which may be treated by the compound, composition and method of this invention are also as follows: depression, including, for example, depression in cancer patients, depression in Parkinson's patients, post-myocardial infarction depression, depression in patients with human immunodeficiency virus (HIV), Subsyndromal Symptomatic depression, depression in infertile women, pediatric depression, major depression, single episode depression, recurrent depression, child abuse induced depression, post partum depression, DSM-IV major depression, treatment-refractory major depression, severe depression, psychotic depression, post-stroke depression, neuropathic pain, manic depressive illness, including manic depressive illness with mixed episodes and manic depressive illness with depressive episodes, seasonal affective disorder, bipolar depression BP I, bipolar depression BP II, or major depression with dysthymia; dysthymia; phobias, including, for example, agoraphobia, social phobia or simple phobias; eating disorders, including, for example, anorexia nervosa or bulimia nervosa; chemical dependencies, including, for example, addictions to alcohol, cocaine, amphetamine and other psychostimulants, morphine, heroin and other opioid agonists, phenobarbital and other barbiturates, nicotine, diazepam, benzodiazepines and other psychoactive substances; Parkinson's diseases, including, for example, dementia in Parkinson's disease, neuroleptic-induced parkinsonism or tardive dyskinesias; headache, including, for example, headache associated with vascular disorders; withdrawal syndrome; age-associated learning and mental disorders; apathy; bipolar disorder; chronic fatigue syndrome; chronic or acute stress; conduct disorder; cyclothymic disorder; somatoform disorders such as somatization disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated disorder, and somatoform NOS; incontinence; inhalation disorders;

intoxication disorders; mania; oppositional defiant disorder; peripheral neuropathy; post-traumatic stress disorder; late luteal phase dysphoric disorder; specific developmental disorders; SSRI "poop out" syndrome, or a patient's failure to maintain a satisfactory response to SSRI therapy after an initial period of satisfactory response; and tic disorders including Tourette's disease.

As an example, the mammal in need of the treatment or prevention may be a human. As another example, the mammal in need of the treatment or prevention may be a mammal other than a human.

Pharmaceutically acceptable salts of the compounds of formula I include the acid addition and base salts thereof.

Suitable acid addition salts are formed from acids that form non-toxic salts. Examples include the acetate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, malate, maleate, malonate, mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, saccharate, stearate, succinate, tartrate, tosylate and trifluoroacetate salts.

Suitable base salts are formed from bases that form non-toxic salts. Examples include the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.

For a review on suitable salts, see "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

The compounds of the invention may exist in both unsolvated and solvated forms. The term 'solvate' is used herein to describe a molecular complex comprising the compound of the invention and a stoichiometric amount of one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term 'hydrate' is employed when said solvent is water.

Included within the scope of the invention are complexes such as clathrates, drug-host inclusion complexes wherein, in contrast to the aforementioned solvates, the drug and host are present in stoichiometric or non-stoichiometric amounts. Also included are complexes of the drug containing two or more organic and/or inorganic components, which may be in stoichiometric or non-stoichiometric amounts. The resulting complexes may be

ionized, partially ionized, or non-ionized. For a review of such complexes, see J Pharm Sci, 64 (8), 1269-1288 by Haleblian (August 1975).

Hereinafter all references to compounds of formula I include references to salts, solvates and complexes thereof and to solvates and complexes of salts thereof.

The compounds of the invention include compounds of formula I as hereinbefore defined, including all polymorphs and crystal habits thereof, and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-labeled compounds of formula I.

Compounds of formula I containing one or more asymmetric carbon atoms can exist as two or more stereoisomers. Where structural isomers are interconvertible via a low energy barrier, tautomeric isomerism ('tautomerism') can occur. This can take the form of proton tautomerism in compounds of formula I containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds that contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.

Included within the scope of the present invention are all stereoisomers, geometric isomers and tautomeric forms of the compounds of formula I, including compounds exhibiting more than one type of isomerism, and mixtures of one or more thereof. Also included are acid addition or base salts wherein the counterion is optically active, for example, d-lactate or l-lysine, or racemic, for example, dl-tartrate or dl-arginine.

Unless otherwise indicated, the term "halo", as used herein includes fluoro, chloro, bromo and iodo.

Unless otherwise indicated, the term "(C_1-C_6)alkyl", as used herein includes saturated, straight-chain or branched hydrocarbon group having from 1 to 6 carbon atoms and includes for example methyl, ethyl, propyl, i-propyl, n-butyl, i-butyl, sec-butyl and t-butyl. This also applies if the alkyl group carries substituents or is a substituent for another group, e.g. in -O-(C_1-C_6)alkyl and -C(O)(C_1-C_6)alkyl.

Unless otherwise indicated, the term "alkoxy", as used herein, includes straight-chain and branched alkoxy groups and includes for example methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, sec-butoxy and t-butoxy.

Unless otherwise indicated, the term "(C_3-C_6)cycloalkyl", as used herein, includes saturated monocyclic carbocyclic group having 3 to 6 carbon atoms and includes for example cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

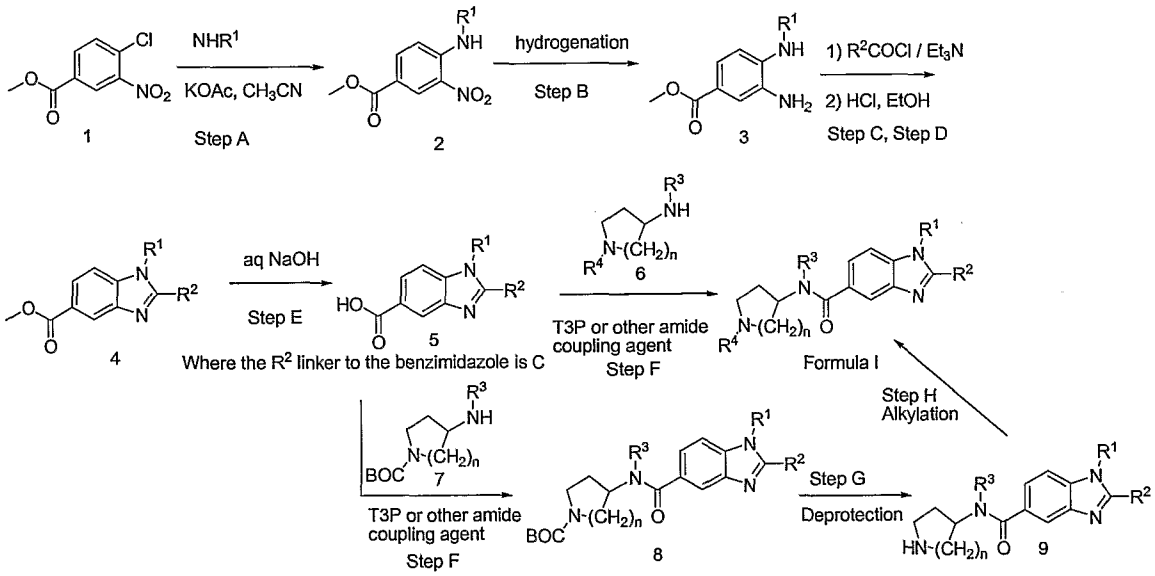
Unless otherwise indicated, the term "aryl", as used herein, includes and organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl, napthyl, indenyl, and fluroenyl. "Aryl" encompases fused ring groups wherein at least one ring is aromatic.

Unless otherwise indicated, the term "heteroaryl" as used herein, includes monocyclic or bicyclic heteroaryl groups having 5 to 9 and 9 to 14 ring members respectively, which contain 1, 2, 3 or 4 heteroatom(s) selected from nitrogen, oxygen and sulphur. The heteroaryl group can be unsubstituted, monosubstituted or disubstituted. Examples of heteroaryl groups include, but are not limited to thiophenyl, furanyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, tetrazolyl, pyranyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, thiadiazinyl, isobenzofuranyl, benzofuranyl, chromenyl, indolizinyl, isoindolyl, indolyl, indazolyl, purinyl, quinolinyl, isoquinolyl, cinnolinyl, phthalazinyl, naphthyridinyl, quinazolinyl, quinoxalinyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, benzothiophenyl, pyrrolopyrazinyl, pyrrolopyridinyl, and imidazopyridinyl.

Detailed Description of the Invention

The compound of formula I according to the invention may be prepared by the general procedure shown in Scheme 1.

Scheme 1



In Scheme 1, compounds of the formula (I) are prepared as follows.

Step A:

Substitution of a halo group, preferable chloride, of (1) can be accomplished using standard condition that appear in the literature. For example, Chauhan et al. have shown that reaction of an aryl nitro chloride with an amine in the presence of a base results in the substitution product (Chauhan, S. M. S.; Singh, Ram; Geetanjali; SYNCAV; Synth. Commun.; EN; 33; 16; 2003; 2899 – 2906). Reaction of (1) with an amine NHR^1 in the presence a base, where the preferred base is potassium acetate, in a solvent, where acetonitrile is preferred, at

a reaction temperature of room temperature to the reflux temperature of the solvent employed, where around 80 °C is preferred affords the displacement product, (2).

Step B:

Reduction of the nitro group, (2) can be accomplished by reaction of (2) in a reaction-inert-solvent, where preferred solvents are low boiling alcohols, where methanol or ethyl alcohol is preferred in the presence of an acid, where HCl is preferred. The reduction is accomplished using a catalyst, where Pd/C is preferred in the presence of hydrogen, around 45 psi, at a reaction temperature of about room temperature to the reflux temperature of the solvent employed, where the reaction temperature is about 45 °C is preferred to afford the reduced product, (3). Alternative reduction conditions can be employed, such as those used by Ates-Alagoz, et al (Ates-Alagoz, Zeynep; Buyukbingol, Erdem; HCOMEX; Heterocycl. Commun.; EN; 7; 5; 2001; 455 – 460).

Step C:

Acylation of (3) can be accomplished using well-established conditions that appear in the literature, and known to one skilled in the art. Reaction of (3) with an acid chloride in the presence of tertiary amine base, where triethylamine is preferred in a reaction inert solvent, where chlorinated solvents are preferred, such as, methylene chloride or 1,2-dichloroethane, at room temperature affords the acylated product.

Step D:

Heterocyclic ring formation can be accomplished by reaction of the acylated product from Step C in ethanol with an inorganic acid, where HCl is preferred, at a reaction temperature from about 50 °C to the reflux temperature of the solvent employed to give the cyclized product (4).

Step E:

Hydrolysis of the ester (4) can be accomplished using standard conditions that appear in the literature, or known to one skilled in the art. Reaction of ester (4) in ethanol with aqueous sodium or potassium hydroxide, where aqueous sodium hydroxide is preferred, at a reaction temperature of about 50 °C to the reflux temperature of the solvents employed gives the acid (5).

Step F:

Intermediate of the general structure (5) may be reacted with primary or secondary amines of general formula (6 or 7) as defined in the specification, in the presence of a coupling reagent such as dicyclohexyl carbodiimide, carbonyl diimidazole, tripropylphosphonic anhydride, alkyl chloroformate, bis(2-oxo-3-oxazolidinyl)phosphinic chloride, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate, or any other such standard literature reagents in the presence of a trialkyl amine base, such as

triethyl amine or diisopropylethyl amine, wherein tripropylphosphonic anhydride and triethylamine are a preferred combination in a reaction inert solvent, where ethyl acetate, from –78 °C to 40 °C, where room temperature is preferred to afford either the *N*-acylated compounds of the general structure (8) or compounds of Formula I.

Step G:

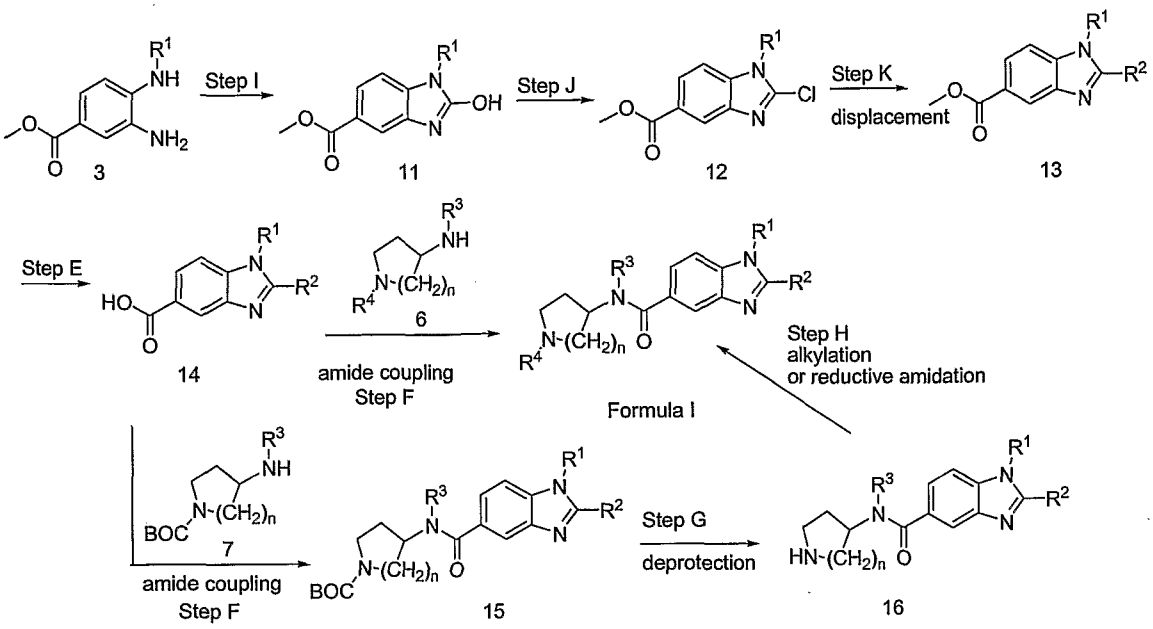
Removal of the BOC protecting group of the compound of formula (8) can be accomplished using conditions described in the literature. The preferred method of protecting group removal is by reaction of (8) in a reaction inert solvent, where methylene chloride is preferred with an acid where preferred acids are TFA, and aqueous HCl at a reaction temperature from about 0 °C to the reflux temperature of the solvent employed, where about room temperature is preferred to give a new compound of the formula (9).

Step H:

Intermediates of general formula (9) may then be reacted with aldehyde or ketone, where R^1 is defined in the specification. This can be accomplished, for example, using a procedure referred to as reductive amination which is a method well known to those skilled in the art. This method may be conducted in a single, concerted process (e.g., see A.F. Abdel-Magid, C. A. Maryanoff and K.G. Carson in Tetrahedron Letters, 1990, 39:5595-5598). Suitable solvents include, among others, tetrahydrofuran (THF) and 1,2-dichloroethane (DCE) and the reactions may be conducted with or without the addition of an organic acid (e.g., acetic acid). In such a conversion, reaction of (9) in a reaction inert solvent, where methylene chloride/DMA is preferred, with an ketone, or aldehyde, where R^1 is defined in the specification, in the presence of tetramethylammonium triacetoxyborohydride, in the presence of diisopropylethylamine, at a reaction temperature of about room temperature gives a compound of the formula I.

Alternatively, intermediates of general formula (9) may be reacted with a R^1-halide, where R^1 is defined in the specification. Reaction of (9) in ethyl alcohol, in the presence of an inorganic base, where potassium carbonate is preferred, with an R^1-halide, at a reaction temperature of about 80 °C gives a compound of the formula I.

Scheme 2



In Scheme 2, compounds of the formula (I) are prepared as follows.

Step I:

Conversion of (3) to intermediate (11) can be accomplished using standard conditions that appear in the literature. For example, Menichincheri, M. et al. (J. Med. Chem.; EN; 47; 26; 2004; 6466 – 6475) have reported the use of 1H, 1'H-1,1'-carbonyl-bis-imidazole as a reagent used to convert 1,2 diamino-phenyl moieties (3), in THF at a reaction temperature of about 0 °C to give hydroxyl-benzoimidazol of the general structure (11). Reaction of (3) with 1,1'-carbonyldiimidazole in a reaction inert solvent, where THF is preferred at a reaction temperature of about room temperature gives a compound of the general structure (11)

Step J:

Conversion of (11) to (12) can be accomplished using conditions described in the literature. The preferred method is by reaction of (11) with $POCl_3$ or $POBr_3$ in a reaction inert solvent, where 1,2-dichloroethane is preferred at a reaction temperature from about 50 °C to the reflux temperature of the solvent employed to give an intermediate of the general formula (12).

Step K:

Substitution reactions of the general conversion from (12) to amino compounds of the general formula (13) are well presented in the literature. For example, Senanayake, Chris H. et al. (Tetrahedron Lett.; EN; 40; 38; 1999; 6875 – 6880) have reported a fluoride-catalyzed TGME-mediated amination process for chloroimidazoles. Reaction of (12) in the presence of R^2, where R^2 is a primary or secondary amine as defined in the specification, in the presence

of cesium fluoride, in DMSO at a reaction temperature of about 50- 110 °C gives amino intermediates of the general structure (13).

Rotomers are possible for an embodiment of the inventive compound of formula I and are within the scope of the invention.

Conventional techniques for the preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). -

Alternatively, the racemate (or a racemic precursor) may be reacted with a suitable optically active compound, for example, an alcohol, or, in the case where the compound of formula I contains an acidic or basic moiety, an acid or base such as tartaric acid or 1-phenylethylamine. The resulting diastereomeric mixture may be separated by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.

Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to 5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the eluate affords the enriched mixture.

Stereoisomeric conglomerates may be separated by conventional techniques known to those skilled in the art - see, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel (Wiley, New York, 1994).

In the examples below the following terms are intended to have the following, general meaning:

DIPEA: diisopropylethylamine

DMF: dimethyformamide

$MgSO_4$: magnesium sulfate

DMA: dimethyl acetamide

LRMS: low resolution mass spectrometry

°C: degrees Celsius

calcd: calculated

d: day(s); doublet (spectral)

DCE: 1,2-dichloroethane

EtOAc: ethyl acetate

g: grams

hr: hours

Hz: hertz
J: coupling constant (in NMR)
L: liter(s)
LAH: lithium aluminum hydride
MHz: megahertz
Min: minute(s)
m/z : mass to charge ratio (in mass spectrometry)
obsd: observed
PPTs: pyridinium p-toluenesulfonate
TsO: p-toluenesulfonate
Rf: retention factor (in chromatography)
Rt: retention time (in chromatography)
RT: room temperature
s: singlet (NMR); second(s)
t: triplet
TFA: trifluoroacetic acid
TFAA: trifluoroacetic anhydride
THF: tetrahydrofuran
TLC: thin layer chromatography
Ts: tosyl, p-toluenesulfonyl
TsOH: p-toluenesulfonic acid
T_3P: 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphorinane-2,4,6-trioxide

Solvents were purchased and used without purification. Yields were calculated for material judged homogenous by thin layer chromatography and NMR. Thin layer chromatography was performed on plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, and stained with either an aqueous $KMnO_4$ solution or an ethanolic solution of 12-molybdophosphoric acid. Flash column chromatography unless otherwise stated, was performed with using either pre-packed Biotage™ or ISCO™ columns using the size indicated. Nuclear magnetic resonance (NMR) spectra were acquired on a Unity 400 or 500 at 400 MHz or 500 MHz for ^1H, respectively, and 100 MHz or 125 MHz for ^{13}C NMR, respectively. Chemical shifts for proton ^1H NMR spectra are reported in parts per million relative to the singlet of $CDCl_3$ at 7.24 ppm. Chemical shifts for ^{13}C NMR spectra are reported in parts per million downfield relative to the centerline of the triplet of $CDCl_3$ at 77.0 ppm. Mass spectra analyses were performed on a APCI Gilson 215, micromass ZMD (50% Acetonitrile / 50% water) spectrometer.

HPLC was performed according to the following methods:

Method A: Preparative conditions LC information: guard column Xterra Prep MS C18 Cartridge, 19x10 mm, 10um, column Xterr Prep MS 19x 50 mm, 10um. Gradients were assigned based on preQC retention times. Flow rate (combined, mL/min= 77), solvent: A (A+C =A) water + modifier; Solvent: B = acetonitrile, modifier 10mM NH3. MS make up solvent = methanol/water/FA, 90/10/0.1, MS make up flow rate, mL/min =2. Online dilution solvent = acetonitrile, online dilution flow rate, mL/min =7. Mobile Phase path information: post column modifier = no, injection solvent = DMSO, Volume = 1600 uL, Flow split: MS, UV. Detection information: MS Manufacturer/ Model = Waters, ZQ; Ionization Mode ES+; Mass range, amu =200-800;Cone Voltage (V) = 20; Capillary Voltage (V) = 3.17; source Temp. C = 140; Desolvation Temp. C= 350; Nebulization Gas (L/Hr.) = 60; Desolvation Gas (L/Hr.) =600; UV Model = Shimadzu SPD 10A, wavelength = 254 nm.

Method B: Preparative conditions LC information: guard column Waters X-terra C18 Cartridge, 19x10 mm, 10um, column Xterr Prep MS 19 x 50 mm, 10 um. Gradients were assined based on preQC retention times. Flow rate (combined, mL/min= 80), solvent: A (A+C =A) water + modifier; Solvent: B = acetonitrile, modifier = 5% ammonia, % solvent C (of total =1%). MS make up solvent = methanol/water/FA, 90/10/0.1, MS make up flow rate, mL/min = 2. Online dilution solvent = acetonitrile, online dilution flow rate, mL/min = 8. Mobile Phase path information: post column modifier = no, injection solvent = DMSO, Volume = 1000 uL, Flow split: MS, UV. Detection information: MS Manufacturer/ Model = Waters, ZQ; Ionization Mode ES+; Mass range, amu = 190-800;Cone Voltage (V) = 20; Capillary Voltage (V) = 3.3; source Temp. C = 140; Desolvation Temp. C = 350; Nebulization Gas (L/Hr.) = 100; Desolvation (L/hr) = 600; UV Model = Shimadzu SPD 10A, wavelength = 254 nm.

Method C: Preparative conditions (Waters 600 & Waters 2767 Sample Manager); Column: Waters Symmetry C_{18}, 5μm, 30 x 150 mm steel column, part # WAT248000, serial # M12921A01; solvent A – 0.1% Trifluoroacetic acid/water; solvent B – Acetonitrile; volume of injection: 850 μL; time 0.0, 90% solvent A, 10% solvent B, flow 20; time 10.0, 0% solvent A, 100% solvent B, flow 20; time 12.0, 0% solvent A, 100% solvent B, flow 20.

General Procedure A: Step 1: Amidation protocol, First, prepare a 0.2 M solution of amine (template) in anhydrous DMF, add neat TEA to aid dissolution when salt is present. Prepare a 0.2 M solution of carboxylic acid in anhydrous DMF. Prepare a 0.5 M solution of TEA in anhydrous DMF. Prepare a 0.5 M solution of HATU in anhydrous DMF. Dispense 250 µL of the 0.2 M carboxylic acid solution to appropriate vials. Dispense 300 µL of the 0.5 M TEA solution to all vials. Dispense 100 µL of the 0.5 M HATU solution to all vials. Dispense 250 µL of the 0.2 M amine (template) solution to the all vials. Cap and shake at 60 C for 18 hours (overnight). Spot Check #1, 20 µL sample diluted with 480 µL DMSO. Remove solvent

by Genevac using the DMF setting. Post Synthesis: Dispense 1000 µL of DMSO to all vials. Make sure all products are in solution. Purify using HPLC method indicated.

General Procedure B: Step 1: Amidation protocol, Scale: 100 µmol, Prepare 0.25 M solutions of acids (Monomer B) in anhydrous DMA. Prepare 0.3 M solution of Triethylamine (TEA) in anhydrous DMA/DCM=2/1 (Solution A). Prepare 0.25 M solutions of amine (template, monomer A) in solution A. Prepare 0.2 M solution of EDCI solution in anhydrous DMA/DCM (2:1). 1 M solution of HOBT in NMP is commercially available (CAS#2592-95-2). Dispense 400 µL of acid solutions into vials. Dispense 50 µL of neat N-methylmorpholine (NMM) into vials. Dispense 400 µL amine into each vial. Vortex. Dispense 150 µL HOBT solution into vials. Dispense 750 µL EDCI solution into vials. Vortex. Shake at room temperature overnight. Spot check 15 µL in 200 µL DMSO Remove solvent. Genevac. Samples can be runny and will help with solubility during workup . Workup: Prepare 50% $NaHCO_3$ that was prepared from 100% saturated $NaHCO_3$ solution. Prepare 1-Butanol/DCE = 2.5/1 solution. Dispense 2000 µL of 1-Butanol/DCE = 2.5/1 solution to vials. Vortex. Dispense 2000 µL of 50% $NaHCO_3$ solution to vials. Vortex well. Centrifuge. Transfer 1750 µL organic TOP layer to collection vial (TV = 4200 µL). Dispense 2000 µL of 1-Butanol/DCE = 2.5/1 solution to vials. Vortex. Centrifuge. Transfer 2000 µL top layer to collection vial (TV = 4450 µL). Remove solvent. Step 2: Boc-Deprotection: Add 1000 µL of methanol to vials containing intermediate. Vortex or shake at RT for 1 hour. Add 400 µL of 4.0 M HCl in dioxane. Cap. Shake vials at 25°C for 6-25 hours (up to 24 hr is ok). Remove solvent. Step 3: Reductive amination. Prepare solution of anhydrous DCE/DMA=7/3 (solution B). Prepare 2.5 M solution of aldehydes in solution B. Prepare 0.7 M suspension of tetramethylammonium triacetoxyborohydride, $NMe4[B(OAc)_3H]$ in solution B. Dispense 800 µL of solution B. Dispense 200 µL of neat DIPEA. Vortex or shake at RT for 1 h. Make sure that the oil or solid on the bottom of each vial is dissolved. Dispense 400 µL (10 equiv.) of aldehydes to vials by hand. Vortex. Add 500 µL of $NMe_4[B(OAc)_3H]$ solution to vials by hand. Vortex. Cap. Shake at RT for 16 hours (24 H is ok). Spotcheck. Remove solvent. Samples can be runny. Work-up. Prepare 50% $NaHCO_3$ solution that was prepared from 100% saturated $NaHCO_3$ solution. Prepare 1-Butanol/DCE = 2.5/1 solution. Dispense 2000 µL of 1-Butanol/DCE = 2.5/1 solution to vials. Vortex. Make sure that the oil or solid on the bottom of each vial is dissolved. Dispense 2000 µL of 50% $NaHCO_3$ solution to vials. Vortex well. Centrifuge. Transfer 1750 µL organic TOP layer to collection vial (TV = 4200 µL). Dispense 2000 µL of 1-Butanol/DCE = 2.5/1 solution to vials. Vortex. Centrifuge. Transfer 2000 µL top layer to collection vial (TV = 4450 µL). Remove solvent. Dispense 1000 µL of DMSO. Vortex to dissolve. Pull pre-QC. Submit to analytical and separation.

The following intermediates may be prepared by the procedures shown:

Intermediate 1

Methyl 4-(isobutylamino)-3-nitrobenzoate.

A 500-mL, RB flask, equipped with nitrogen gas inlet and a magnetic stirring bar was charged with methyl 4-chloro-3-nitrobenzoate (50.0 g, 231.9 mmol), KOAc (45.5 g, 463.8 mmol), isobutylamine (25.5 g, 347.9 mmol) and 120 mL of acetonitrile. The mixture was heated at 80 °C for 3 h. Then the mixture was cooled to RT and diluted with 800 mL of water, then stirred for 1 h. The precipitate was collected by filtration, washed with water (2x150 mL), then with cold ether (2x100 mL), and dried under vacuum to give 50.7 g (86 %) of pure product as a yellow solid. LCMS (M+H): 253.1, ^{1}H NMR (300 MHz, $CDCl_3$): □ 8.89 (d, J = 2.07 Hz, 1H), 8.50 (br., 1H), 8.04 (dd, J1 = 9.03 Hz, J2 = 2.07 Hz, 1H), 6.86 (d, J = 9.24 Hz, 1H), 3.90 (s, 3H), 3.18 (m, 2H), 2.04 (m, 1H), 1.07 (d, J = 6.78 Hz, 6H).

Intermediate 2

Methyl 3-amino-4-(isobutylamino)benzoate hydrochloride.

A 1 L Parr vessel, equipped with a heater, was charged with methyl 4-(isobutylamino)-3-nitrobenzoate (50.0 g, 198.2 mmol), Pd/C (10%, 5.0 g) mixed with conc. HCl (16.5 mL), and MeOH (500 mL). The mixture was hydrogenated in Parr apparatus at 50 °C and 40 psi for 1.5 h. Then the mixture was cooled to RT and the catalyst was removed by filtration through celite. Some product was left as a solid on celite cake. This product was dissolved by washing the cake with DCM/MeOH 1:1 mixture (5x200 mL). The combined filtrate was evaporated and the residue dried under vacuum to give 50.6 g (99%) of pure product as a white solid. LCMS (M+H): 223.4; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.6 (br., 2H), 7.72 (m, 2H), 6.76 (d, J = 8.64 Hz, 1H), 6.3 (br., 1H), 3.78 (s, 3H), 2.96 (d, J = 6.96 Hz, 2H), 1.92 (m, 1H), 0.98 (d, J = 6.6 Hz, 6H).

Intermediate 3

Synthesis of methyl 3-[(cyclopentylcarbonyl)amino]-4-(isobutylamino)benzoate.

A 1 L RB flask, equipped with a magnetic stirring bar, nitrogen gas inlet and septum, was charged with methyl 3-amino-4-(isobutylamino)benzoate hydrochloride (25 g, 96.7 mmol), dichloroethane (220 mL) and triethylamine (29.6 mL, 213 mmol). Then cyclopentanecarbonyl chloride (14.10 g, 106 mmol) was added dropwise via syringe. The mixture was stirring at RT for 12 h, then quenched with 200 mL of sat. $NaHCO_3$, and diluted with 500 mL of DCM. The organic layer was separated and the aqueous layer was extracted with DCM (2x100 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated to give 32.8 g (quantitative) of pure product as a white solid. LCMS (M+H): 319.4; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, J = 8.67 Hz, 1H), 7.72 (s, 1H), 6.96 (s, 1H), 6.67 (d, J = 8.85 Hz, 1H), 4.67 (br., 1H), 3.84 (s, 3H), 2.98 (m, 2H), 2.78 (m, 1H), 1.58-2.01 (m, 10H), 1.00 (d, J = 6.78 Hz, 6H).

Intermediate 4

2-Cyclopentyl-1-isobutyl-1H-benzimidazole-5-carboxylic acid.

A 250 mL RB flask, equipped with a magnetic stirring bar and reflux condenser, was charged with methyl 3-[(cyclopentylcarbonyl)amino]-4-(isobutylamino)benzoate (32.8 g, 96.7 mmol), ethanol (100 mL) and conc. HCl (20 mL). The mixture was stirring at reflux for 1.5 h. LCMS showed completed cyclization to intermediate methyl ester (LCMS: 301.0 (M+H)). Then a solution of NaOH (17.5 g, 437 mmol) in 50 mL of water was added and heated at 90 °C for 1 h. Then EtOH was evaporated under vacuum, the resulting residue was dissolved in 100 mL of water and acidified to pH 3 with conc. HCl. The precipitate was filtered, washed with water (2x50 mL), then with ether (2x50 mL), and dried under vacuum to give 27.5 g (99%) of pure product as a tan solid. LCMS (M+H): 287.0; ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.67 (s, 1H), 8.13 (s, 1H), 7.82 (d, J = 8.46 Hz, 1H), 7.64 (d, J = 8.46 Hz, 1H), 4.10 (d, J = 7.71 Hz, 2H), 3.43 (m, 1H), 2.07-2.18 (m, 3H), 1.78-1.96 (m, 4H), 1.66-174 (m, 2H), 0.88 (d, J = 6.6 Hz, 6H).

Intermediate 5

Tert-butyl 4-(pyridin-2-ylamino)piperidine-1-carboxylate.

A 1 L RB flask, equipped with a magnetic stirring bar and reflux condenser, was charged with tert-butyl 4-aminopiperidine-1-carboxylate (10.0 g, 51.43 mmol), 2-bromopyridine (16.3 g, 9.88 mL, 102.86 mmol), $Pd_2(dba)_3$ (2.82 g, 3.08 mmol), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (2.42 g, 6.17 mmol), NaOtBu (13.8 g, 144.0 mmol), and 250 mL of anhydrous dioxane. The mixture was stirred under nitrogen at 90 °C for 3 h. LCMS showed only the product. The mixture was evaporated, and the residue was dissolved in 200 mL of DCM and 200 mL of water. The mixture was extracted with DCM (3x200 mL), the extract was dried over Na_2SO_4 and evaporated to give a black residue. This residue was purified by column chromatography (DCM 97%, MeOH 2%, NH4OH 1%, Rf = 0.52 in DCM 94%, MeOH 5%, NH4OH 1%) to give 8.28 g (58 %) of pure product as a tan solid. LCMS (M+H): 278.5; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (m, 1H), 7.40 (m, 1H), 6.56 (m, 1H), 6.36 (d, J = 8.28 Hz, 1H), 4.30 (d, J = 7.53 Hz, 1H), 4.04 (m, 2H), 3.81 (m, 1H), 2.95 (m, 2H), 2.04 (m, 2H), 1.47 (s, 9H), 1.37 (m, 2H).

Intermediate 6

N-pyridin-2-yl-1-isobutyl-2-cyclopentyl-N-(1-tert-butoxycarbonylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide.

A 60 mL screw cap vial, equipped with a magnetic stirring bar, was charged with 2-cyclopentyl-1-isobutyl-1H-benzimidazole-5-carboxylic acid (2.00 g, 6.99 mmol), THF (20 mL), and DIPEA (2.71 g, 21.0 mmol). Then T_3P (3.34 g, 10.5 mmol, 6.68 mL of 50% solution in EtOAc) was added and the mixture became almost clear. The mixture was stirring for 20 min, then tert-butyl 4-(pyridin-2-ylamino)piperidine-1-carboxylate (2.32 g, 8.38 mmol) was added

and stirred at 90 °C for 12 h. LCMS showed almost completed conversion. The mixture was cooled to RT, diluted with 100 mL of sat. Na_2CO_3 and 100 mL of water, then stirred for 1 h. Then 200 mL of ether was added and stirred for 20 min. The insoluble precipitate was collected by vacuum filtration, washed with water (2x10 mL), then with cold ether (2x10 mL) and dried to give 647 mg (17%) of pure product as a tan solid. (Note: More product was contained in the organic extract that was not worked on). LCMS (M+H): 546.8; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 (m, 1H), 7.74 (s, 1H), 7.36 (m, 1H), 7.12 (d, J = 8.31 Hz, 1H), 7.01 (m, 2H), 6.75 (d, J = 7.92 Hz, 1H), 4.90 (m, 1H), 4.18 (br., 2H), 3.83 (d, J = 7.71 Hz, 2H), 3.16 (m, 1H), 2.83 (m, 2H), 1.6-2.2 (m, 13H), 1.43 (s, 9H), 0.89 (d, J = 6.6 Hz, 6H).

Example 1

Synthesis of N-pyridin-2-yl-1-isobutyl-2-cyclopentyl-N-(1-isopropylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide hydrochloride.

A 40 mL screw cap vial, equipped with a magnetic stirring bar, was charged with N-pyridin-2-yl-1-isobutyl-2-cyclopentyl-N-(1-tert-butoxycarbonylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide (644 mg, 1.18 mmol), DCM (10 mL), and TFA (4 mL). The mixture was stirring for 30 min at RT, then evaporated, coevaporated with 10 mL of EtOH and dried to give clear gum. LCMS showed complete removal of the Boc group. LCMS: 446.9 (M+H). One half of this gum (0.53 mmol) was dissolved in 4 mL of EtOH, then K_2CO_3 (732 mg, 5.3 mmol) and iPrI (104 mg, 61 μL, 0.61 mmol) was added and stirred at 80 °C for 32 h. LCMS showed presence of coeluting SM and the product. The mixture was diluted with water (10 mL) and extracted with ether (2x10 mL), then with DCM (10 mL). Organic extracts were combined, dried over Na_2SO_4 and evaporated to give 260 mg of crude residue. The crude residue was purified by column (from DCM 100% to DCM 93%, MeOH 5%, Et_3N 2%, Rf = 0.28 in upper solvent mixture) to give 82 mg of pure free base product as oil. This oil was dissolved in 3 mL of DCM, then 1 mL of 2M HCl/ether was added, evaporated and dried to give 48.6 mg (18%) of hydrochloride as a white solid. LCMS (M+H): 488.4; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.54 (br., 1H), 8.46 (s, 1H), 7.70-7.77 (m, 3H), 7.25-7.32 (m, 3H), 4.88 (m, 1H), 4.20 (d, J = 7.32 Hz, 2H), 3.62 (m, 1H), 3.39 (m, 3H), 3.17 (m, 2H), 2.11 (m, 7H), 1.90 (m, 4H), 1.70 (m, 2H), 1.24 (d, J = 6.6 Hz, 6H), 0.86 (d, J = 6.6 Hz, 6H).

Example 2

N-pyridin-2-yl-1-isobutyl-2-cyclopentyl-N-(1-ethylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide hydrochloride.

A 40 mL screw cap vial, equipped with a magnetic stirring bar, was charged with N-pyridin-2-yl-1-isobutyl-2-cyclopentyl-N-(1-tert-butoxycarbonylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide (644 mg, 1.18 mmol), DCM (10 mL), and TFA (4 mL). The mixture was stirring for 30 min at RT, then evaporated, coevaporated with 10 mL of EtOH and dried to give clear gum. LCMS showed complete removal of the Boc group. LCMS: 446.9 (M+H). One half

of this gum (0.53 mmol) was dissolved in 4 mL of EtOH, then K_2CO_3 (732 mg, 5.3 mmol) and EtI (95 mg, 50 μL, 0.61 mmol) was added and stirred at 80 °C for 32 h. LCMS showed presence of coeluting SM, product and dialkylated byproduct. The mixture was diluted with water (10 mL) and extracted with ether (2x10 mL), then with DCM (10 mL). Organic extracts were combined, dried over Na_2SO_4 and evaporated to give 253 mg of crude residue. The crude residue was purified by column chromatography (from DCM 100% to DCM 93%, MeOH 5%, Et_3N 2%, Rf = 0.28) to give 155 mg of pure free base product as white solid. This solid was dissolved in 3 mL of DCM, then 1 mL of 2M HCl/ether was added, evaporated and dried to give 162.7 mg (60%) of hydrochloride as a white solid. LCMS (M+H): 474.5; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.68 (br., 1H), 8.47 (m, 1H), 7.69-7.78 (m, 3H), 7.23-7.31 (m, 3H), 4.84 (m, 1H), 4.20 (d, J = 7.35 Hz, 2H), 3.49-3.63 (m, 3H), 3.04-3.12 (m, 3H), 1.8-2.2 (m, 12H), 1.20 (t, J = 7.25 Hz, 3H), 0.86 (d, J = 6.6 Hz, 6H).

Intermediate 7

1-Isobutyl-2-cyclopentyl-N-(1-tert-butoxycarbonylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide.

A 500 mL RB flask, equipped with a magnetic stirring bar and reflux condenser, was charged with 2-cyclopentyl-1-isobutyl-1H-benzimidazole-5-carboxylic acid (5.0 g, 17.48 mmol), THF (150 mL), DIEA (6.77 g, 52.44 mmol), and T_3P (6.67 g, 20.98 mmol, 13.3 mL of 50% solution in EtOAc). The mixture was stirring for 10 min, then tert-butyl 4-aminopiperidine-1-carboxylate (3.5 g, 17.48 mmol) was added and stirring continued at 40 °C for 1.5 h. LCMS showed 60% conversion. Then another 3.0g (14.98 mmol) of tert-butyl 4-aminopiperidine-1-carboxylate was added and stirred at 50 °C for 3.5 h. The mixture was cooled to RT, concentrated to 50 mL, diluted with 200 mL of sat Na_2CO_3 and 100 mL of water, and stirred for 1 h. The precipitate was filtered, washed and dried to give 3.9 g of pure product. After overnight, the aqueous filtrate produced an additional amount of the precipitated product, which was filtered and dried to give 0.74 g. The combined yield is 4.64 g (57%) as a white solid . LCMS (M+H): 469.4; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.16 (d, J = 7.71 Hz, 1H), 8.09 (s, 1H), 7.69 (d, J = 8.46 Hz, 1H), 7.55 (d, J = 8.46 Hz, 1H), 4.06 (d, J = 7.53 Hz, 2H), 3.92-3.97 (m, 3H), 3.39 (m, 1H), 2.85 (br., 2H), 2.00-2.17 (m, 3H), 1.77-1.95 (m, 6H), 1.62-1.70 (m, 2H), 1.35-1.45 (m, 10H), 0.87 (d, J = 6.6 Hz, 6H).

Intermediate 8

N-ethyl-1-isobutyl-2-cyclopentyl-N-(1-tert-butoxycarbonylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide.

A 100 mL RB flask, equipped with a magnetic stirring bar, was charged with 1-isobutyl-2-cyclopentyl-N-(1-tert-butoxycarbonylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide (1.0 g, 2.14 mmol) and 50 mL of anhydrous toluene. The solution was evaporated to dryness to remove residual water. The residue was dissolved in 20 mL of THF,

then $KN(SiMe_3)_2$ (0.5M solution in toluene, 6.42 mL, 3.21 mmol) was added. Then EtI (0.5 g, 0.26 mL, 3.21 mmol) was added and stirred for 2 h at RT. LCMS showed that product is formed, but it was coeluting with starting material. Then another 0.26 mL (3.21 mmol) of EtI was added and heated at 50 °C for 2 h. LCMS showed still incomplete reaction. Then another 3 mL (37.12 mmol) of EtI and 6.4 mL (3.21 mmol) of $KN(SiMe_3)_2$ was added and heated at 50 °C for 20 h. LCMS still showed a lot of starting material left. The mixture was evaporated, the residue was dissolved in 10 mL of MeOH and diluted with 100 mL of water. The gummy precipitate was collected by decantation and coevaporated two times with 20 mL of iPrOH and dried. The dry residue was dissolved in 5 mL of boiling EtOAc, cooled to RT and left overnight. The formed precipitate was collected by filtration and dried to give 172 mg (16%) of pure product. The filtrate was evaporated (no additional precipitate formed), coevaporated with toluene (2x100 mL), dried under vacuum at 80 °C and resubmitted to the same alkylation conditions and work-up to give additional 364 mg (34%) of product after recrystallizations from EtOAc. Total yield is 536 mg (50%) as a white solid. LCMS (M+H): 497.5; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.21-7.32 (m, 3H), 4.13 (br., 2H), 3.95 (d, J = 7.53 Hz, 2H), 3.40 (br., 2H), 3.25 (m, 1H), 2.56 (br., 2H), 1.92-2.28 (m, 8H), 1.71-1.75 (m, 7H), 1.45 (s, 9H), 1.16 (br., 3H), 0.97 (d, J = 6.6 Hz, 6H).

Example 3

N-ethyl-1-isobutyl-2-cyclopentyl-N-(1-isopropylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide hydrochloride.

A 20 mL screw cap vial, equipped with a magnetic stirring bar, was charged with N-ethyl-1-isobutyl-2-cyclopentyl-N-(1-tert-butoxycarbonylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide (360 mg, 0.726 mmol), DCM (4 mL), and TFA (1.2 mL). The mixture was stirring for 30 min at RT, then evaporated, coevaporated with 4 mL of EtOH and dried to give clear gum. LCMS showed complete removal of the Boc group. LCMS: 397.4 (M+H). This gum was dissolved in 6 mL of EtOH, then K_2CO_3 (995 mg, 7.2 mmol) and iPrI (184 mg, 108 μL, 1.08 mmol) was added and stirred at 80 °C for 3 h. LCMS showed that SM and product coelute. Then another 108 μL of iPrI was added and heated at 80 °C for 2 h. LCMS still showed SM. Then another 216 μL of iPrI was added and heated at 80 °C for 5 h. LCMS still showed SM, but product mass ion has most intensity. The mixture was diluted with water (20 mL) and extracted with ether (2x10 mL), then with DCM (10 mL). Organic extracts were combined, dried over Na_2SO_4 and evaporated to give 264 mg of crude oil. The crude oil was purified by Prep TLC (DCM 93%, MeOH 5%, NH_4OH 2%, Rf = 0.45) to give pure free base product as colorless oil. This oil was dissolved in 3 mL of DCM, then 1 mL of 2M HCl/ether was added, evaporated and dried to give 167 mg (49%) of hydrochloride as a white solid. LCMS (M+H): 439.5; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.36 (br., 1H), 8.00 (d, J = 6.78 Hz,

1H), 7.74 (s, 1H), 7.50 (d, J = 9.21 Hz, 1H), 4.31 (d, J = 7.35 Hz, 2H), 3.2-3.8 (m, 17H), 2.1-2.3 (m, 3H), 1.8-2.0 (m, 6H), 1.74 (m, 2H), 1.06-1.22 (m, 10H), 0.95 (d, J = 6.4 Hz, 6H).

Intermediate 9

N-methyl-1-isobutyl-2-cyclopentyl-N-(1-tert-butoxycarbonylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide.

A 40 mL screw cap vial, equipped with a magnetic stirring bar, was charged with 2-cyclopentyl-1-isobutyl-1H-benzimidazole-5-carboxylic acid (2.57 g, 9.00 mmol), THF (20 mL), and DIEA (3.48 g, 27.0 mmol). The cap was closed and the mixture was stirred at 70 °C for 30 min to form a fine suspension. Then the mixture was cooled to RT and T_3P (3.55 g, 11.16 mmol, 7.1 mL of 50% solution in EtOAc) was added and the mixture became almost clear. The mixture was stirring for 15 min, then tert-butyl 4-methylaminopiperidine-1-carboxylate (2.0 g, 9.35 mmol) was added and stirred at 70 °C for 2 h. LCMS showed almost completed conversion. The mixture was cooled to RT and evaporated under vacuum. The residue was dissolved in 200 mL of DCM, the solution was washed with 100 mL of sat Na_2CO_3, dried over Na_2SO_4 and evaporated to give

4.22 g of crude tan solid. This solid was purified by column chromatography (from DCM 100% to DCM 96%, MeOH 3%, NH_4OH 1%, Rf = 0.42 in DCM 96%, MeOH 3%, NH_4OH 1%) to give an oily product, which was dissolved in 10 mL of ether, then 70 mL of hexane was added, and the mixture was concentrated to 20 mL. The resulting precipitate was filtered and dried to give 2.42 g (56%) of pure product as a white solid. LCMS (M+H): 483.5; ^1H NMR (300 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.31 (s, 2H), 4.1-4.3 (br., 2H), 3.95 (d, J = 7.71 Hz, 2H), 3.25 (s, 1H), 2.91 (br., 3H), 1.89-2.28 (m, 8H), 1.65-1.85 (m, 8H), 1.46 (s, 9H), 0.96 (d, J = 6.78 Hz, 6H).

Example 4

N-methyl-1-isobutyl-2-cyclopentyl-N-(1-isopropylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide hydrochloride.

A 40 mL screw cap vial, equipped with a magnetic stirring bar, was charged with N-methyl-1-isobutyl-2-cyclopentyl-N-(1-tert-butoxycarbonylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide (101770-150, 1.5 g, 3.11 mmol), DCM (10 mL), and TFA (6 mL). The mixture was stirring for 30 min at RT, then evaporated, coevaporated with 10 mL of EtOH and dried to give clear gum. LCMS showed complete removal of the Boc group. LCMS: 383.5 (M+H). One half of this gum (1.55 mmol) was dissolved in 10 mL of EtOH, then K_2CO_3 (2.14 g, 15.5 mmol) and iPrI (790 mg, 465 μL, 4.65 mmol) was added and stirred at 80 °C for 3 h. LCMS showed that SM and product coelute. Then another 465 μL of iPrI was added and heated at 80 °C for 5 h. LCMS still showed SM, but product mass ion has most intensity. The mixture was diluted with water (20 mL) and extracted with ether (2x10 mL), then with DCM (10 mL). Organic extracts were combined, dried over Na_2SO_4 and evaporated to give 680 mg of crude oil. One third of the crude oil (227 mg) was purified by column chromatography (from DCM 100% to

DCM 93%, MeOH 5%, Et_3N 2%, Rf = 0.45) to give pure free base product as a white solid. This solid was dissolved in 3 mL of DCM, then 1 mL of 2M HCl/ether was added, evaporated and dried to give 208 mg (82%) of hydrochloride as a white solid. LCMS (M+H): 425.6; ^1H NMR (300 MHz, DMSO-d_6): δ 10.57 (br., 1H), 8.01 (d, J = 8.28 Hz, 1H), 7.80 (s, 1H), 7.56 (d, J = 7.71 Hz, 1H), 4.33 (d, J = 7.35 Hz, 2H), 3.6-3.8 (br., 5H), 3.3-3.5 (br., 4H), 3.1-3.2 (br., 1H), 2.7-2.9 (br., 4H), 2.3-2.5 (br., 2H), 2.1-2.3 (br., 3H), 1.8-2.0 (br., 6H), 1.74 (m, 2H), 1.2-1.3 (br., 6H), 0.95 (d, J = 6.6 Hz, 6H).

Example 5

N-methyl-1-isobutyl-2-cyclopentyl-N-(1-ethylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide hydrochloride.

A 40 mL screw cap vial, equipped with a magnetic stirring bar, was charged with N-methyl-1-isobutyl-2-cyclopentyl-N-(1-tert-butoxycarbonylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide (1.5 g, 3.11 mmol), DCM (10 mL), and TFA (6 mL). The mixture was stirring for 30 min at RT, then evaporated, coevaporated with 10 mL of EtOH and dried to give a clear gum. LCMS showed complete removal of the Boc group. LCMS: 383.5 (M+H). One half of this gum (1.55 mmol) was dissolved in 10 mL of EtOH, then K_2CO_3 (2.14 g, 15.5 mmol) and EtI (386 mg, 200 μL, 2.48 mmol) were added and stirred at 80 °C for 3 h. LCMS showed that SM and product coelute. Then another 200 μL of EtI was added and heated at 80 °C for 3 h. LCMS still showed SM, but product mass ion has most intensity, some of the dialkylated byproduct was observed as well. The mixture was diluted with water (20 mL) and extracted with ether (2x10 mL), then with DCM (10 mL). Organic extracts were combined, dried over Na_2SO_4 and evaporated to give 607 mg of crude oil. One half of the crude oil (304 mg) was purified by column (from DCM 100% to DCM 93%, MeOH 5%, Et_3N 2%, Rf = 0.45) to give pure free base product as white solid. This solid was dissolved in 3 mL of DCM, then 1 mL of 2M HCl/ether was added, evaporated and dried to give 272.8 mg (78%) of hydrochloride as a white solid. LCMS (M+H): 411.5; ^1H NMR (300 MHz, DMSO-d_6): δ 10.47 (br., 1H), 7.99 (d, J = 6.96 Hz, 1H), 7.78 (s, 1H), 7.54 (d, J = 8.1 Hz, 1H), 4.31 (d, J = 7.53 Hz, 2H), 3.4-3.8 (br., 11H), 2.7-3.1 (br., 6H), 2.1-2.3 (m, 5H), 1.8-2.0 (6H), 1.65-1.75 (m, 2H), 1.15-1.30 (br., 3H), 0.95 (d, J = 6.57 Hz, 6H).

Intermediate 10

N-ethyl-1-isobutyl-2-cyclopentyl-N-(1-tert-butoxycarbonylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide.

A 100 mL RB flask, equipped with a magnetic stirring bar, was charged with 1-isobutyl-2-cyclopentyl-N-(1-tert-butoxycarbonylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide (1.0 g, 2.14 mmol) and 50 mL of anhydrous toluene. The solution was evaporated to dryness to remove residual water. The residue was dissolved in 20 mL of THF, then $KN(SiMe_3)_2$ (0.5M solution in toluene, 6.42 mL, 3.21 mmol) was added. Then EtI (0.5 g,

0.26 mL, 3.21 mmol) was added and stirred for 2 h at RT. LCMS showed that product is formed, but it was coeluting with starting material. Then another 0.26 mL (3.21 mmol) of EtI was added and heated at 50 °C for 2 h. LCMS showed still incomplete reaction. Then another 3 mL (37.12 mmol) of EtI and 6.4 mL (3.21 mmol) of $KN(SiMe_3)_2$ was added and heated at 50 °C for 20 h. LCMS still showed a lot of starting material left. The mixture was evaporated, the residue was dissolved in 10 mL of MeOH and diluted with 100 mL of water. The gummy precipitate was collected by decantation and coevaporated two times with 20 mL of iPrOH and dried. The dry residue was dissolved in 5 mL of boiling EtOAc, cooled to RT and left overnight. The formed precipitate was collected by filtration and dried to give 172 mg (16%) of pure product. The filtrate was evaporated (no additional precipitate formed), coevaporated with toluene (2x100 mL), dried under vacuum at 80 °C and resubmitted to the same alkylation conditions and work-up to give additional 364 mg (34%) of product after recrystallizations from EtOAc. Total yield is 536 mg (50%) as a white solid. LCMS (M+H): 497.5; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 (s, 1H), 7.21-7.32 (m, 3H), 4.13 (br., 2H), 3.95 (d, J = 7.53 Hz, 2H), 3.40 (br., 2H), 3.25 (m, 1H), 2.56 (br., 2H), 1.92-2.28 (m, 8H), 1.71-1.75 (m, 7H), 1.45 (s, 9H), 1.16 (br., 3H), 0.97 (d, J = 6.6 Hz, 6H).

Example 6

N-ethyl-1-isobutyl-2-cyclopentyl-N-(1-ethylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide hydrochloride.

A 20 mL screw cap vial, equipped with a magnetic stirring bar, was charged with N-ethyl-1-isobutyl-2-cyclopentyl-N-(1-tert-butoxycarbonylpiperidin-4-yl)-1H-benzimidazole-5-carboxamide (168 mg, 0.33 mmol), DCM (2 mL), and TFA (0.6 mL). The mixture was stirring for 1 h at RT, then evaporated and dried to give clear gum. LCMS showed complete removal of the Boc group. LCMS: 397.4 (M+H). This gum was dissolved in 3 mL of EtOH, then K_2CO_3 (456 mg, 3.3 mmol) and EtI (51 mg, 27 μL, 0.33 mmol) was added and stirred at 75 °C for 2 h. LCMS showed that SM and product coelute, but ion peak of product was more intense. Then another 15 μL of EtI was added and heated at 80 °C for 1 h. LCMS showed mostly product and very little of SM. The mixture was diluted with water (10 mL) and extracted with ether (2x10 mL), then with DCM (10 mL). Organic extracts were combined, dried over Na_2SO_4 and evaporated to give 160 mg of crude oil. The crude oil was purified by Prep TLC (DCM 93%, MeOH 5%, NH_4OH 2%, Rf = 0.45) to give 126 mg (90%) of product as colorless oil. This oil was dissolved in 2 mL of ether and 1 mL of DCM, then 0.6 mL of 2M HCl/ether was added, evaporated and dried to give 130 mg of hydrochloride as a white solid. LCMS (M+H): 425.3; ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.32 (br., 1H), 7.98 (m, 1H), 7.73 (s, 1H), 7.45 (m, 1H), 4.30 (m, 2H), 3.2-3.8 (m, 14H), 2.9-3.1 (m, 3H), 2.1-2.3 (m, 4H), 1.8-2.0 (m, 5H), 1.74 (m, 2H), 1.06-1.22 (m, 6H), 0.94 (d, J = 6.6 Hz, 6H).

Intermediate 11

Methyl 3-Nitro-4-(propylamino)benzoate.

Methyl 4-chloro-3-nitrobenzoate (80.0 g, 0.371 mol) was dissolved in recently distilled acetonitrile (400 mL) under stirring. Sodium acetate (61.0 g, 0.744 mol) and then propylamine (32.49 g, 0.55 mol) and distilled water (30 mL) were added to this solution under vigorous stirring, and the obtained mixture was refluxed for 17 h, during which time the course of the reaction was monitored by TLC (dichloromethane). The yellow reaction mixture was concentrated under reduced pressure to remove MeCN (200 mL). The residue was cooled and diluted with cold water (1.5 L). The obtained yellow precipitate was triturated in aqueous suspension, separated by filtration, washed with cold water (2 × 500 mL) and dried to give the title compound as bright yellow powder in 86.1 g, (97.4%) yield.

Intermediate 12

Methyl 3-amino-4-(propylamino)benzoate.

Methyl 3-nitro-4-(propylamino)benzoate (60.0 g, 0.252 mol) was dissolved under vigorous stirring in anhydrous 1,2-dimethoxyethane (400 mL). Activated charcoal (3.0 g) was added to the solution, and the obtained suspension was refluxed for 2 h and then cooled to 30 °C. The catalyst Pd/C (10%) (1.8 g) was then added to the mixture, and the latter was heated to 45 °C. Hydrazine monohydrate (37.8 g, 0.755 mol) was carefully added dropwise to the warm reaction mixture under vigorous stirring within 3 h. The mixture was then refluxed for 7.5 h . The catalyst was removed by filtration using Celite, which was washed with methanol (2 L). The filtrate was concentrated under reduced pressure. The residue was diluted with benzene (400 mL), and the mixture was concentrated under reduced pressure (to remove water). This operation was repeated using toluene (1 L) and then dioxane (300 mL) to furnish 56.8 g of the title compound as an almost black viscous mass.

Intermediate 13

Methyl 2-oxo-1-propyl-2,3-dihydro-1*H*-benzimidazole-5-carboxylate.

Methyl 3-amino-4-(propylamino)benzoate (56.8 g, ~0.27 mol) was dissolved in anhydrous dioxane (300 mL). 1,1'-Carbonyldiimidazole (CDI; 49.95 g, 0.308 mol) was added to this solution in several small portions with stirring. The reaction mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was dissolved in chloroform (1 L). The obtained solution was washed with 15% (w/w) HCl (2 × 400 mL) and then with water (2 × 400 mL), dried over $CaCl_2$ and concentrated under reduced pressure. The product was recrystallized from acetonitrile to give the title compound as a light-pink powder in 70.5% (41.8 g) yield.

Intermediate 14

Methyl 2-bromo-1-propyl-1*H*-benzimidazole-5-carboxylate.

Phosphoryl bromide ($POBr_3$) (73.4 g, 0.256 mol) was dissolved in dichloroethane (300 mL). Methyl 2-oxo-1-propyl-2,3-dihydro-1*H*-benzimidazole-5-carboxylate (30.0 g, 0.128 mol) was added to this solution in several small portions with stirring, and the obtained mixture was refluxed until TLC (chloroform/methanol 30:1) indicated disappearance (~24 h) of the starting material. Then the reaction mixture was carefully diluted with ice-water with cooling and then neutralized with solid Na_2CO_3 to reach pH 7. The obtained mixture was diluted with dichloromethane (to reach a volume of organic layer ~2 L). The organic layer was separated and washed with brine (1 L) and water (2 × 600 mL). The final emulsion was dried over $MgSO_4$ and then Na_2SO_4. The organic solution was concentrated under reduced pressure to give a pale-gray solid, which was then placed onto a column containing silica gel (750 g). The target product was removed with chloroform (~2 L). The filtrate was concentrated under reduced pressure to furnish the title compound as a white solid in 83% (31.5 g) yield.

Intermediate 15

Methyl 2-morpholin-4-yl-1-propyl-1*H*-benzimidazole-5-carboxylate.

A mixture of Methyl 2-bromo-1-propyl-1*H*-benzimidazole-5-carboxylate (15.0 g, 0.05 mol), morpholine (10.7 g, 0.123 mol), Cs_2CO_3 (23.0 g, 0.071 mol), CsF (10.7 g, 0.071 mol), and DMSO (150 mL) was placed into a reactor vessel of a MILESTONE Microwave Labstation. The reaction mixture was irradiated with microwaves with stirring at an internal temperature of 110 °C for 5 h. The reaction mixture was then decanted from precipitated inorganic salts, and the latter was washed with chloroform (2 × 200 mL). The organic mother liquid (DMSO-solution) was diluted with water
(600 mL), and the product was extracted with chloroform (2 × 250 mL). The combined chloroform extracts were washed with brine (2 × 150 mL), dried over $CaCl_2$ and concentrated under reduced pressure. The residue was placed onto a column containing silica gel, and the product was eluted using hexane/ethyl acetate (5:1), then (3:1) and finally (1:1) mixture under TLC control. The extracts were combined and concentrated under reduced pressure to give the title compound in 61.8% (18.29 g) yield.

Intermediate 16

2-Morpholin-4-yl-1-propyl-1*H*-benzimidazole-5-carboxylic Acid.

A solution of Methyl 2-morpholin-4-yl-1-propyl-1*H*-benzimidazole-5-carboxylate (18.29 g, 0.0603 mol) in methanol (60 mL) was mixed with 2 N aqueous NaOH (60 mL). The mixture was stirred at 50 °C for 70 min. The reaction mixture was cooled and concentrated under reduced pressure to remove methanol. The residue was acidified using 10% aqueous

solution of citric acid (~170 mL) to reach pH 3.5-4. The white precipitate that formed was separated by filtration, washed with water and dried. The crude product was mixed with dioxane (150 mL), and the solvent was evaporated under reduced pressure to remove water. This operation was repeated twice to give **7** as a white crystalline solid in 93.4% (16.3 g) yield. LRMS m/z Calcd for C15 H19 N3 O3 289.3; obsd LCMS APCI (M+1) m/z 290.3.

Intermediate 17

Methyl 2-(3-hydroxypiperidin-1-yl)-1-propyl-1*H*-benzimidazole-5-carboxylate.

A mixture of Methyl 2-bromo-1-propyl-1*H*-benzimidazole-5-carboxylate (38.0 g, 0.128 mol), piperidin-3-ol (31.0 g, 0.307 mol), Cs_2CO_3 (58.33 g, 0.179 mol), CsF (27.2 g, 0.179 mol), and DMSO (300 mL) was placed into a reactor vessel of a MILESTONE Microwave Labstation. The reaction mixture was irradiated with microwaves with stirring at an internal temperature of 110 °C for 7 h. The reaction mixture was then decanted from the precipitated inorganic salts, and the latter was washed with dichloromethane (2 × 150 mL). The rinsing liquid was mixed with organic mother liquid (DMSO-solution), and the combined solution was diluted with aqueous 15% solution of citric acid to reach pH 3. The aqueous layer was extracted with dichloromethane (4 × 250 mL) and then with chloroform (4 × 250 mL). The combined extracts were washed with brine (2 × 150 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was placed into a column containing silica gel, and the product was eluted with ethyl acetate under TLC control. The extracts were combined and concentrated under reduced pressure to give the title compound in 70% (28.6 g) yield.

Intermediate 18

2-(3-Hydroxypiperidin-1-yl)-1-propyl-1*H*-benzimidazole-5-carboxylic Acid Hydrate.

A solution of Methyl 2-(3-hydroxypiperidin-1-yl)-1-propyl-1*H*-benzimidazole-5-carboxylate (25.4 g, 0.08 mol) in methanol (80 mL) was mixed with 2 N aqueous NaOH (80 mL). The mixture was refluxed under stirring for 2 h. The reaction mixture was cooled and concentrated under reduced pressure to remove methanol. The residue was acidified using 10% aqueous solution of citric acid to reach pH 3 and placed into an ice-bath. The white precipitate that formed was separated by filtration, washed with water and dried. The crude product was mixed with dioxane (150 mL), and the solvent was evaporated under reduced pressure to remove water. This operation was repeated twice to give **7** as a white crystalline solid in 97% (23.5 g) yield. LRMS m/z Calcd for C16 H31 N3 O3 303.4; obsd LCMS APCI (M+1) m/z 304.3.

Intermediate 19

Methyl 4-[(Cyclopropylmethyl)amino]-3-nitrobenzoate.

Methyl 4-chloro-3-nitrobenzoate (80.0 g, 0.371 mol) was suspended in freshly distilled acetonitrile (400 mL) under stirring. Sodium acetate (61.0 g, 0.744 mol) and then (cyclopropylmethyl)amine (39.4 g, 0.554 mol) were added to this solution under vigorous stirring, and the obtained mixture was refluxed for 26 h, during which time the course of the reaction was monitored by TLC (chloroform). The yellow reaction mixture was concentrated under reduced pressure to remove MeCN (200 mL). The residue was cooled and diluted with cold water (1500 mL). The obtained yellow precipitate was triturated in aqueous suspension, separated by filtration, washed with cold water (2 × 500 mL) and dried to give the title compound as a bright yellow powder in 97.7% (90.7 g) yield.

Intermediate 20

Methyl 3-amino-4-[(cyclopropylmethyl)amino]benzoate .

Methyl 4-[(cyclopropylmethyl)amino]-3-nitrobenzoate (60.1 g, 0.24 mol) was suspended under vigorous stirring in anhydrous methanol (700 mL). A suspension of freshly prepared (by treatment of nickel-aluminum 50/50 alloy with 2 N aq. NaOH) Raney nickel (25 g) in methanol (50 mL) was then added to the solution of starting material. The resulting mixture was heated to 40-45 °C under vigorous stirring, and hydrazine monohydrate (30 mL) was added dropwise to the suspension over 1 h, keeping the temperature below 55 °C. The mixture was refluxed for 2.5 h (to complete the reaction and decompose any excessive hydrazine), then cooled and diluted with chloroform (700 mL). The obtained suspension was passed through a column (15 cm in diameter) of Celite (upper layer 1 cm) and silica gel (lower layer 3 cm). The layers were washed with a chloroform/methanol (1:1) mixture (3.5 L). The filtrate was concentrated under reduced pressure. The residue was diluted with benzene (400 mL), and the mixture was concentrated under reduced pressure (to remove water). This operation was repeated to furnish 53.9 g of **3** as a dark-brown solid.

Intermediate 21

Methyl 1-(cyclopropylmethyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-5-carboxylate.

The Methyl 3-amino-4-[(cyclopropylmethyl)amino]benzoate (53.9 g, ~0.245 mol) was dissolved in anhydrous dioxane (400 mL). 1,1'-Carbonyldiimidazole (CDI; 51.7 g, 0.319 mol) was added to this solution in several small portions under stirring. The reaction mixture was

stirred at room temperature for 6 h and then stirred overnight. The solvent was removed under reduced pressure, and the residue was mixed with water (1 L). The obtained mixture was diluted with dissolved HCl (1:1) (200 mL) to reach
pH 2. The formed precipitate was separated by filtration, washed with water (3 × 200 mL), hexane/ether (1:1) mixture (2 × 500 mL) and then with neat ether (500 mL) and dried to give the title compound as a light-pink powder in 94% (56.6 g) yield.

Intermediate 22

Methyl 2-bromo-1-(cyclopropylmethyl)-1*H*-benzimidazole-5-carboxylate.

Phosphoryl bromide ($POBr_3$; 100.4 g, 0.35 mol) was dissolved in dichloroethane (300 mL). Methyl 1-(cyclopropylmethyl)-2-oxo-2,3-dihydro-1*H*-benzimidazole-5-carboxylate (41.0 g, 0.166 mol) was added to this solution in several small portions under stirring, and the obtained mixture was refluxed until TLC (chloroform/methanol 20:1) indicated disappearance of the starting material. After the reaction was completed
(~25 h), the reaction mixture was carefully diluted with ice-water under cooling and then neutralized with solid Na_2CO_3 to reach pH 7. The obtained mixture was diluted with dichloromethane to increase the volume of the organic layer to ~2.5 L. The organic layer was separated and washed with brine (1 L) and water (2 × 500 mL). The final emulsion was dried over $MgSO_4$ and then over Na_2SO_4. The organic solution was concentrated under reduced pressure to give pale-gray solid that was placed onto a column containing silica gel (1 kg), and eluted with chloroform (~2 L). The filtrate was concentrated under reduced pressure to furnish the title compound as a white solid in 75% (38.6 g) yield.

Intermediate 23

Methyl 1-(cyclopropylmethyl)-2-(2-methylpiperidin-1-yl)-1*H*-benzimidazole-5-carboxylate.

A mixture of Methyl 2-bromo-1-(cyclopropylmethyl)-1*H*-benzimidazole-5-carboxylate (36.0 g, 0.116 mol), 2-methylpiperidine (27.7 g, 0.28 mol), Cs_2CO_3 (53.11 g, 0.163 mol), CsF (24.76 g, 0.163 mol), and DMSO (300 mL) was placed into a reactor vessel of a MILESTONE Microwave Labstation. The reaction mixture was irradiated with microwaves under stirring at 110 °C for 9 h. The reaction mixture was then decanted from the precipitated inorganic salts and diluted with aqueous 10% solution of citric acid (1.2 L). The product was extracted with chloroform (4 × 300 mL). Combined chloroform extracts were washed with brine (2 × 150 mL), dried over $CaCl_2$ and concentrated under reduced pressure. The residue was placed onto a column containing silica gel, and the product was eluted using a hexane/ethyl acetate (3:1)

mixture (TLC control). The product fractions were combined and concentrated under reduced pressure to give the title compound as a yellow syrup in 87% (33.2 g) yield.

Intermediate 24

1-(Cyclopropylmethyl)-2-(2-methylpiperidin-1-yl)-1*H*-benzimidazole-5-carboxylic Acid Hydrate.

A solution of Methyl 1-(cyclopropylmethyl)-2-(2-methylpiperidin-1-yl)-1*H*-benzimidazole-5-carboxylate (33.2 g, 0.101 mol) in methanol (120 mL) was mixed with 2 N aqueous NaOH (150 mL). The mixture was refluxed for 1 h. The reaction mixture was cooled and concentrated under reduced pressure to remove methanol. The residue was acidified using 10% aqueous citric acid (~170 mL) to reach pH 3.5-4. The formed white precipitate was separated by filtration, washed with water and dried. The obtained crude product was mixed with dioxane (150 mL), and the solvent was evaporated under reduced pressure to remove water. This operation was repeated twice to give **8** as white crystalline solid in 72% (22.9 g) yield. LRMS m/z Calcd for C18 H23 N3 O2 313.4; obsd LCMS APCI (M+1) m/z 314.3.

Intermediate 25

Methyl 4-(Methylamino)-3-nitrobenzoate.

Methyl 4-chloro-3-nitrobenzoate (72.01 g, 0.334 mol) was suspended in freshly distilled acetonitrile (360 mL) under stirring. Anhydrous sodium acetate (41.1 g, 0.5 mol) and then a 30% w/w aqueous solution of methylamine (69 mL, 0.67 mol) were added to this suspension under vigorous stirring. The obtained mixture was refluxed for 7 h while the course of the reaction was monitored by TLC (chloroform/CCl_4 1:2). The yellow precipitate was separated by filtration and mixed with a solution of K_2CO_3 (25 g) in water (500 mL). The mixture was stirred for 30 min and then filtered. The yellow precipitate was washed with water to attain pH 7. The filtrate was concentrated under reduced pressure to a volume of ~200 mL and then mixed with a solution of K_2CO_3 (5 g) in water (100 mL). The mixture was stirred for 30 min and then filtered. The yellow precipitate was washed with water to attain pH 7. Two above precipitates were combined and dried to give the title compound as a yellow powder in 96% (67.63 g) yield.

Intermediate 26

Methyl 3-amino-4-(methylamino)benzoate.

Methyl 4-(methylamino)-3-nitrobenzoate (63.06 g, 0.3 mol) was suspended under vigorous stirring in methanol (700 mL). A suspension of Raney nickel (15 g, freshly prepared by treatment of nickel/aluminum 50:50 alloy with aq. 2N NaOH) in methanol (30 mL) was added to the suspension. The resulting mixture was heated to 40-45°C under vigorous stirring, and hydrazine monohydrate (60 mL, 1.2 mol) was added dropwise to the suspension for 3 h. The temperature of the reaction mixture was kept below 55°C. The obtained mixture was stirred at 50-55°C for 3 h and then kept overnight at room temperature. The reaction mixture was heated again to 40-45°C under vigorous stirring, and additional amount of hydrazine hydrate (5 mL) was added to the mixture. The suspension was refluxed for 2 h under vigorous stirring, then cooled, and diluted with chloroform (1000 mL). The mixture was passed through Celite (the upper layer 2 cm thick, the diameter of 17 cm) and silica gel (the lower layer 5 cm) to remove Raney nickel. The layers were washed with the chloroform/methanol 1:1 mixture (5 x 600 mL). The filtrate was concentrated under reduced pressure. The residue was diluted with benzene (100 mL), and the mixture was concentrated under reduced pressure to remove water. This operation was repeated to give the title compound as a brown crystalline solid in 99% (53.6 g) yield.

Intermediate 27

Methyl 1-methyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-5-carboxylate.

Methyl 3-amino-4-(methylamino)benzoate (53.6 g, 0.3 mol) was dissolved in anhydrous dichloromethane (700 mL). 1,1'-Carbonyldiimidazole (CDI) (62.59 g, 0.386 mol) was added to this solution in several small portions under stirring for 2 h. The reaction mixture was stirred at room temperature overnight. The formed precipitate was separated by filtration, washed with cold ether (3 × 50 mL), and dried to give the title compound as light-pink crystals in 81% (49.75 g) yield.

Intermediate 28

Methyl 2-bromo-1-methyl-1*H*-benzimidazole-5-carboxylate .

Phosphoryl bromide ($POBr_3$) (102.4 g, 0.357 mol) was dissolved in dichloroethane (400 mL). Methyl 1-methyl-2-oxo-2,3-dihydro-1*H*-benzimidazole-5-carboxylate (36.7 g, 0.178 mol) was added to this solution in several small portions under stirring, and the obtained suspension was refluxed until the starting substance disappeared (TLC monitoring, chloroform/1,2-dimethoxyethane 10:1). After the reaction was completed (approximately 19 h), the reaction mixture was cooled on an ice-bath and then carefully neutralized for 3 h with water (50 mL) and then with a solution of Na_2CO_3 (100 g) in water (800 mL) (strong foaming!).

The obtained mixture was extracted with chloroform (2 L). The layers were separated, and the aqueous layer was extracted again with chloroform (500 mL). The organic layers were combined, washed with water (3 × 250 mL), and dried over $CaCl_2$. The organic solution was concentrated under reduced pressure to give a pale-gray solid that was recrystallized from acetonitrile to give the title compound as white solid in 77.5% (37.1 g) yield.

Intermediate 29

Methyl 2-{[(1*R*)-1,2-dimethylpropyl]amino}-1-methyl-1*H*-benzimidazole-5-carboxylate.

A mixture of Methyl 2-bromo-1-methyl-1*H*-benzimidazole-5-carboxylate (32.2 g, 0.12 mol), [(1*R*)-1,2-dimethylpropyl]amine (25.0 g, 0.287 mol), cesium fluoride CsF (25.4 g, 0.167 mol), and DMSO (240 mL) was placed into a reactor of a MILESTONE Microwave Labstation. The reaction mixture was irradiated with microwaves under stirring at 110 °C for 9 h. Then the reaction mixture was poured into ice-cold water (1.5 L) with stirring. The obtained mixture was acidified with citric acid to attain pH 5, and the product was extracted with chloroform (3 × 400 mL). The extract was washed with water (2 × 200 mL) and with the 5% NaCl aqueous solition (2 × 100 mL), and dried over $CaCl_2$. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (800 g), chloroform/1,2-dimethoxyethane 20:1 → 5:2 (TLC monitoring). The product fractions were combined and concentrated under reduced pressure to give the title compound as a white crystal solid in 65% (21.43 g) yield.

Intermediate 30

2-{[(1*R*)-1,2-Dimethylpropyl]amino}-1-methyl-1*H*-benzimidazole-5-carboxylic Acid.

A suspension of Methyl 2-{[(1*R*)-1,2-dimethylpropyl]amino}-1-methyl-1*H*-benzimidazole-5-carboxylate (21.4 g, 0.078 mol) in methanol (100 mL) was mixed with a solution of KOH (8.7 g, 0.155 mol) in water (100 mL). The mixture was refluxed for 2 h. The reaction mixture was cooled and concentrated under reduced pressure to remove methanol. The residue was mixed with a solution of $KHSO_4$ (21.14 g, 0.155 mol) in water (150 mL). The mixture was stirred for 2 h and kept overnight at room temperature. The formed precipitate was separated by filtration, washed with water (2 × 250 mL) and hexane (2 × 250 mL), and dried to give the title compound as a white crystal solid in 91% (18.5 g) yield. LRMS m/z Calcd for C14 H19 N3 O2 261.3; obsd LCMS APCI (M+1) m/z 262.1.

Intermediate 31

Methyl 2-[(2,2-dimethylpropyl)amino]-1-methyl-1*H*-benzimidazole-5-carboxylate.

A mixture of Methyl 2-bromo-1-methyl-1*H*-benzimidazole-5-carboxylate (35.0 g, 0.13 mol), neopentylamine (27.23 g, 0.312 mol), cesium fluoride CsF (27.68 g, 0.182 mol), and DMSO (260 mL) was placed into a reactor of a MILESTONE Microwave Labstation. The reaction mixture was irradiated with microwaves under stirring at 115 °C for 7 h. The reaction mixture was poured into ice/water mixture (1.4 L) under stirring. The white precipitate was separated by filtration, washed with water, and dried to give the title compound in 98% (35.0 g) yield.

Intermediate 32

2-[(2,2-Dimethylpropyl)amino]-1-methyl-1*H*-benzimidazole-5-carboxylic Acid Dihydrate.

A suspension of Methyl 2-[(2,2-dimethylpropyl)amino]-1-methyl-1*H*-benzimidazole-5-carboxylate (35.0 g, 0.127 mol) in methanol (150 mL) was mixed with a solution of KOH (14.36 g, 0.256 mol) in water (150 mL). The mixture was refluxed for 3 h, cooled, and concentrated under reduced pressure to remove methanol. The residue was diluted with water (150 mL) and neutralized with a solution of $KHSO_4$ (34.87 g, 0.256 mol) in water (150 mL) to attain pH 4. The white precipitate was separated by filtration, washed with water (2 × 250 mL), hexane (3 × 300 mL), and dried to give the title compound as a white crystalline solid in 99% (33.1 g) yield. LRMS m/z Calcd for C14 H19 N3 O2 261.3; obsd LCMS APCI (M+1) m/z 262.1.

Intermediate 33

Methyl 2-[(*trans*-4-hydroxycyclohexyl)amino]-1-methyl-1*H*-benzimidazole-5-carboxylate.

A mixture of Methyl 2-bromo-1-methyl-1*H*-benzimidazole-5-carboxylate (37.0 g, 0.137 mol), *trans*-4-aminocyclohexanol (38.0 g, 0.33 mol), cesium fluoride CsF (29.24 g, 0.29 mol), and DMSO (350 mL) was stirred at 110 °C for 6 h and kept overnight at room temperature (TLC control, silica gel, chloroform/ethanol 20:1). The reaction mixture was poured into cold water (1.5 L). The precipitate was separated by filtration and recrystallized from acetonitrile (900 mL) to give the title compound in 84% (35.0 g) yield.

Intermediate 34

2-[(*trans*-4-Hydroxycyclohexyl)amino]-1-methyl-1*H*-benzimidazole-5-carboxylic Acid Hydrate.

A suspension of Methyl 2-[(*trans*-4-hydroxycyclohexyl)amino]-1-methyl-1*H*-benzimidazole-5-carboxylate (35.0 g, 0.115 mol) in methanol (200 mL) was mixed with a solution of KOH (13.03 g, 0.233 mol) in water (200 mL). The mixture was stirred at 55–60 °C for 5 h. The reaction mixture was cooled and concentrated under reduced pressure to remove methanol. The residue was mixed with a solution of $KHSO_4$ (31.64 g, 0.233 mol) in water (100 mL). The mixture was stirred for 2 h and kept overnight at room temperature. The formed precipitate was separated by filtration, washed with water (3 × 100 mL), hexane (3 × 200 mL), and dried to give the title compound as a white crystalline solid in 93% (31.0 g) yield. LRMS m/z Calcd for C15 H19 N3 O3 289.3; obsd LCMS APCI (M+1) m/z 290.1.

Intermediate 35

Methyl 2-[benzyl(methyl)amino]-1-methyl-1*H*-benzimidazole-5-carboxylate.

A mixture of Methyl 2-bromo-1-methyl-1*H*-benzimidazole-5-carboxylate (31.0 g, 0.115 mol), benzyl(methyl)amine (33.5 g, 0.277 mol), cesium fluoride (24.5 g, 0.161 mol), and DMSO (250 mL) was stirred at 110–115 °C for 7 h in a flask equipped with a KOH tube to protect the mixture from atmospheric CO_2 and kept overnight at room temperature. The reaction mixture was poured into ice-cold water (750 mL). The oily precipitate rapidly solidified. The solid was separated by filtration, washed with water, and mixed with acetonitrile (500 mL). The mixture was concentrated under a reduced pressure to remove residual water. The residue was triturated with ether (200 mL). The mixture was filtered to remove a white precipitate, and the clear filtrate was evaporated to give the title compound as a pale-yellow solid in 79% (28.17 g) yield.

Intermediate 36

2-[Benzyl(methyl)amino]-1-methyl-1*H*-benzimidazole-5-carboxylic Acid Hydrate.

A suspension of Methyl 2-[benzyl(methyl)amino]-1-methyl-1*H*-benzimidazole-5-carboxylate (28.17 g, 0.091 mol) in methanol (50 mL) was mixed with a solution of KOH (10.2 g, 0.182 mol) in water (200 mL). The mixture was refluxed for 2.5 h, cooled, and concentrated under a reduced pressure to remove methanol. The residue was diluted with water (300 mL) and neutralized with a solution of $KHSO_4$ (24.78 g, 0.182 mol) in water (200 mL) to attain pH 4. The white precipitate was separated by filtration, washed with water (2 × 300 mL), hexane

(2 × 200 mL), and dried to give the title compound as a white crystalline solid in 97% (27.7 g) yield. LRMS m/z Calcd for C17 H17 N3 O2 295.3; obsd LCMS APCI (M+1) m/z 296.1.

Intermediate 37

Methyl 1-methyl-2-[(2-phenylethyl)amino]-1*H*-benzimidazole-5-carboxylate.

A mixture of Methyl 2-bromo-1-methyl-1*H*-benzimidazole-5-carboxylate (30.0 g, 0.111 mol), phenethylamine (32.4 g, 0.267 mol), cesium fluoride (23.7 g, 0.156 mol), and DMSO (240 mL) was stirred at 110–115 °C for 8 h. The reaction mixture was cooled and poured into ice-cold water (1.25 L) under stirring. The sticky precipitate was separated by decantation, washed with water, and dissolved in chloroform (1.8 L). The aqueous layer was extracted with chloroform (3 × 300 mL). The organic extracts were combined, washed with a 10% aqueous solution of citric acid (2 × 900 mL), and dried over Na_2SO_4. The inorganic precipitate was separated by filtration and washed with chloroform (180 mL). The combined extracts were concentrated under a reduced pressure to give the title compound as a viscous yellow oil in 94% (32.57 g) yield.

Intermediate 38

1-Methyl-2-[(2-phenylethyl)amino]-1*H*-benzimidazole-5-carboxylic Acid.

A suspension of Methyl 1-methyl-2-[(2-phenylethyl)amino]-1*H*-benzimidazole-5-carboxylate (32.57 g, 0.105 mol) in methanol (100 mL) was mixed with a solution of KOH (15.0 g, 0.27 mol) in water (100 mL). The mixture was refluxed for 12 h with TLC monitoring (silica gel, chloroform/1,2-dimethoxyethane 10:1), cooled, and concentrated under a reduced pressure to remove methanol. The residue (approximately 100 mL) was diluted with water (200 mL). The mixture was filtered through cotton to remove a brown oily precipitate. The pale-yellow turbid filtrate was diluted with a solution of $KHSO_4$ (32.9 g, 0.24 mol) in water (100 mL) to attain pH ~4. The white precipitate was separated by filtration, washed with water (2 × 250 mL), acetone (50 mL), and dried to give the title compound as a pale-yellow crystalline solid in 73% (22.72 g) yield. LRMS m/z Calcd for C17 H17 N3 O2 295.3; obsd LCMS APCI (M+1) m/z 296.1.

Intermediate 39

Methyl 1-methyl-2-pyrrolidin-1-yl-1*H*-benzimidazole-5-carboxylate.

A mixture of Methyl 2-bromo-1-methyl-1*H*-benzimidazole-5-carboxylate (40.0 g, 0.149 mol), pyrrolidine (25.37 g, 30 mL, 0.357 mol), cesium fluoride CsF (31.61 g,

0.208 mol), and DMSO (240 mL) was placed into a reactor of a MILESTONE Microwave Labstation. The reaction mixture was irradiated with microwaves under stirring at an internal temperature of 115 °C for 8 h, cooled, and poured into ice-cold water (1 L). The formed precipitate was separated by filtration, washed with cold water (2 × 50 mL), hexane (2 × 100 mL), and dried. The product was mixed with ether (250 mL) and acetonitrile (20 mL), and the mixture was placed into an ultrasonic bath for 1.5 h. The precipitate was separated by filtration, washed with ether (2 × 50 mL), and dried to give the title compound in 75% (28.82 g) yield.

Intermediate 40

1-Methyl-2-pyrrolidin-1-yl-1*H*-benzimidazole-5-carboxylic Acid.

A suspension of Methyl 1-methyl-2-pyrrolidin-1-yl-1*H*-benzimidazole-5-carboxylate (28.8 g, 0.111 mol) in methanol (200 mL) was mixed with a solution of KOH (12.44 g, 0.222 mol) in water (200 mL). The mixture was refluxed for 3 h and kept overnight at room temperature. The reaction mixture was concentrated under a reduced pressure to remove methanol. The residue was mixed with a solution of $KHSO_4$ (30.21 g, 0.222 mol) in water (200 mL), and the mixture was stirred for 1 h. The reaction mixture was concentrated under a reduced pressure to dryness, and the product was extracted from the solid residue with a warm mixture of chloroform and isopropanol (1:1, ~7 L). The obtained extract was concentrated under a reduced pressure, and the residue was dissolved in a boiling mixture of dichloromethane and isopropanol (1:1, 500 mL). The solution was refluxed for 30 min and cooled in a freezer. The formed precipitate was separated by filtration and dried to give the title compound as a pale-yellow crystalline solid in 67% (18.3 g) yield. LRMS m/z Calcd for C13 H15 N3 O2 245.3; obsd LCMS APCI (M+1) m/z 246.2.

Intermediate 41

Methyl 1-(cyclopropylmethyl)-2-{[(1*S*)-2-methoxy-1-methylethyl]amino}-1*H*-benzimidazole-5-carboxylate.

A mixture of Methyl 2-bromo-1-(cyclopropylmethyl)-1*H*-benzimidazole-5-carboxylate (35.9 g, 0.116 mol), [(1*S*)-2-methoxy-1-methylethyl]amine (24.8 g, 0.278 mol), CsF (24.6 g, 0.162 mol), and DMSO (300 mL) was placed into a reaction vessel of a MILESTONE Microwave Labstation. The reaction mixture was iradiated with microwaves under stirring at 110 °C for 25 h and monitored by TLC using hexane/ethyl acetate mixture (1:1) as eluent. The reaction mixture was poured into cold water (1.2 L) under stirring to form a pale-yellow emulsion. The product was extracted with chloroform (4 × 300 mL). The combined chloroform

extracts were washed with water (4 × 300 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give a pale-yellow crystal solid that was washed with ether (200 mL) using an ultrasonic bath. The white crystals were separated by filtration and dried to give the title compound in 74% (27.3 g) yield.

Intermediate 42

1-(Cyclopropylmethyl)-2-{[(1*S*)-2-methoxy-1-methylethyl]amino}-1*H*-benzimidazole-5-carboxylic Acid.

A solution of Methyl 1-(cyclopropylmethyl)-2-{[(1*S*)-2-methoxy-1-methylethyl]amino}-1*H*-benzimidazole-5-carboxylate (27.3 g, 0.086 mol) in methanol (70 mL) was mixed with 2 N aqueous solution of NaOH (60 mL). The mixture was refluxed for 1 h. The reaction mixture was cooled and concentrated under reduced pressure to remove methanol. The residue was acidified with a 15% aqueous HCl solution to attain pH 3. Water was evaporated under reduced pressure, and the residue was mixed with dioxane (150 mL). The mixture was evaporated under reduced pressure to remove water. This operation was repeated to form a foaming mass that was dissolved in chloroform/*tert*-butanol mixture (3:1, 200 mL). The solution was filtered to remove inorganic impurities, and the filtrate was concentrated under reduced pressure. The residue was dissolved in hot chloroform (400 mL), and the solution was kept in a freezer overnight. The white crystalline solid that formed was separated by filtration and dried to give the crude product (19.8 g) containing residual *tert*-butanol. The product was dissolved in water (150 mL), and the aqueous solution was alkalized with KOH (8 g) under stirring for 30 min. The solution obtained was neutralized with a solution of $KHSO_4$ (19.43 g) in water (150 mL) to attain pH 4–5. Water was removed under reduced pressure, and the residue was mixed with acetonitrile (150 mL). The mixture was concentrated under reduced pressure to remove water. This operation was repeated to form a solid mass that was treated with CH_2Cl_2 (1.5 mL) using an ultrasonic bath to extract the target product. The extract was concentrated under reduced pressure, and the residue was triturated with ether (500 mL) to form a white crystalline solid that was separated by filtration and dried to afford the title compound in 58% (15.15 g) yield. LRMS m/z Calcd for C16 H21 N3 O3 303.4; obsd LCMS APCI (M+1) m/z 304.2.

Example 7

2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure A, using the appropriate starting materials, A and B. Reagent A, 2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazole-5-carboxylic acid and Reagent B, Methyl-(1-methyl-piperidin-4-yl)-

amine. The product was purified by HPLC (Preparative Purification Method A) to give 37.05 μmol, HPLC purity = 100 %, retention time (min) = 0.8; LRMS m/z Calcd for C23 H35 N5 O2 413.5625; obsd LRMS APCI (M+1) m/z 414.5.

Example 8

2-(4-Hydroxy-cyclohexylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure A: using the appropriate starting materials, A and B. Reagent A, 2-(4-Hydroxy-cyclohexylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid and Reagent B, Methyl-(1-methyl-piperidin-4-yl)-amine. The product was purified by HPLC (Preparative Purification Method A) to give 36.4 μmol, HPLC purity = 100 %, retention time (min) = 0.65;LRMS m/z Calcd for C22 H33 N5 O2399.5357; obsd LRMS APCI (M+1) m/z 400.4.

Example 9

1-Methyl-2-phenethylamino-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure A: using the appropriate starting materials, A and B. Reagent A, 1-Methyl-2-phenethylamino-1H-benzoimidazole-5-carboxylic acid and Reagent B, Methyl-(1-methyl-piperidin-4-yl)-amine. The product was purified by HPLC (Preparative Purification Method A) to give 32.6 μmol, HPLC purity = 100 %, retention time (min) = 0.90; LRMS m/z Calcd for C24 H31 N5 O405.5429; obsd LRMS APCI (M+1) m/z 406.5.

Example 10

2-Ethyl-1-phenyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure A: using the appropriate starting materials, A and B. Reagent A, 2-Ethyl-1-phenyl-1H-benzoimidazole-5-carboxylic acid and Reagent B, Methyl-(1-methyl-piperidin-4-yl)-amine. The product was purified by HPLC (Preparative Purification Method A) to give 34.1 μmol, HPLC purity = 100 %, retention time (min) = 0.95;LRMS m/z Calcd for C23 H28 N4 O 376.5012; obsd LRMS APCI (M+1) m/z 377.3.

Example 11

1-(2-Fluoro-phenyl)-2-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure A: using the appropriate starting materials, A and B. Reagent A, 1-(2-Fluoro-phenyl)-2-propyl-1H-benzoimidazole-5-carboxylic acid and Reagent B, Methyl-(1-methyl-piperidin-4-yl)-amine. The product was purified by HPLC (Preparative Purification Method A) to give35.5 uMoles,

HPLC purity = 100 %, retention time (min) = 1.03;LRMS m/z Calcd for C24 H29 F N4 O 408.5181; obsd LRMS APCI (M+1) m/z 409.4.

Example 12

2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure A: using the appropriate starting materials, A and B. Reagent A, 2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid and Reagent B, Methyl-(1-methyl-piperidin-4-yl)-amine. The product was purified by HPLC (Preparative Purification Method A) to give 38.4 μmol, HPLC purity = 100 %, retention time (min) = 0.83 LRMS m/z Calcd for C22 H33 N5 O2 399.5357; obsd LRMS APCI (M+1) m/z 400.4.

Example 13

2-(Benzyl-methyl-amino)-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure A: using the appropriate starting materials, A and B. Reagent A, 2-(Benzyl-methyl-amino)-1-methyl-1H-benzoimidazole-5-carboxylic acid and Reagent B, Methyl-(1-methyl-piperidin-4-yl)-amine. The product was purified by HPLC (Preparative Purification Method A) to give 40.3 μmol, HPLC purity = 100 %, retention time (min) = 0.98 LRMS m/z Calcd for C24 H31 N5 O 405.5429; obsd LRMS APCI (M+1) m/z 406.4.

Example 14

2-Ethyl-1-(4-methoxy-phenyl)-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure A: using the appropriate starting materials, A and B. Reagent A, 2-Ethyl-1-(4-methoxy-phenyl)-1H-benzoimidazole-5-carboxylic acid and Reagent B, Methyl-(1-methyl-piperidin-4-yl)-amine. The product was purified by HPLC (Preparative Purification Method A) to give39.1 μmol, HPLC purity = 100 %, retention time (min) = 0.99 LRMS m/z Calcd for C24 H30 N4 O2 406.527; obsd LRMS APCI (M+1) m/z 407.3.

Example 15

2-(2,2-Dimethyl-propylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure A: using the appropriate starting materials, A and B. Reagent A, 2-(2,2-Dimethyl-propylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid and Reagent B, Methyl-(1-methyl-piperidin-4-yl)-amine. The product was purified by HPLC (Preparative Purification Method A) to give 41.2

μmol, HPLC purity = 100 %, retention time (min) = 0.89LRMS m/z Calcd for C21 H33 N5 O 371.5257; obsd LRMS APCI (M+1) m/z 372.3.

Example 16

2-((R)-1,2-Dimethyl-propylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure A: using the appropriate starting materials, A and B. Reagent A, 2-((R)-1,2-Dimethyl-propylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid and Reagent B, Methyl-(1-methyl-piperidin-4-yl)-amine. The product was purified by HPLC (Preparative Purification Method A) to give 37.2 μmol, HPLC purity = 100 %, retention time (min) = 0.87 LRMS m/z Calcd for C21 H33 N5 O 371.5257; obsd LRMS APCI (M+1) m/z 372.3.

Example 17

1-Cyclopropylmethyl-2-((S)-2-methoxy-1-methyl-ethylamino)-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure A: using the appropriate starting materials, A and B. Reagent A, 1-Cyclopropylmethyl-2-((S)-2-methoxy-1-methyl-ethylamino)-1H-benzoimidazole-5-carboxylic acid and Reagent B, Methyl-(1-methyl-piperidin-4-yl)-amine. The product was purified by HPLC (Preparative Purification Method A) to give 42.8 μmol, HPLC purity = 100 %, retention time (min) = 0.86 LRMS m/z Calcd for C23 H35 N5 O2413.5625; obsd LRMS APCI (M+1) m/z 414.4.

Example 18

1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure A: using the appropriate starting materials, A and B. Reagent A, 1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid and Reagent B, Methyl-(1-methyl-piperidin-4-yl)-amine. The product was purified by HPLC (Preparative Purification Method A) to give36.4 μmol, HPLC purity = 100 %, retention time (min) = 1.17 LRMS m/z Calcd for C25 H37 N5 O 423.6013; obsd LRMS APCI (M+1) m/z 424.4.

Example 19

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure A: using the appropriate starting materials, A and B. Reagent A, 1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid and Reagent B, Methyl-(1-methyl-piperidin-4-yl)-amine. The product was purified by HPLC (Preparative Purification Method A) to give 36.3 μmol,

HPLC purity = 100 %, retention time (min) = 0.8 LRMS m/z Calcd for C20 H29 N5 O 355.4831; obsd LRMS APCI (M+1) m/z 356.3.

Example 20

1-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure A: using the appropriate starting materials, A and B. Reagent A, 1-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-propyl-1H-benzoimidazole-5-carboxylic acid and Reagent B, Methyl-(1-methyl-piperidin-4-yl)-amine. The product was purified by HPLC (Preparative Purification Method A) to give 43.3 μmol, HPLC purity = 100 %, retention time (min) = 1.05 LRMS m/z Calcd for C26 H32 N4 O3 448.5638; obsd LRMS APCI (M+1) m/z 449.3.

Example 21

[3-(Ethyl-methyl-amino)-pyrrolidin-1-yl]-[2-(3-hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazol-5-yl]-methanone.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, Methyl-pyrrolidin-3-yl-carbamic acid tert-butyl ester, Reagent B, 2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and acetaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 31 μmol, HPLC purity = 100 %, retention time (min) = 0.78 LRMS m/z Calcd for C23 H35 N5 O2 413.5625; obsd LRMS APCI (M+1) m/z 414.3.

Example 22

[3-(Ethyl-methyl-amino)-pyrrolidin-1-yl]-(2-morpholin-4-yl-1-propyl-1H-benzoimidazol-5-yl)-methanone.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, Methyl-pyrrolidin-3-yl-carbamic acid tert-butyl ester, Reagent B, 2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Acetaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 30.6 μmol, HPLC purity = 100 %, retention time (min) = 0.8 LRMS m/z Calcd for C22 H33 N5 O2 399.5357; obsd LRMS APCI (M+1) m/z 400.3.

Example 23

[1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazol-5-yl]-[3-(ethyl-methyl-amino)-pyrrolidin-1-yl]-methanone.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, Methyl-pyrrolidin-3-yl-carbamic acid tert-butyl ester, Reagent B, 1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-

benzoimidazole-5-carboxylic acid, Reagent C, and Acetaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 31.7 μmol, HPLC purity = 100 %, retention time (min) = 1.09 LRMS m/z Calcd for C25 H37 N5 O 423.6013; obsd LRMS APCI (M+1) m/z 424.3.

Example 24

1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid (1-ethyl-piperidin-4-yl)-(2-methoxy-ethyl)-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-(2-Methoxy-ethylamino)-piperidine-1-carboxylic acid tert-butyl ester, Reagent B, 1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Acetaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 12.8 μmol, HPLC purity = 100 %, retention time (min) = 1.19LRMS m/z Calcd for C28 H43 N5 O2 481.6807; obsd LRMS APCI (M+1) m/z 481.8.

Example 25

1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Ethylamino-piperidine-1-carboxylic acid tert-butyl ester, Reagent B, 1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Acetaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 14.8 μmol, HPLC purity = 100 %, retention time (min) = 0.21 LRMS m/z Calcd for C27 H41 N5 O 451.6549; obsd LRMS APCI (M+1) m/z 452.3.

Example 26

2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Ethylamino-piperidine-1-carboxylic acid tert-butyl ester, Reagent B, 2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Acetaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 28.8 μmol, HPLC purity = 100 %, retention time (min) = 0.88 LRMS m/z Calcd for C24 H37 N5 O2 427.5893; obsd LRMS APCI (M+1) m/z 428.3.

Example 27

1-Cyclopropylmethyl-2-((S)-2-methoxy-1-methyl-ethylamino)-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Ethylamino-piperidine-1-carboxylic acid tert-butyl ester, Reagent B, 1-Cyclopropylmethyl-2-((S)-2-methoxy-1-methyl-ethylamino)-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Acetaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 13.8 μmol, HPLC purity = 100 %, retention time (min) = 0.9 LRMS m/z Calcd for C25 H39 N5 O2 441.6161; obsd LRMS APCI (M+1) m/z 442.3.

Example 28

2-Cyclopentylamino-1-methyl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Ethylamino-piperidine-1-carboxylic acid tert-butyl ester, Reagent B, 2-Cyclopentylamino-1-methyl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Acetaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 23.7 μmol, HPLC purity = 100 %, retention time (min) = 0.88 LRMS m/z Calcd for C23 H35 N5 O 397.5635; obsd LRMS APCI (M+1) m/z 398.2.

Example 29

2-(Cyclopropylmethyl-amino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-azepan-4-yl)-methyl-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Methylamino-azepane-1-carboxylic acid tert-butyl ester, Reagent B, 2-(Cyclopropylmethyl-amino)-1-methyl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Acetaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 17 μmol, HPLC purity = 100 %, retention time (min) = 0.86 LRMS m/z Calcd for C22 H33 N5 O 383.5367; obsd LRMS APCI (M+1) m/z 384.2.

Example 30

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Ethylamino-piperidine-1-carboxylic acid tert-butyl ester, Reagent B, 1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Acetaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 22.2 μmol, HPLC purity = 100 %, retention time (min) = 0.84 LRMS m/z Calcd for C22 H33 N5 O 383.5367; obsd LRMS APCI (M+1) m/z 384.3.

Example 31

2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-azepan-4-yl)-methyl-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Methylamino-azepane-1-carboxylic acid tert-butyl ester, Reagent B, 2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Acetaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 22.2 μmol, HPLC purity = 100 %, retention time (min) = 0.92 LRMS m/z Calcd for C24 H37 N5 O2 427.5893; obsd LRMS APCI (M+1) m/z 428.3.

Example 32

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-azepan-4-yl)-methyl-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Methylamino-azepane-1-carboxylic acid tert-butyl ester, Reagent B, 1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Acetaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 19.4 μmol, HPLC purity = 100 %, retention time (min) = 0.88 LRMS m/z Calcd for C22 H33 N5 O 383.5367; obsd LRMS APCI (M+1) m/z 384.3.

Example 33

2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-azepan-4-yl)-methyl-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Methylamino-azepane-1-carboxylic acid tert-butyl ester, Reagent B, 2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Acetaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 31.7 μmol, HPLC purity = 100 %, retention time (min) = 0.89 LRMS m/z Calcd for C25 H39 N5 O2 441.6161; obsd LRMS APCI (M+1) m/z 442.3.

Example 34

[3-(Methyl-propyl-amino)-pyrrolidin-1-yl]-(2-morpholin-4-yl-1-propyl-1H-benzoimidazol-5-yl)-methanone.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, Methyl-pyrrolidin-3-yl-carbamic acid tert-butyl ester, Reagent B, 2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Propionaldehyde. The product was purified by HPLC

(Preparative Purification Method B) to give 52.1 μmol, HPLC purity = 100 %, retention time (min) = 0.89 LRMS m/z Calcd for C23 H35 N5 O2 413.5625; obsd LRMS APCI (M+1) m/z 414.3.

Example 35

[2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazol-5-yl]-[3-(methyl-propyl-amino)-pyrrolidin-1-yl]-methanone.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, Methyl-pyrrolidin-3-yl-carbamic acid tert-butyl ester, Reagent B, 2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Propionaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 47.2 μmol, HPLC purity = 100 %, retention time (min) = 0.86 LRMS m/z Calcd for C24 H37 N5 O2 427.5893; obsd LRMS APCI (M+1) m/z 428.3.

Example 36

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-(1-propyl-piperidin-4-yl)-amide.

This reaction conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-(2-Methoxy-ethylamino)-piperidine-1-carboxylic acid tert-butyl ester, Reagent B, 1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Propionaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 26.2 μmol, HPLC purity = 100 %, retention time (min) = 0.91 LRMS m/z Calcd for C24 H37 N5 O2 427.5893; obsd LRMS APCI (M+1) m/z 428.3.

Example 37

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-propyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Ethylamino-piperidine-1-carboxylic acid tert-butyl ester, Reagent B, 1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Propionaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 19.4 μmol, HPLC purity = 100 %, retention time (min) = 0.94 LRMS m/z Calcd for C23 H35 N5 O 397.5635; obsd LRMS APCI (M+1) m/z 398.2.

Example 38

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid (4-methyl-1-propyl-piperidin-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, Amino-4-methyl-piperidine-1-carboxylic acid tert-butyl ester, Reagent B, 1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Propionaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 22.3 μmol, HPLC purity = 100 %, retention time (min) = 0.91 LRMS m/z Calcd for C22 H33 N5 O 383.5367; obsd LRMS APCI (M+1) m/z 384.2.

Example 39

2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Methylamino-azepane-1-carboxylic acid tert-butyl ester, Reagent B, 2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Propionaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 49.2 μmol, HPLC purity = 100 %, retention time (min) = 0.96 LRMS m/z Calcd for C26 H41 N5 O2 455.6429; obsd LRMS APCI (M+1) m/z 456.3.

Example 40

2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Methylamino-azepane-1-carboxylic acid tert-butyl ester, Reagent B, 2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Propionaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 52.8 μmol, HPLC purity = 100 %, retention time (min) = 1.01 LRMS m/z Calcd for C25 H39 N5 O2 441.6161; obsd LRMS APCI (M+1) m/z 442.3.

Example 41

1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Methylamino-azepane-1-carboxylic acid tert-butyl ester, Reagent B, 1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Propionaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 39.3 μmol, HPLC purity = 100 %, retention time (min) = 1.4 LRMS m/z Calcd for C28 H43 N5 O 465.6817; obsd LRMS APCI (M+1) m/z 466.4.

Example 42

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Methylamino-azepane-1-carboxylic acid tert-butyl ester, Reagent B, 1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Propionaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 24.5 μmol, HPLC purity = 100 %, retention time (min) = 0.96 LRMS m/z Calcd for C23 H35 N5 O 397.5635; obsd LRMS APCI (M+1) m/z 398.2.

Example 43

2-Cyclopentylamino-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Methylamino-azepane-1-carboxylic acid tert-butyl ester, Reagent B, 2-Cyclopentylamino-1-methyl-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Propionaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 46.3 μmol, HPLC purity = 100 %, retention time (min) = 1.03 LRMS m/z Calcd for C24 H37 N5 O 411.5903; obsd LRMS APCI (M+1) m/z 412.3.

Example 44

1-Cyclopropylmethyl-2-((S)-2-methoxy-1-methyl-ethylamino)-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide.

This reaction was conducted using the conditions described in General Procedure B: using the appropriate starting materials, A, B and C. Reagent A, 4-Methylamino-azepane-1-carboxylic acid tert-butyl ester, Reagent B, 1-Cyclopropylmethyl-2-((S)-2-methoxy-1-methyl-ethylamino)-1H-benzoimidazole-5-carboxylic acid, Reagent C, and Propionaldehyde. The product was purified by HPLC (Preparative Purification Method B) to give 50.3 μmol, HPLC purity = 100 %, retention time (min) = 1.04 LRMS m/z Calcd for C26 H41 N5 O2 455.6429; obsd LRMS APCI (M+1) m/z 456.3.

The composition of the present invention may be a composition comprising a compound of formula I and optionally a pharmaceutically acceptable carrier. The composition of the present invention may also be a composition comprising a compound of formula I, a histamine H_1 antagonist and optionally a pharmaceutically acceptable carrier. The composition of the present invention may also be a composition comprising a compound of formula I, a neurotransmitter re-uptake blocker and optionally a pharmaceutically acceptable carrier.

The composition of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers. The composition may be formulated for oral, buccal, intranasal, parenteral (e.g., intravenous, intramuscular, intraperitoneal, or subcutaneous or through an implant) nasal, vaginal, sublingual, rectal or topical administration or in a form suitable for administration by inhalation or insufflation.

Pharmaceutically acceptable salts of compounds of formula I may be prepared by one or more of three methods: (i) by reacting the compound of formula I with the desired acid or base; (ii) by removing an acid- or base-labile protecting group from a suitable precursor of the compound of formula I or by ring-opening a suitable cyclic precursor, for example, a lactone or lactam, using the desired acid or base; or (iii) by converting one salt of the compound of formula I to another by reaction with an appropriate acid or base or by means of a suitable ion exchange column.

All three reactions are typically carried out in solution. The resulting salt may precipitate out and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionisation in the resulting salt may vary from completely ionised to almost non-ionised.

Also included within the scope of the invention are metabolites of compounds of formula I, that is, compounds formed in vivo upon administration of the drug. Some examples of metabolites in accordance with the invention include: (i) where the compound of formula (I) contains a methyl group, an hydroxymethyl derivative thereof ($-CH_3 \rightarrow -CH_2OH$); (ii) where the compound of formula (I) contains an alkoxy group, an hydroxy derivative thereof ($-OR \rightarrow -OH$); (iii) where the compound of formula (I) contains a tertiary amino group, a secondary amino derivative thereof ($-NR^aR^b \rightarrow -NHR^a$ or $-NHR^b$); (iv) where the compound of formula (I) contains a secondary amino group, a primary derivative thereof ($-NHR^a \rightarrow -NH_2$); (v) where the compound of formula (I) contains an amide group, a carboxylic acid derivative thereof ($-CONR^cR^d \rightarrow COOH$).

Isotopically labeled compounds of formula I of this invention can generally be prepared by carrying out the procedures disclosed in the preceeding Schemes and/or in the Examples and Preparations, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

For oral administration, the pharmaceutical composition may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents such as pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose; fillers such as lactose, microcrystalline cellulose or calcium phosphate; lubricants such as magnesium stearate, talc or silica; disintegrants such as potato starch or sodium starch glycolate; or wetting agents such as

sodium lauryl sulphate. The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents such as sorbitol syrup, methyl cellulose or hydrogenated edible fats; emulsifying agents such as lecithin or acacia, non-aqueous vehicles such as almond oil, oily esters or ethyl alcohol; and preservatives such as methyl or propyl p-hydroxybenzoates or sorbic acid.

For buccal administration, the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition of the invention may be formulated for parenteral administration by injection, including using conventional catheterization techniques or infusion. Formulations for injection may be presented in unit dosage form, for example, in ampoules or in multi-dose containers, with an added preservative. The composition may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulating agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredient or ingredients in a composition may be in powder form for reconstitution with a suitable vehicle, for example, sterile pyrogen-free water, before use. The term "active ingredient" as used herein refers to a compound of the formula I, a histamine H_1 antagonist, or a neurotransmitter re-uptake blocker.

The composition of the invention may also be formulated in a rectal composition such as suppositories or retention enemas, for example, containing conventional suppository bases such as cocoa butter or other glycerides. A composition for vaginal administration is preferably a suppository that may contain, in addition to the active ingredient or ingredients, excipients such as cocoa butter or a suppository wax. A composition for nasal or sublingual administration is also prepared with standard excipients well known in the art.

For intranasal administration or administration by inhalation, the composition may be conveniently delivered in the form of a solution or suspension from a pump spray container that is squeezed or pumped by the patient or as an aerosol spray presentation from a pressurized container or a nebulizer, with the use of a suitable propellant, for example, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurized container or nebulizer may contain a solution or suspension of the active ingredient or ingredients. Capsules and cartridges, made, for example, from gelatin, for use in an inhaler or insufflator may be formulated containing a powder mix of an active ingredient or ingredients and a suitable

powder base such as lactose or starch. The active ingredient or ingredients in the composition may range in size from nanoparticles to microparticles.

An exemplary dose of the composition of the invention comprising a compound of formula I for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to herein is about 0.01 to about 1000 mg of the compound of formula I per unit dose which could be administered, for example, 1 to 3 times per day.

An exemplary dose of the composition of the invention comprising a compound of formula I and a histamine H_1 antagonist or a neurotransmitter re-uptake blocker for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to herein is about 0.01 to about 500 mg of the compound of formula I and of about 0.01 mg to about 500 mg of the histamine H_1 antagonist or the neurotransmitter re-uptake blocker per unit dose which could be administered, for example, 1 to 3 times per day.

Aerosol formulations for treatment of the conditions referred to herein in the average adult human are preferably arranged so that each metered dose or "puff" of aerosol contains about 20 μg to about 1000 μg of the compound of formula I. The overall daily dose with an aerosol will be within the range about 100 μg to about 10 mg. Administration may be several times daily, for example 2, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time. Aerosol formulations containing a compound of formula I and a histamine H_1 antagonist or a neurotransmitter re-uptake blocker are preferably arranged so that each metered dose or "puff" of aerosol contains about 100 μg to about 10,000 μg of the compound of formula I and about 100 μg to about 30,000 μg of the histamine H_1 antagonist or the neurotransmitter re-uptake blocker. Administration may be several times daily, for example 1, 3, 4 or 8 times, giving for example, 1, 2 or 3 doses each time. The composition of the invention comprising a compound of formula I and a histamine H_1 antagonist or a neurotransmitter re-uptake blocker may optionally contain a pharmaceutically acceptable carrier and may be administered in both single and multiple dosages as a variety of different dosage forms, such as tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspension, injectable solutions, elixirs, syrups, and the like. The pharmaceutically acceptable carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Oral pharmaceutical formulations can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for such purposes. In general, the compound of formula I is present in such dosage forms at concentration levels ranging from about 0.1% to about 99.9% by weight of the total composition, i.e., in amounts which are sufficient to provide the desired unit dosage, and the histamine H_1 antagonist or the neurotransmitter re-uptake blocker is present in such dosage forms at concentration levels ranging from about 0.1% to about 99.9% by weight of the total composition, i.e., in amounts which are sufficient to provide the desired unit dosage.

The compound of formula I and the histamine H_1 antagonist may be administered together or separately. When administered separately, the compound of formula I and the histamine H_1 antagonist may be administered in either order, provided that after administration of the first of the two active ingredients, the second active ingredient is administered within 24 hours or less, preferably 12 hours or less.

The compound of formula I and the neurotransmitter re-uptake blocker may be administered together or separately. When administered separately, the compound of formula I and the neurotransmitter re-uptake blocker may be administered in either order, provided that after administration of the first of the two active ingredients, the second active ingredient is administered within 24 hours or less, preferably 12 hours or less.

A preferred dose ratio of compound of formula I to the histamine H_1 antagonist or to the neurotransmitter re-uptake blocker for oral, parenteral or buccal administration to the average adult human for the treatment of the conditions referred to herein is from about 0.001 to about 1000, preferably from about 0.01 to about 100.

The composition may be homogeneous, wherein by homogeneous it is meant that the active ingredient or ingredients are dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid composition is then subdivided into unit dosage forms of the type described herein containing from about 0.1 to about 1000 mg of the active ingredient or ingredients. Typical unit dosage forms contain from about 1 to about 300 mg, for example about 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient or ingredients. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The dosage of the active ingredient or ingredients in the composition and methods of this invention may be varied; however, it is necessary that the amount of the active ingredient or ingredients in such a composition be such that a suitable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, the particular compounds administered, the duration of the treatment, and other factors. All dosage ranges and dosage levels mentioned herein refer to each active ingredient present in the pharmaceutical composition of the present invention, as well as those used in the methods of the present invention. Generally, dosage levels of between about 0.01 and about

100 mg/kg of body weight daily are administered to humans and other mammals. A preferred dosage range in humans is about 0.1 to about 50 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses. A preferred dosage range in mammals other than humans is about 0.01 to about 10.0 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses. A more preferred dosage range in mammals other than humans is about 0.1 to about 5.0 mg/kg of body weight daily which can be administered as a single dose or divided into multiple doses.

The pharmaceutical composition comprising the compound of formula I and the histamine H_1 antagonist or the neurotransmitter re-uptake blocker may be administered at dosages of a therapeutically effective amount of the compound of formula I and of the second active ingredient in single or divided doses.

The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age. However, some variation in dosage will necessarily occur depending upon the condition of the subject being treated. The person responsible for administration will, in any event, determine the appropriate dose for the individual subject.

The dosage amounts set forth in this description and in the appended claims may be used, for example, for an average human subject having a weight of about 65 kg to about 70 kg. The skilled practitioner will readily be able to determine any variation in the dosage amount that may be required for a subject whose weight falls outside the about 65 kg to about 70 kg range, based upon the medical history of the subject. The pharmaceutical combinations may be administered on a regimen of up to 6 times per day, preferably 1 to 3 times per day, such as 2 times per day or once daily.

Determination of Biological Activity

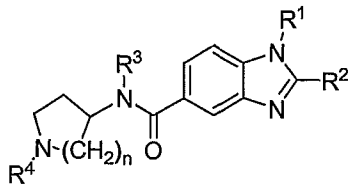
The *in vitro* affinity of the compounds in the present invention at the rat or human histamine H3 receptors can be determined according to the following procedure. Frozen rat frontal brain or frozen human post-mortem frontal brain is homogenized in 20 volumes of cold 50 mM Tris HCl containing 2 mM $MgCl_2$ (pH to 7.4 at 4 °C). The homogenate is then centrifuged at 45,000 G for 10 minutes. The supernatant is decanted and the membrane pellet resuspended by Polytron in cold 50 mM Tris HCl containing 2 mM MgCl2 (pH to 7.4 at 4 °C) and centrifuged again. The final pellet is resuspended in 50 mM Tris HCl containing 2 mM MgCl2 (pH to 7.4 at 25 °C) at a concentration of 12 mg/mL. Dilutions of compounds are made in 10% DMSO / 50 mM Tris buffer (pH 7.4) (at 10 x final concentration, so that the final DMSO concentration is 1%). Incubations are initiated by the addition of membranes (200 microliters) to 96 well V-bottom polypropylene plates containing 25 microliters of drug dilutions and 25 microliters of radioligand (1 nM final concentration 3H-N-methyl-histamine). After a 1 hour

incubation, assay samples are rapidly filtered through Whatman GF/B filters and rinsed with ice-cold 50 mM Tris buffer (pH 7.4) using a Skatron cell harvester. Radioactivity is quantified using a BetaPlate scintillation counter. The percent inhibition of specific binding can then be calculated.

A person of ordinary skill in the art could adapt the above procedure to other assays.

CLAIMS

1. A compound of formula I,



or a pharmaceutically acceptable salt thereof, wherein

R^1 is selected from the group consisting of $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-aryl, $(C_1\text{-}C_6)$alkyl-$(C_3\text{-}C_6)$cycloalkyl, and aryl optionally substituted with 1 to 4 substituents selected from the group consisting of halo, methoxy, CN, CO-NH$(C_1\text{-}C_6)$alkyl, and CO-N$((C_1\text{-}C_6)\text{alkyl})_2$;

R^2 is selected from the group consisting of $(C_3\text{-}C_6)$cycloalkyl, piperidine, morpholine, pyrrolidine, amino $(C_1\text{-}C_6)$alkyl, amino di-$(C_1\text{-}C_6)$alkyl, aminobenzyl, $(C_1\text{-}C_6)$alkylaryl, and $(C_1\text{-}C_6)$alkyl-$(C_1\text{-}C_6)$alkoxy; wherein R^2 may be optionally substituted with 1 to 3 substituents selected independently from hydroxyl, $(C_1\text{-}C_6)$alkyl, aryl, and heteroaryl;

R^3 is $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkyl-$(C_1\text{-}C_6)$alkoxy, heteroaryl or $(C_1\text{-}C_6)$alkylaryl;

R^4 is $(C_1\text{-}C_6)$alkyl; and

n is 0, 1, 2, 3, or 4.

2. A compound of formula I, according to claim 1, wherein R^1 is $C_1\text{-}C_6$ alkyl, R^2 is $(C_3\text{-}C_6)$cycloalkyl, R^3 is $C_1\text{-}C_6$ alkyl, and n is 2.

3. A compound of formula I, according to claim 1, wherein R^1 is $C_1\text{-}C_6$ alkyl, R^2 is pyrrolidine, R^3 is methyl, R^4 is ethyl, and n is 2.

4. A compound of formula I, according to claim on, selected from the group consisting of

2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-(4-Hydroxy-cyclohexylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

1-Methyl-2-phenethylamino-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-Ethyl-1-phenyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

1-(2-Fluoro-phenyl)-2-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-(Benzyl-methyl-amino)-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-Ethyl-1-(4-methoxy-phenyl)-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-(2,2-Dimethyl-propylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-((R)-1,2-Dimethyl-propylamino)-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

1-Cyclopropylmethyl-2-((S)-2-methoxy-1-methyl-ethylamino)-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

1-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-2-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

2-Ethyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-methyl-piperidin-4-yl)-amide,

[3-(Ethyl-methyl-amino)-pyrrolidin-1-yl]-[2-(3-hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazol-5-yl]-methanone,

[3-(Ethyl-methyl-amino)-pyrrolidin-1-yl]-(2-morpholin-4-yl-1-propyl-1H-benzoimidazol-5-yl)-methanone,

[1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazol-5-yl]-[3-(ethyl-methyl-amino)-pyrrolidin-1-yl]-methanone,

1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid (1-ethyl-piperidin-4-yl)-(2-methoxy-ethyl)-amide,

1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide,

2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide,

1-Cyclopropylmethyl-2-((S)-2-methoxy-1-methyl-ethylamino)-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide,

2-Cyclopentylamino-1-methyl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide,

2-(Cyclopropylmethyl-amino)-1-methyl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-azepan-4-yl)-methyl-amide,

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide,

2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-azepan-4-yl)-methyl-amide,

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-azepan-4-yl)-methyl-amide,

2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-azepan-4-yl)-methyl-amide,

[3-(Methyl-propyl-amino)-pyrrolidin-1-yl]-(2-morpholin-4-yl-1-propyl-1H-benzoimidazol-5-yl)-methanone,

[2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazol-5-yl]-[3-(methyl-propyl-amino)-pyrrolidin-1-yl]-methanone,

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid (2-methoxy-ethyl)-(1-propyl-piperidin-4-yl)-amide,

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-propyl-piperidin-4-yl)-amide,

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid (4-methyl-1-propyl-piperidin-4-yl)-amide,

2-(3-Hydroxy-piperidin-1-yl)-1-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide,

2-Morpholin-4-yl-1-propyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide,

1-Cyclopropylmethyl-2-(2-methyl-piperidin-1-yl)-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide,

1-Methyl-2-pyrrolidin-1-yl-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide,

2-Cyclopentylamino-1-methyl-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide,

1-Cyclopropylmethyl-2-((S)-2-methoxy-1-methyl-ethylamino)-1H-benzoimidazole-5-carboxylic acid methyl-(1-propyl-azepan-4-yl)-amide,

2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-ethyl-piperidin-4-yl)-amide,

2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid ethyl-(1-isopropyl-piperidin-4-yl)-amide,

2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid (1-isopropyl-piperidin-4-yl)-methyl-amide,

2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-piperidin-4-yl)-methyl-amide,

2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid (1-ethyl-piperidin-4-yl)-pyridin-2-yl-amide,

2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carboxylic acid (1-isopropyl-piperidin-4-yl)-pyridin-2-yl-amide,

4-[(2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carbonyl)-amino]-piperidine-1-carboxylic acid tert-butyl ester, and

4-[(2-Cyclopentyl-1-isobutyl-1H-benzoimidazole-5-carbonyl)-methyl-amino]-piperidine-1-carboxylic acid tert-butyl ester.

5. A pharmaceutical composition for treating a disorder or condition that may be treated by antagonizing histamine-3 receptors, the composition comprising a compound of formula I as described in claim 1, and optionally a pharmaceutically acceptable carrier.

6. A method of treatment of a disorder or condition that may be treated by antagonizing histamine-3 receptors, the method comprising administering to a mammal in need of such treatment a compound of formula I as described in claim 1.

7. The method of claim 6 wherein the disorder or condition is selected from the group consisting of depression, mood disorders, schizophrenia, anxiety disorders, cognitive disorders, Alzheimer's disease, attention-deficit disorder, attention-deficit hyperactivity disorder, psychotic disorders, sleep disorders, obesity, dizziness, epilepsy, motion sickness, respiratory diseases, allergy, allergy- induced airway responses, allergic rhinitis, nasal congestion, allergic congestion, congestion, hypotension, cardiovascular disease, diseases of the GI tract, hyper and hypo motility and acidic secretion of the gastro- intestinal tract, the method comprising administering to a mammal in need of such treatment a compound of formula I as described in claim 1.

8. The method of claim 7, wherein the disorder or condition is selected from the group consisting of anxiety disorders, attention-deficit hyperactivity disorder, attention-deficit disorder, respiratory diseases, obesity, cognitive disorders, and psychotic disorders.

9. The method of claim 7, wherein the disorder or condition is a respiratory disease selected from the group consisting of adult respiratory distress syndrome, acute respiratory distress syndrome, bronchitis, chronic bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, asthma, emphysema, rhinitis and chronic sinusitis.

10. A pharmaceutical composition for treating allergic rhinitis, nasal congestion or allergic congestion comprising:

(a) an H3 receptor antagonist compound of formula I; or a pharmaceutically acceptable salt thereof;

(b) an H1 receptor antagonist or a pharmaceutically acceptable salt thereof; and

(c) a pharmaceutically acceptable carrier;

wherein the active ingredients (a) and (b) above are present in amounts that render the composition effective in treating allergy rhinitis, nasal congestion or allergic congestion.

11. The pharmaceutical composition according to claim 10, wherein said H1 receptor antagonist is selected from the group consisting of cetirizine chlorpheniramine, loratidine, fexofenadine, and desloradine.

12. A pharmaceutical composition for treating attention-deficit disorder, attention-deficit hyperactivity disorder, depression, mood disorders, or cognitive disorders comprising:

a) an H3 receptor antagonist compound of Formula I or a pharmaceutically acceptable salt thereof;

b) a neurotransmitter re-uptake blocker or a pharmaceutically acceptable salt thereof;

c) a pharmaceutically acceptable carrier;

wherein the active ingredients (a) and (b) above are present in amounts that render the composition effective in treating depression, mood disorders, and cognitive disorders.

13. The pharmaceutical composition according to claim 12, wherein the neurotransmitter re-uptake blocker is selected from the group consisting of sertraline, fluoxetine and paroxetine.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/003611

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 C07D401/14 C07D403/12 C07D403/14 A61K31/4184
A61P11/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/076925 A (LILLY CO ELI [US]; BEAVERS LISA SELSAM [US]; GADSKI ROBERT ALAN [US];) 3 October 2002 (2002-10-03) cited in the application example 22	1-13

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 March 2007	13/04/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	De Jong, Bart

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2006/003611

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6-9 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2006/003611

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02076925 A	03-10-2002	AU 2002254114 A1	08-10-2002
		CA 2441080 A1	03-10-2002
		EP 1379493 A2	14-01-2004
		JP 2004532834 T	28-10-2004