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(54) Title: SUBSTITUTED AMINOPYRIMIDINES AS CHOLECYSTOKININ-1 RECEPTOR MODULATORS

(57) Abstract: Certain novel substituted aminopyrimidines are ligands of the human cholecystokinin receptor and, in particular, are selective ligands of the human cholecystokinin-1 receptor (CCK-1R). They are therefore useful for the treatment, control, or prevention of diseases and disorders responsive to the modulation of CCK-1R, such as obesity, and diabetes.

TITLE OF THE INVENTION
SUBSTITUTED AMINOPYRIMIDINES AS CHOLECYSTOKININ-1 RECEPTOR
MODULATORS

5 BACKGROUND OF THE INVENTION

Obesity is a major health concern in Western societies. It is estimated that about 97 million adults in the United States are overweight or obese. Obesity is now recognized as a chronic disease that requires treatment to reduce its associated health risks. The medical problems associated with obesity, which can be serious and life-threatening, include
10 hypertension; type 2 diabetes mellitus; elevated plasma insulin concentrations; insulin resistance; hyperinsulinemia; glucose intolerance; dyslipidemias; hyperlipidemia; endometrial, breast, prostate and colon cancer; osteoarthritis; respiratory complications, such as obstructive sleep apnea; cholecystitis; cholelithiasis; gout; gallstones; gall bladder disease; respiratory problems; psychological disorders (such as depression, eating disorders, distorted body image and low self
15 esteem); arteriosclerosis; heart disease; abnormal heart rhythms; angina pectoris; and heart arrhythmias (Kopelman, P.G., *Nature* 404, 635-643 (2000)). Obesity is further associated with premature death and with a significant increase in mortality and morbidity from stroke, myocardial infarction, congestive heart failure, coronary heart disease, and sudden death. Recent studies have found that obesity and its associated health risks also affect children and
20 adolescents. According to the Centers for Disease Control, 15 percent of children and adolescents are defined as overweight and obese, a doubling since the early 1970s. Important outcomes for the treatment of obesity include weight loss, and weight management to improve cardiovascular and metabolic health and to reduce obesity-related morbidity and mortality. It has been shown that 5-10% loss of body weight can substantially improve metabolic values, such as
25 blood glucose, blood pressure, and lipid concentrations, and may reduce morbidity and mortality.

Cholecystokinin (CCK) is a brain-gut peptide that acts as a gastrointestinal hormone, neurotransmitter and neuromodulator in the central and the peripheral nervous systems. It has been shown that CCK is released from mucosal I-cells of the duodenum and jejunum in response to a meal, particularly in response to fat or protein in the meal. Once released, CCK initiates a
30 number of responses coordinated to promote digestion and regulate food intake, including mediating bile emptying from the gall bladder, regulating the release of digestive enzymes from the pancreas, controlling gastric emptying by regulation of the pyloric sphincter, as well as neuronal signaling to the central nervous system via vagal afferent neurons. Neuronal CCK is believed to mediate a number of events within the CNS, including modulating dopaminergic
35 neurotransmission and anxiogenic effects, as well as affecting cognition and nociception. See, e.g., J. N. Crawley and R. L. Corwin, 1994, *Peptides*, 15:731-755; N. S. Baber, C. T. Dourish, and D. R. Hill, *Pain* (1989), 39(3), 307-28; and P. De Tullio, J. Delarge and B. Pirotte, *Expert*

Opinion on Investigational Drugs (2000), 9(1), 129-146. Cholecystokinin has been shown to mediate its diverse hormonal and neuromodulatory functions through two receptor subtypes: the CCK-A (CCK-1) and CCK-B (CCK-2) subtypes (see, e.g., G. N. Woodruff and J. Hughes, *Annu. Rev. Pharmacol. Toxicol.* (1991), 31: 469-501). Both CCK-1 and CCK-2 receptor subtypes
5 belong to the seven transmembrane G-protein-coupled superfamily of receptors. A number of studies suggest that CCK mediates its satiety effect through the CCK-1 receptor, which relays the postprandial satiety signal via the vagal afferents to the CNS. See, e.g., G. P. Smith et al., *Science* 213 (1981) pp. 1036-1037; and J. N. Crawley et al., *J. Pharmacol. Exp. Ther.*, 257 (1991) pp. 1076-1080. The nucleotide sequences of the peripheral CCK-1 receptor and central
10 CCK-1 receptor are identical in humans. See, e.g., S. A. Wank et al., (1994), *NY Acad. Sci.* 713, pp. 49-66.

It has been reported that cholecystokinin (CCK) inhibits gastric emptying and increases satiety in a variety of species, including humans, resulting in a reduction of food intake (Moran, T. H. *Physiology & Behavior* 2004, 82, 175-180). Selective CCK1R antagonists have been
15 shown to reverse the anorexigenic effect of CCK thus increasing food intake and meal size in several species, including humans (Beglinger, C. et. al. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 2001, 280, R1149-R1154). Conversely, administration of CCK1R agonists to a variety of species, including humans, results in a reduction of food intake (Geary, N. *Physiology & Behavior* 2004, 81, 719-733). Consequently, selective small molecule CCK1R agonists are
20 useful for the treatment or prevention of obesity and related metabolic disorders such as diabetes and dyslipidemia (Woods, S. C. *Am. J. Gastrointest. Liver Physiol.* 2004, 286, G7-13; Moran, T. H., Kinzig, K. P. *Am. J. Gastrointest. Liver Physiol.* 2004, 286, G183-G188). In humans, bulimia nervosa has been linked with reduced secretion of postprandial CCK (Deylin, M. J. et. al. *J. Pharmacol. Exp. Ther.* 1987, 241, 100-116), lower CCK concentrations in cerebrospinal fluid
25 (Lydiard, R. B. et. al. *Am. J. Psychiatry* 1993, 150, 1099-1101), and lower CCK levels in T lymphocytes which could reflect central CCK secretion levels (Brambilla, F. et. al. *Psychiatry Research* 1995, 37, 51-56). Accordingly, CCK1R agonists are also useful in treating, preventing, or diagnosing bulimia nervosa and related eating disorders.

CCK agonists stimulate gallbladder contraction, stimulate pancreatic enzyme secretions,
30 stimulate intestinal blood flow, and affect intestinal motor activity (See Rehfeld, J. F. *Best Practice & Res. Clin. Endocrin. & Metab.* 2004, 18, 569-586). Consequently, CCK1R agonists are useful for the treatment, prevention, or diagnosis of disorders related to the gall bladder including, but not limited to, cholecystitis (inflammation of the gallbladder) and cholelithiasis (gallstones). Furthermore, CCK agonists are useful for the treatment, prevention, or diagnosis of
35 disorders related to the pancreas. Finally, CCK1R agonists are useful for the treatment, prevention, or diagnosis of disorders related to the gastrointestinal tract and gastrointestinal motility. CCK receptors are abundant in the central nervous system, and agonists can be used for

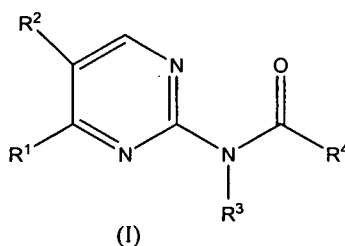
the treatment, prevention, or diagnosis of emotional or sexual behavior disorders and memory disorders (Itoh, S.; et. al. Drug Develop. Res. 1990, 21, 257-276). Furthermore, CCK agonists can be used for the treatment, prevention, or diagnosis of tardive dyskinesia (Nishikawa, T. et. al. Prog. Neuropsychopharmacol. Biol. Psych. 1988, 12, 903-812; Bignon, E. et. al. J. Pharm. Exp. Ther. 1999, 289, 752-761), Parkinson's disease (Bednar, I. et. al. Biogenic Amine, 1996, 12, 275-284), schizophrenia, and psychosis (Crawley, J. N. Trends in Pharmacol. Sci., 1991, 12, 232-236).

Imidazole compounds useful for the treatment of obesity and obesity related disorders have been disclosed in WO 01/085723, WO 03/040107, WO 03/063781, WO 03/007887, WO 2004/094407, WO 2005/009974, WO 2005/040130, WO 2005/063716, WO 2005/095354, US 2005/0054679, US 2005/0124660, US 2005/0197377, US 6,960,601, and J. Med. Chem. 2005, 48, 1823-1838. Other imidazoles are disclosed in J. Med. Chem. 2005, 48, 2638-2645; J. Med. Chem., 2002, 45, 4655-4668; J. Med. Chem. 2000, 43, 3168-3185; and J. Med. Chem. 1997, 40, 1634-1647.

Because of the unresolved deficiencies of the various pharmacological agents discussed above, there is a continuing need for a weight loss treatment with enhanced efficacy and fewer undesirable side effects. The instant invention addresses this problem by providing CCK receptor agonists, and in particular selective agonists of the cholecystinin-1 receptor (CCK-1R), useful in the treatment and prevention of obesity and obesity-related disorders, including diabetes. The present invention provides substituted aminopyrimidines which are selective agonists of the cholecystinin-1 (CCK-1R) receptor.

SUMMARY OF THE INVENTION

The present invention relates to novel substituted aminopyrimidines of formula I:



The compounds of formula I are effective as cholecystinin receptor ligands and are particularly effective as selective ligands of the cholecystinin-1 receptor. They are therefore useful for the treatment and/or prevention of disorders responsive to the modulation of the cholecystinin-1 receptor, such as obesity, diabetes, and obesity-related disorders.

The present invention also relates to pharmaceutical compositions comprising the compounds of the present invention and a pharmaceutically acceptable carrier.

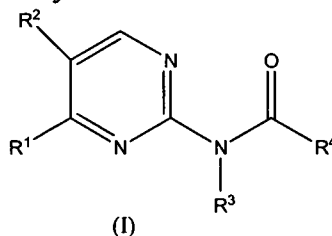
The present invention also relates to methods for the treatment or prevention of disorders, diseases, or conditions responsive to the modulation of the cholecystokinin-1 receptor in a mammal in need thereof by administering the compounds and pharmaceutical compositions of the present invention.

5 The present invention further relates to the use of the compounds of the present invention in the preparation of a medicament useful for the treatment or prevention of disorders, diseases, or conditions responsive to the modulation of the cholecystokinin-1 receptor in a mammal in need thereof by administering the compounds and pharmaceutical compositions of the present invention.

10

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to substituted aminopyrimidines useful as cholecystokinin receptor modulators, in particular, as selective cholecystokinin-1 receptor agonists. Compounds of the present invention are described by formula I:



15

or a pharmaceutically acceptable salt thereof; wherein

R¹ is phenyl, unsubstituted or substituted with 1-5 substituents selected from R⁵;

R² is selected from the group consisting of:

- (1) -(CH₂)_mC₃₋₈cycloalkyl,
- 20 (2) -(CH₂)_mC₃₋₈heterocycloalkyl,
- (3) -(CH₂)_qaryl, and
- (4) -(CH₂)_qheteroaryl,

wherein cycloalkyl, heterocycloalkyl, aryl, heteroaryl and -(CH₂) are unsubstituted or substituted with one to five substituents selected from halogen, OH, -C₁₋₆alkyl, and -C₁₋₆alkoxy;

25 R³ is selected from the group consisting of:

- (1) hydrogen, and
- (2) -C₁₋₆alkyl,

wherein alkyl is unsubstituted or substituted with one to five substituents selected from halogen and -OH;

30 R⁴ is a mono- or bicyclic ring selected from the group consisting of:

- (1) -C₃₋₈cycloalkyl,
- (2) -C₃₋₈heterocycloalkyl,
- (3) aryl, and

(4) heteroaryl,

wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with one to five substituents selected from R⁶;

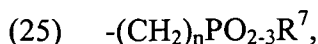
each R⁵ is independently selected from the group consisting of:

- 5 (1) $-(\text{CH}_2)_n\text{halogen}$,
 (2) $-(\text{CH}_2)_n\text{OR}^7$,
 (3) $-(\text{CH}_2)_n\text{NR}^3\text{R}^3$,
 (4) $-(\text{CH}_2)_n\text{SC}_{1-6}\text{alkyl}$, and
 (5) $-\text{C}_{1-6}\text{alkyl}$,

10 wherein alkyl and $-(\text{CH}_2)_n$ are unsubstituted or substituted with one to five substituents selected from halogen, OH, $-\text{C}_{1-6}\text{alkyl}$, and $-\text{C}_{1-6}\text{alkoxy}$;

each R⁶ is independently selected from the group consisting of:

- 15 (1) $-(\text{CH}_2)_n\text{halogen}$,
 (2) $-(\text{CH}_2)_n\text{CN}$,
 (3) $-\text{C}_{1-6}\text{alkyl}$,
 (4) $-\text{C}_{2-6}\text{alkenyl}$,
 (5) $-(\text{CH}_2)_n\text{C}_{2-8}\text{heterocycloalkyl}$,
 (6) $-(\text{CH}_2)_n\text{C}_{3-8}\text{cycloalkyl}$,
 20 (7) $-(\text{CH}_2)_n\text{aryl}$,
 (8) $-(\text{CH}_2)_n\text{heteroaryl}$,
 (9) $-(\text{CH}_2)_n\text{OR}^7$,
 (10) $-(\text{CH}_2)_n\text{COR}^7$,
 (11) $-(\text{CH}_2)_n\text{CO}_2\text{R}^7$,
 25 (12) $-(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^7\text{R}^7$,
 (13) $-(\text{CH}_2)_n\text{CONR}^7\text{COR}^7$,
 (14) $-(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^7(\text{CH}_2)_n\text{CO}_2\text{R}^7$,
 (15) $-(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^7\text{CH}(\text{CO}_2\text{R}^7)_2$,
 (16) $-(\text{CH}_2)_n\text{NR}^7\text{R}^7$,
 30 (17) $-(\text{CH}_2)_n\text{NR}^7\text{C}(\text{O})\text{NR}^7\text{R}^7$,
 (18) $-(\text{CH}_2)_n\text{NR}^7\text{C}(\text{O})\text{R}^7$,
 (19) $-(\text{CH}_2)_n\text{OC}(\text{O})\text{NR}^7\text{R}^7$,
 (20) $-(\text{CH}_2)_n\text{NR}^7\text{CO}_2\text{R}^7$,
 (21) $-(\text{CH}_2)_n\text{NR}^7\text{SO}_2\text{R}^7$,
 35 (22) $-(\text{CH}_2)_n\text{SO}_2\text{NR}^7\text{R}^7$,
 (23) $-(\text{CH}_2)_n\text{SO}_2\text{R}^7$,
 (24) $-(\text{CH}_2)_n\text{SO}_3\text{H}$, and



wherein alkyl, alkenyl, -cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and $-(\text{CH}_2)_n$ are unsubstituted or substituted with one to five substituents selected from R^8 ;

each R^7 is independently selected from the group consisting of:

- 5 (1) hydrogen,
 (2) $-(\text{CH}_2)_n\text{OH}$,
 (3) $-\text{C}_{1-6}\text{alkyl}$,
 (4) $-(\text{CH}_2)_n\text{C}_{2-8}\text{heterocycloalkyl}$,
 (5) $-(\text{CH}_2)_n\text{C}_{3-8}\text{cycloalkyl}$,
 10 (6) $-(\text{CH}_2)_n\text{aryl}$, and
 (7) $-(\text{CH}_2)_n\text{heteroaryl}$,

wherein alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and $(\text{CH}_2)_n$ are unsubstituted or substituted with one to five substituents selected from R^8 ;

15 each R^8 is independently selected from the group consisting of:

- (1) oxo,
 (2) $-(\text{CH}_2)_n\text{halogen}$,
 (3) $-\text{C}_{1-6}\text{alkyl}$,
 (4) $-\text{C}_{1-6}\text{alkoxy}$,
 20 (5) $-(\text{CH}_2)_{0-1}\text{OH}$,
 (6) $-(\text{CH}_2)_n\text{CN}$,
 (7) $-(\text{CH}_2)_n\text{CF}_3$,
 (8) $-(\text{CH}_2)_n\text{SO}_3\text{H}$,
 (9) $-(\text{CH}_2)_n\text{CO}_2\text{H}$,
 25 (10) $-(\text{CH}_2)_n\text{CO}_2\text{C}_{1-6}\text{alkyl}$, and
 (11) $-(\text{CH}_2)_n\text{CO}_2\text{C}_{2-6}\text{alkene}$;

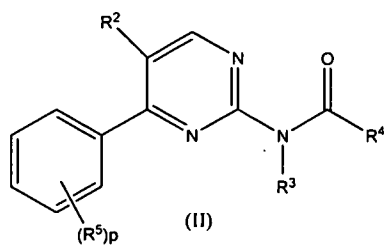
each n is independently 0, 1, 2, 3, 4, 5, 6, 7 or 8;

each m is independently 0, 1, 2, 3, or 4;

each p is independently 0, 1, 2, 3, 4 or 5; and

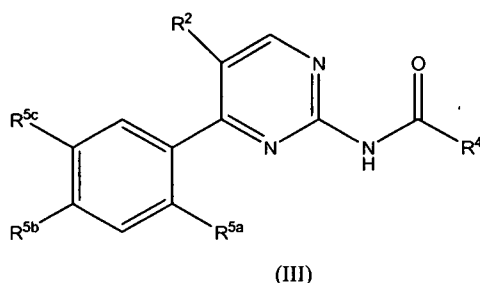
30 each q is independently 1, 2, 3, or 4.

In a further embodiment of the compounds of the present invention, there are provided compounds of formula II:



or a pharmaceutically acceptable salt thereof.

In a further embodiment of the compounds of the present invention, there are provided compounds of formula III:



5 or a pharmaceutically acceptable salt thereof.

In one class of the embodiments, R^1 is phenyl substituted with 1-5 substituents selected from R^5 .

In another class of the embodiments, R^2 is selected from the group consisting of: -
 (CH₂)_mcycloalkyl, and -(CH₂)_qaryl, wherein cycloalkyl, aryl and -(CH₂) are unsubstituted or
 10 substituted with one to five substituents selected from halogen, OH, -C₁₋₆alkyl, and -C₁₋₆alkoxy. In a subclass of this class, R^2 is selected from the group consisting of: -(CH₂)₀₋₂cyclohexyl, -
 (CH₂)₀₋₂cyclopentyl, -(CH₂)₀₋₂cycloheptyl, and -(CH₂)₁₋₂phenyl, wherein R^2 is unsubstituted or
 substituted with one to five substituents selected from halogen, OH, -C₁₋₆alkyl, and -C₁₋₆alkoxy. In subclass of this class, R^2 is selected from the group consisting of: -(CH₂)₀₋₂cyclohexyl, and -
 15 (CH₂)₀₋₂cyclopentyl, wherein R^2 is unsubstituted or substituted with one to five substituents
 selected from halogen, OH, -C₁₋₆alkyl, and -C₁₋₆alkoxy. In another subclass of this class, R^2 is
 selected from the group consisting of: -(CH₂)₁₋₂cyclohexyl, and -(CH₂)₁₋₂cyclopentyl, wherein R^2
 is unsubstituted or substituted with one to five substituents selected from halogen, OH, -C₁₋₆
 6alkyl, and -C₁₋₆alkoxy. In a subclass of this subclass, R^2 is -CH₂-cyclohexyl, wherein R^2 is
 20 unsubstituted or substituted with one to five substituents selected from halogen, OH, -C₁₋₆alkyl,
 and -C₁₋₆alkoxy.

In another class of the embodiments, R^2 is -(CH₂)_mcycloalkyl, wherein cycloalkyl and -
 (CH₂) are unsubstituted or substituted with one to five substituents selected from halogen, OH, -
 C₁₋₆alkyl, and -C₁₋₆alkoxy. In a subclass of this class, R^2 is selected from the group consisting
 25 of: -(CH₂)₀₋₂cyclohexyl, -(CH₂)₀₋₂cyclopentyl, and -(CH₂)₀₋₂cycloheptyl, wherein R^2 is
 unsubstituted or substituted with one to five substituents selected from halogen, OH, -C₁₋₆alkyl,
 and -C₁₋₆alkoxy. In a subclass of this class, R^2 is selected from the group consisting of: -(CH₂)₀₋₂
 cyclohexyl, and -(CH₂)₀₋₂cyclopentyl, wherein R^2 is unsubstituted or substituted with one to five
 substituents selected from halogen, OH, -C₁₋₆alkyl, and -C₁₋₆alkoxy. In a subclass of this class,
 30 R^2 is -(CH₂)₀₋₂cyclopentyl unsubstituted or substituted with one to five substituents selected from
 halogen, OH, -C₁₋₆alkyl, and -C₁₋₆alkoxy. In a subclass of this class, R^2 is selected from the
 group consisting of: -(CH₂)₀₋₂cyclohexyl unsubstituted or substituted with one to five substituents

selected from halogen, OH, -C₁₋₆alkyl, and -C₁₋₆alkoxy. In a subclass of this subclass, R² is -CH₂-cyclohexyl unsubstituted or substituted with one to five substituents selected from halogen, OH, -C₁₋₆alkyl, and -C₁₋₆alkoxy.

5 In another class of the embodiments, R² is -(CH₂)_qaryl, wherein aryl and -(CH₂) are unsubstituted or substituted with one to five substituents selected from halogen, OH, -C₁₋₆alkyl, and -C₁₋₆alkoxy. In a subclass of this class, R² is -(CH₂)₁₋₂phenyl unsubstituted or substituted with one to five substituents selected from halogen, OH, -C₁₋₆alkyl, and -C₁₋₆alkoxy.

10 In another embodiment of the present invention, R³ is hydrogen. In another embodiment of the present invention, R³ is -C₁₋₆alkyl, wherein alkyl is unsubstituted or substituted with one to five substituents selected from halogen and -OH.

15 In another embodiment of the present invention, R⁴ is a mono or bicyclic ring selected from the group consisting of: -C₃₋₈cycloalkyl, -C₃₋₈heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with one to five substituents selected from R⁶, provided that R⁶ is -(CH₂)₀₋₅CO₂H, or a substituent containing -(CH₂)₀₋₅CO₂H.

20 In another embodiment of the present invention, R⁴ is a mono or bicyclic ring selected from the group consisting of: -C₃₋₈cycloalkyl and -C₃₋₈heterocycloalkyl, wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with one to five substituents selected from R⁶. In another embodiment of the present invention, R⁴ is a mono or bicyclic ring selected from the group consisting of: -C₃₋₈cycloalkyl and -C₃₋₈heterocycloalkyl, wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with one to five substituents selected from R⁶, provided that R⁶ is -(CH₂)₀₋₅CO₂H, or a substituent containing -(CH₂)₀₋₅CO₂H.

25 In another embodiment of the present invention, R⁴ is a mono or bicyclic ring selected from the group consisting of: aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with one to five substituents selected from R⁶. In a class of this embodiment, R⁴ is selected from the group consisting of: phenyl, naphthalene, 1,2,3,4-tetrahydroquinoline, quinoline, 7-azaquinoline, indole, 1*H*-pyrrolo[2,3-*b*]pyridine, and pyridine, wherein R⁴ is unsubstituted or substituted with one to five substituents selected from R⁶. In another class of this embodiment, R⁴ is selected from the group consisting of: quinoline, indole, and naphthalene, wherein R⁴ is unsubstituted or substituted with one to five substituents selected from R⁶. In another class of this embodiment, R⁴ is selected from the group consisting of: quinoline, and indole, wherein R⁴ is unsubstituted or substituted with one to five substituents selected from R⁶. In another class of this embodiment, R⁴ is indole unsubstituted or substituted with one to five substituents selected from R⁶.

35 In another embodiment of the present invention, R⁴ is a mono or bicyclic ring selected from the group consisting of: aryl, and heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted with one to five substituents selected from R⁶, provided that R⁶ is -(CH₂)₀₋₅CO₂H,

or a substituent containing $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$. In a class of this embodiment, R^4 is selected from the group consisting of: phenyl, naphthalene, 1,2,3,4-tetrahydroquinoline, quinoline, 7-azaquinoline, indole, 1*H*-pyrrolo[2,3-*b*]pyridine, and pyridine, wherein R^4 is unsubstituted or substituted with one to five substituents selected from R^6 , provided that R^6 is $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$, or a substituent containing $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$. In another class of this embodiment, R^4 is selected from the group consisting of: quinoline, indole, and naphthalene, wherein R^4 is unsubstituted or substituted with one to five substituents selected from R^6 , provided that R^6 is $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$, or a substituent containing $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$. In another class of this embodiment, R^4 is selected from the group consisting of: quinoline, and indole, wherein R^4 is unsubstituted or substituted with one to five substituents selected from R^6 , provided that R^6 is $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$, or a substituent containing $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$. In another class of this embodiment, R^4 is indole unsubstituted or substituted with one to five substituents selected from R^6 , provided that R^6 is $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$, or a substituent containing $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$.

In another embodiment of the present invention, R^4 is a mono or bicyclic ring selected from the group consisting of: aryl unsubstituted or substituted with one to five substituents selected from R^6 . In a class of this embodiment, R^4 is phenyl or naphthalene, wherein phenyl and naphthalene are unsubstituted or substituted with one to five substituents selected from R^6 .

In another embodiment of the present invention, R^4 is a mono- or bicyclic ring selected from the group consisting of: aryl unsubstituted or substituted with one to five substituents selected from R^6 , provided that R^6 is $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$, or a substituent containing $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$. In a class of this embodiment, R^4 is phenyl or naphthalene, wherein phenyl and naphthalene are unsubstituted or substituted with one to five substituents selected from R^6 , provided that R^6 is $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$, or a substituent containing $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$.

In another embodiment of the present invention, R^4 is mono- or bicyclic ring selected from the group consisting of: heteroaryl unsubstituted or substituted with one to five substituents selected from R^6 . In a class of this embodiment, R^4 is selected from the group consisting of: 1,2,3,4-tetrahydroquinoline, quinoline, 7-azaquinoline, indole, 1*H*-pyrrolo[2,3-*b*]pyridine, and pyridine, wherein R^4 is unsubstituted or substituted with one to five substituents selected from R^6 . In a subclass of this class, R^4 is indole unsubstituted or substituted with one to five substituents selected from R^6 .

In another embodiment of the present invention, R^4 is a mono- or bicyclic ring selected from the group consisting of: heteroaryl unsubstituted or substituted with one to five substituents selected from R^6 , provided that R^6 is $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$, or a substituent containing $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$. In a class of this embodiment, R^4 is selected from the group consisting of: 1,2,3,4-tetrahydroquinoline, quinoline, 7-azaquinoline, indole, 1*H*-pyrrolo[2,3-*b*]pyridine, and pyridine, wherein R^4 is unsubstituted or substituted with one to five substituents selected from R^6 , provided that R^6 is $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$, or a substituent containing $-(\text{CH}_2)_{0.5}\text{CO}_2\text{H}$. In a subclass of

this class, R^4 is indole unsubstituted or substituted with one to five substituents selected from R^6 , provided that R^6 is $-(CH_2)_{0-5}CO_2H$, or a substituent containing $-(CH_2)_{0-5}CO_2H$.

In another embodiment of the present invention, R^4 is selected from the group consisting of: 1,2,3,4-tetrahydroquinoline, quinoline, 7-azaquinoline, indole, 1*H*-pyrrolo[2,3-*b*]pyridine, and pyridine, wherein R^4 is unsubstituted or substituted with one to five substituents selected from R^6 . In a class of this embodiment, R^4 is 1,2,3,4-tetrahydroquinoline, unsubstituted or substituted with one to five substituents selected from R^6 . In another class of this embodiment, R^4 is quinoline, unsubstituted or substituted with one to five substituents selected from R^6 . In another class of this embodiment, R^4 is 7-azaquinoline, unsubstituted or substituted with one to five substituents selected from R^6 . In another class of this embodiment, R^4 is indole, 1*H*-pyrrolo[2,3-*b*]pyridine, and pyridine, wherein R^4 is unsubstituted or substituted with one to five substituents selected from R^6 . In another class of this embodiment, R^4 is 1*H*-pyrrolo[2,3-*b*]pyridine, unsubstituted or substituted with one to five substituents selected from R^6 . In another class of this embodiment, R^4 is pyridine, unsubstituted or substituted with one to five substituents selected from R^6 . In yet another class of this embodiment, R^4 is pyridine, unsubstituted or substituted with one to five substituents selected from R^6 , provided that R^6 is not selected from the group consisting of $-(CH_2)_{2-6}CN$, $-(CH_2)_{2-6}$ heteroaryl wherein heteroaryl is tetrazolyl, $-(CH_2)_{2-6}CO_2R^7$, and $-(CH_2)_{2-6}C(O)NR^7R^7$.

In another embodiment of the present invention, R^4 is a mono or bicyclic ring selected from the group consisting of: $-C_{3-8}$ cycloalkyl, $-C_{3-8}$ heterocycloalkyl, aryl, and heteroaryl, wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with one to five substituents selected from R^6 , provided that when R^4 is phenyl, naphthalene, pyridine, pyrazine, piperidine, or piperazine, then R^6 is not selected from the group consisting of $-(CH_2)_{2-6}CN$, $-(CH_2)_{2-6}CO_2R^7$, and $-(CH_2)_{2-6}C(O)NR^7R^7$, and $-(CH_2)_{2-6}$ heteroaryl wherein heteroaryl is tetrazolyl. In a class of this embodiment, R^4 is selected from the group consisting of: 1,2,3,4-tetrahydroquinoline, quinoline, 7-azaquinoline, indole, 1*H*-pyrrolo[2,3-*b*]pyridine, and pyridine, wherein R^4 is unsubstituted or substituted with one to five substituents selected from R^6 , provided that when R^4 is pyridine then R^6 is not selected from the group consisting of $-(CH_2)_{2-6}CN$, $-(CH_2)_{2-6}$ heteroaryl wherein heteroaryl is tetrazolyl, $-(CH_2)_{2-6}CO_2R^7$, and $-(CH_2)_{2-6}C(O)NR^7R^7$.

In another embodiment of the present invention, R^4 is a mono or bicyclic ring selected from the group consisting of: $-C_{3-8}$ cycloalkyl, and $-C_{3-8}$ heterocycloalkyl, wherein cycloalkyl and heterocycloalkyl are unsubstituted or substituted with one to five substituents selected from R^6 .

In another embodiment of the present invention, R^4 is a mono or bicyclic ring selected from the group consisting of: aryl and heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted with one to five substituents selected from R^6 .

In another embodiment of the present invention, R^4 is a mono or bicyclic ring selected from the group consisting of: aryl and heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted with one to five substituents selected from R^6 , provided that when R^4 is phenyl, naphthalene, pyridine, pyrazine, piperidine, piperazine, then R^6 is not selected from the group consisting of $-(CH_2)_{2-6}CN$, $-(CH_2)_{2-6}CO_2R^7$, and $-(CH_2)_{2-6}C(O)NR^7R^7$, and $-(CH_2)_{2-6}$ heteroaryl wherein heteroaryl is tetrazolyl.

In another embodiment of the present invention, R^4 is a mono or bicyclic ring selected from the group consisting of: aryl, wherein aryl is unsubstituted or substituted with one to five substituents selected from R^6 . In a class of this embodiment, R^4 is phenyl or naphthalene.

10 In another embodiment of the present invention, R^4 is a mono or bicyclic ring selected from the group consisting of: aryl, wherein aryl is unsubstituted or substituted with one to five substituents selected from R^6 , provided that when R^4 is phenyl or naphthalene then R^6 is not selected from the group consisting of $-(CH_2)_{2-6}CN$, $-(CH_2)_{2-6}CO_2R^7$, and $-(CH_2)_{2-6}C(O)NR^7R^7$, and $-(CH_2)_{2-6}$ heteroaryl wherein heteroaryl is tetrazolyl. In a class of this embodiment, R^4 is
15 phenyl or naphthalene.

In another embodiment of the present invention, R^4 is a mono or bicyclic ring selected from the group consisting of: heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to five substituents selected from R^6 .

20 In another embodiment of the present invention, R^4 is a mono or bicyclic ring selected from the group consisting of: heteroaryl, wherein heteroaryl is unsubstituted or substituted with one to five substituents selected from R^6 , provided that when R^4 is pyridine, pyrazine, piperidine, piperazine, then R^6 is not selected from the group consisting of $-(CH_2)_{2-6}CN$, $-(CH_2)_{2-6}CO_2R^7$, and $-(CH_2)_{2-6}C(O)NR^7R^7$, and $-(CH_2)_{2-6}$ heteroaryl wherein heteroaryl is tetrazolyl.

25 In another embodiment, R^5 is independently selected from the group consisting of: $-(CH_2)_n$ halogen, $-(CH_2)_nOR^7$, and $-C_{1-6}$ alkyl, wherein alkyl and $-(CH_2)_n$ are unsubstituted or substituted with one to five substituents selected from halogen, OH, $-C_{1-6}$ alkyl, and $-C_{1-6}$ alkoxy. In a class of this embodiment, each R^5 is independently selected from the group consisting of: Cl, Br, F, I, $-OCH_3$ and $-CH_3$, wherein $-OCH_3$ and $-CH_3$ are unsubstituted or substituted with one to
30 five substituents selected from halogen, OH, $-C_{1-6}$ alkyl, and $-C_{1-6}$ alkoxy. In a subclass of this class, each R^5 is independently selected from the group consisting of: Cl, Br, $-OCH_3$ and $-CH_3$, wherein $-OCH_3$ and $-CH_3$ are unsubstituted or substituted with one to five substituents selected from halogen, OH, $-C_{1-6}$ alkyl, and $-C_{1-6}$ alkoxy. In another subclass of this class, each R^5 is independently selected from the group consisting of: Cl, $-OCH_3$ and $-CH_3$.

35 In another embodiment of the present invention, each R^6 is independently selected from the group consisting of: $-(CH_2)_n$ halogen, $-C_{1-6}$ alkyl, $-(CH_2)_n$ aryl, $-(CH_2)_nCO_2R^7$, and $-(CH_2)_nC(O)NR^7(CH_2)_nCO_2R^7$, wherein alkyl, aryl, and $-(CH_2)_n$ are unsubstituted or substituted

with one to five substituents selected from R^8 . In a class of this embodiment, R^6 is $-(CH_2)_{0-5}CO_2H$, or a substituent containing $-(CH_2)_{0-5}CO_2H$.

In another embodiment of the present invention, each R^6 is independently selected from the group consisting of: $-(CH_2)_n$ halogen, $-C_{1-6}$ alkyl, $-(CH_2)_n$ phenyl, $-(CH_2)_nCO_2R^7$, and $-(CH_2)_nC(O)NR^7(CH_2)_nCO_2R^7$, wherein alkyl, phenyl, and $-(CH_2)_n$ are unsubstituted or substituted with one to five substituents selected from R^8 . In a class of this embodiment, R^6 is $-(CH_2)_{0-5}CO_2H$, or a substituent containing $-(CH_2)_{0-5}CO_2H$.

In another embodiment of the present invention, each R^6 is independently selected from the group consisting of: Cl, $-CH_3$, $-CH_2$ phenyl, $-(CH_2)_{0-5}CO_2CH_3$, $-(CH_2)_{0-5}CO_2H$, $-CH_2CO_2CH_3$, $-CH_2CO_2H$, and $-CH_2C(O)NHCH_2CO_2H$, wherein $-CH_3$, $-CH_2$ phenyl, and $-(CH_2)_n$ are unsubstituted or substituted with one to five substituents selected from R^8 . In a class of this embodiment, R^6 is $-(CH_2)_{0-5}CO_2H$, or a substituent containing $-(CH_2)_{0-5}CO_2H$.

In another embodiment of the present invention, each R^7 is independently selected from the group consisting of: hydrogen, $-(CH_2)_nOH$, $-C_{1-6}$ alkyl, $-(CH_2)_nC_{2-8}$ heterocycloalkyl, $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_n$ aryl, and $-(CH_2)_n$ heteroaryl. In a class of this embodiment, each R^7 is independently selected from the group consisting of: hydrogen, and $-C_{1-6}$ alkyl. In a class of this embodiment, R^7 is hydrogen. In another class of this embodiment, R^7 is $-C_{1-6}$ alkyl.

In another embodiment of the present invention, each R^8 is independently selected from the group consisting of: oxo, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkoxy, $-(CH_2)_{0-1}OH$, $-(CH_2)_nCO_2H$, and $-(CH_2)_nCO_2C_{1-6}$ alkyl.

In another class of the embodiments, each n is independently 0, 1, 2, 3, 4, 5, 6, 7 or 8. In a subclass of this class, each n is independently 0, 1, 2, 3, 4, 5 or 6. In a subclass of this class, n is 0, 1, 2, 3 or 4. In another subclass of this class, n is 0. In another subclass of this class, n is 1. In another subclass of this class, n is 2. In another subclass of this class, n is 3. In another subclass of this class, n is 4. In another subclass of this class, n is 5. In another subclass of this class, n is 6. In another class of the embodiments of the present invention, n is 1 or 2. In another class of the embodiments of the present invention, n is 0, 1, 2, 3, and 4.

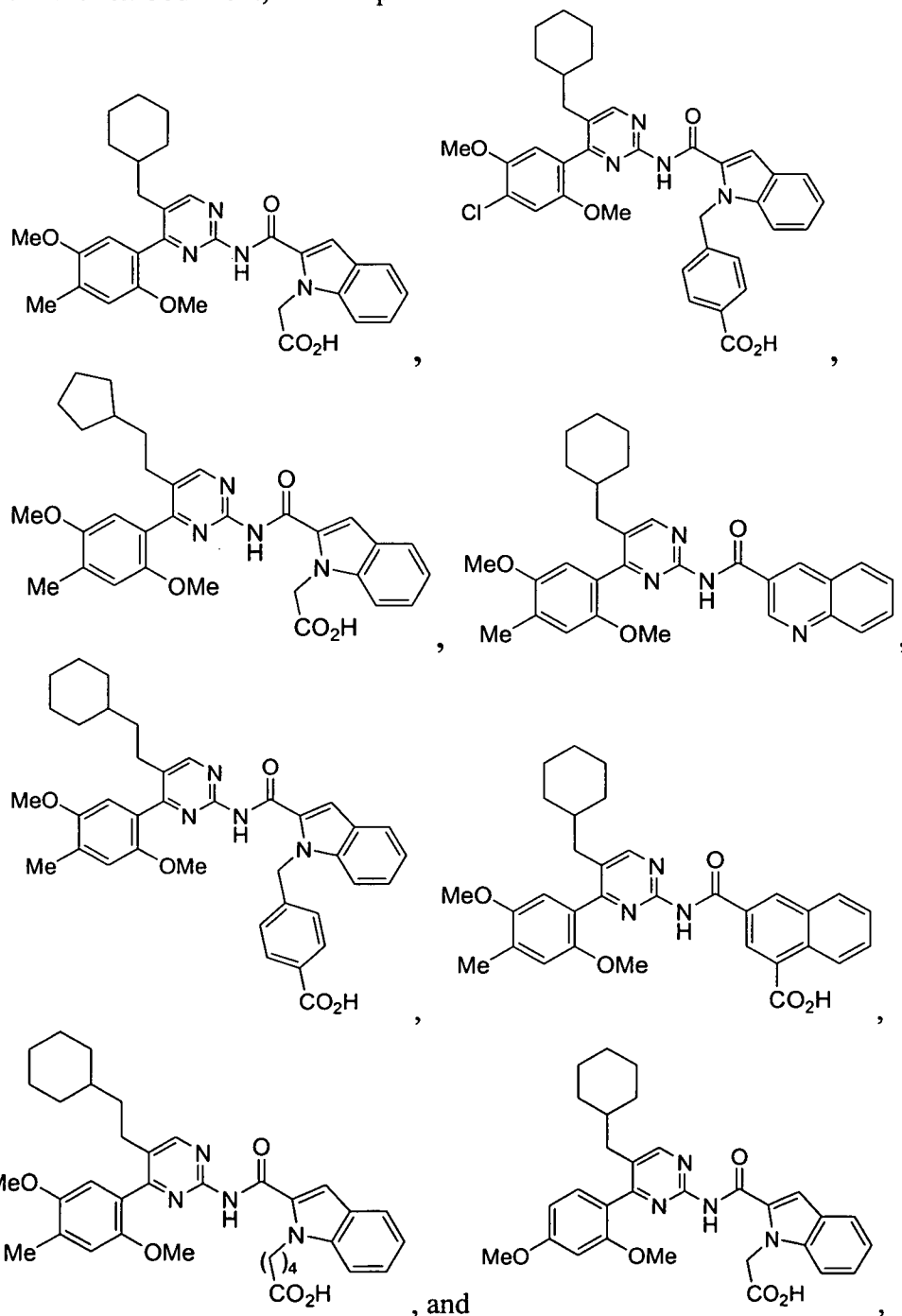
In another class of the embodiments of the present invention, each m is independently selected from the group consisting of each m is independently 1, 2, 3 and 4. In a subclass of this class, m is 1, 2 or 3. In another subclass of this class, m is 1. In a nother subclass of this class m is 2. In another subclass of this class, m is 3. In another subclass of this class, m is 4. In another class of this embodiment, m is 0.

In another class of the embodiments of the present invention, p is 1, 2, or 3. In another class of the embodiments of the present invention, each p is independently 0, 1, 2, 3 or 4. In a subclass of this class, p is 0. In another subclass of this class, p is 1. In another subclass of this class, p is 2. In another subclass of this class, p is 3. In a subclass of this class, p is 4. In another

class of the embodiments of the present invention, each p is 5. In another class of the embodiments of the present invention, p is 2 or 3.

In another class of the embodiments of the present invention, each q is independently 1, 2, or 3. In another subclass of this class, q is 1. In another subclass of this class, q is 2. In another subclass of this class, q is 3. In another class of the embodiments of the present invention, each q is independently 4.

In another embodiment, the compound of formula I is selected from:



or a pharmaceutically acceptable salt thereof.

In another class of the embodiments, the pharmaceutically acceptable salt is a trifluoroacetic acid salt. In another class of the embodiments, the pharmaceutically acceptable salt is a hydrochloric acid salt.

5 The compounds of formula I, II and III are effective as cholecystokinin receptor ligands and are particularly effective as selective ligands of the cholecystokinin-1 receptor. They are therefore useful for the treatment and/or prevention of disorders responsive to the modulation of the cholecystokinin-1 receptor, such as obesity, diabetes, and obesity-related disorders. More particularly, the compounds of formula I, II and III are selective cholecystokinin-1 receptor (CCK-1R) agonists useful for the treatment of disorders responsive to the activation of the
10 cholecystokinin-1 receptor, such as obesity, diabetes, as well as the treatment of gallstones.

One aspect of the present invention provides a method for the treatment or prevention of disorders, diseases or conditions responsive to the modulation of the cholecystokinin-1 receptor in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula I, II or III, or a pharmaceutically
15 acceptable salt thereof.

Another aspect of the present invention provides a method for the treatment or prevention of obesity, diabetes, or an obesity related disorder in a subject in need thereof which comprises administering to said subject a therapeutically or prophylactically effective amount of a cholecystokinin-1 receptor agonist of the present invention. Another aspect of the present
20 invention provides a method for the treatment or prevention of obesity in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula I, II or III, or a pharmaceutically acceptable salt thereof. Another aspect of the present invention provides a method for reducing food intake in a subject in need thereof which comprises administering to the subject a therapeutically or
25 prophylactically effective amount of a compound of formula I, II or III, or a pharmaceutically acceptable salt thereof. Another aspect of the present invention provides a method for increasing satiety in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula I, II or III, or a pharmaceutically acceptable salt thereof. Another aspect of the present invention provides a method for reducing
30 appetite in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula I, II or III, or a pharmaceutically acceptable salt thereof. Another aspect of the present invention provides a method for delaying gastric emptying in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula I,
35 II or III, or a pharmaceutically acceptable salt thereof. Another aspect of the present invention provides a method for the treatment or prevention of bulimia nervosa in a subject in need thereof

which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula I, II or III, or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention provides a method for the treatment or prevention of diabetes mellitus in a subject in need thereof comprising administering to the subject a
5 therapeutically or prophylactically effective amount of a compound of formula I, II or III, or a pharmaceutically acceptable salt thereof. Another aspect of the present invention provides a method for the treatment or prevention of dyslipidemia in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a
10 compound of formula I, II or III, or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention provides a method for the treatment or prevention of tardive dyskinesia in a subject in need thereof which comprises administering to said subject a
15 therapeutically or prophylactically effective amount of a cholecystokinin-1 receptor agonist of the present invention.

Another aspect of the present invention provides a method for the treatment or prevention
15 of an obesity-related disorder selected from the group consisting of overeating, binge eating, hypertension, elevated plasma insulin concentrations, insulin resistance, hyperlipidemia, endometrial cancer, breast cancer, prostate cancer, colon cancer, kidney cancer, osteoarthritis, obstructive sleep apnea, heart disease, abnormal heart rhythms and arrhythmias, myocardial
20 infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovary disease, craniopharyngioma, metabolic syndrome, insulin resistance syndrome, sexual and reproductive dysfunction, infertility, hypogonadism, hirsutism, obesity-related gastro-esophageal reflux, Pickwickian syndrome, inflammation, systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease,
25 gout, constipation, irritable bowel syndrome, inflammatory bowel syndrome, cardiac hypertrophy, left ventricular hypertrophy, in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula I, II or III, or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention provides a method for the treatment or prevention of cognitive and memory deficiency, including the treatment of Alzheimer's disease, in a subject
30 in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula I, II or III, or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention provides a method for the treatment or prevention of pain in a subject in need thereof which comprises administering to the subject a therapeutically
35 or prophylactically effective amount of a compound of formula I, II or III, or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention provides a method for the treatment or prevention of cholelithiasis (gallstones) in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula I, II or III, or a pharmaceutically acceptable salt thereof.

5 Another aspect of the present invention provides a method for the treatment or prevention of cholecystitis (inflammation of the gallbladder) in a subject in need thereof which comprises administering to the subject a therapeutically or prophylactically effective amount of a compound of formula I, II or III, or a pharmaceutically acceptable salt thereof.

10 The present invention also relates to methods for treating or preventing obesity by administering a cholecystokinin-1 receptor agonist of the present invention in combination with a therapeutically or prophylactically effective amount of another agent known to be useful to treat or prevent the condition. The present invention also relates to methods for treating or preventing diabetes by administering the cholecystokinin-1 receptor agonist of the present invention in combination with a therapeutically or prophylactically effective amount of another agent known to be useful to treat or prevent the condition. The present invention also relates to methods for treating or preventing obesity related disorders by administering the cholecystokinin-1 receptor agonist of the present invention in combination with a therapeutically or prophylactically effective amount of another agent known to be useful to treat or prevent the condition.

15 Another aspect of the present invention provides a pharmaceutical composition comprising a compound of formula I, II or III and a pharmaceutically acceptable carrier. Yet another aspect of the present invention relates to the use of a compound of formula I, II or III for the manufacture of a medicament useful for the treatment or prevention, or suppression of a disease mediated by the cholecystokinin-1 receptor in a subject in need thereof. Yet another aspect of the present invention relates to the use of a cholecystokinin-1 agonist of the present invention for the manufacture of a medicament useful for the treatment or prevention, or suppression of a disease mediated by the cholecystokinin-1 receptor, wherein the disease is selected from the group consisting of obesity, diabetes and an obesity-related disorder in a subject in need thereof. Yet another aspect of the present invention relates to the use of a cholecystokinin-1 agonist of the present invention for the manufacture of a medicament useful for the treatment or prevention of gallstones in a subject in need thereof. Yet another aspect of the present invention relates to the use of a cholecystokinin-1 agonist of the present invention for the manufacture of a medicament useful for the treatment or prevention of dyslipidemia in a subject in need thereof. Yet another aspect of the present invention relates to the use of a cholecystokinin-1 agonist of the present invention for the manufacture of a medicament useful for the treatment or prevention of bulimia nervosa in a subject in need thereof. Yet another aspect of the present invention relates to the use of a cholecystokinin-1 agonist of the present invention for the manufacture of a medicament useful for the treatment or prevention of

constipation in a subject in need thereof. Yet another aspect of the present invention relates to the use of a cholecystokinin-1 agonist of the present invention for the manufacture of a medicament useful for the treatment or prevention of irritable bowel syndrome in a subject in need thereof.

5 Yet another aspect of the present invention relates to the use of a therapeutically effective amount of a cholecystokinin -1 receptor agonist of formula I, II or III, or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of an agent selected from the group consisting of an insulin sensitizer, an insulin mimetic, a sulfonylurea, an α -glucosidase inhibitor, a dipeptidyl peptidase 4 (DPP-4 or DP-IV) inhibitor, a glucagons like peptide 1 (GLP-
10 1) agonist, a HMG-CoA reductase inhibitor, a serotonergic agent, a β 3-adrenoreceptor agonist, a neuropeptide Y1 antagonist, a neuropeptide Y2 agonist, a neuropeptide Y5 antagonist, a pancreatic lipase inhibitor, a cannabinoid CB₁ receptor antagonist or inverse agonist, a melanin-concentrating hormone receptor antagonist, a melanocortin 4 receptor agonist, a bombesin receptor subtype 3 agonist, a ghrelin receptor antagonist, PYY, PYY₃₋₃₆, and a NK-1 antagonist,
15 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful for the treatment, control, or prevention of obesity, diabetes or an obesity-related disorder in a subject in need of such treatment. Yet another aspect of the present invention relates to the use of a therapeutically effective amount of a cholecystokinin-1 receptor agonist of formula I, II or III, and pharmaceutically acceptable salts and esters thereof, and a therapeutically effective amount
20 of an agent selected from the group consisting of an insulin sensitizer, an insulin mimetic, a sulfonylurea, an α -glucosidase inhibitor, a dipeptydyl peptidase 4 inhibitor, a glucagon-like peptide 1 agonist, a HMG-CoA reductase inhibitor, a serotonergic agent, a β 3-adrenoreceptor agonist, a neuropeptide Y1 antagonist, a neuropeptide Y2 agonist, a neuropeptide Y5 antagonist, a pancreatic lipase inhibitor, a cannabinoid CB₁ receptor antagonist or inverse agonist, a
25 melanin-concentrating hormone receptor antagonist, a melanocortin 4 receptor agonist, a bombesin receptor subtype 3 agonist, a ghrelin receptor antagonist, PYY, PYY₃₋₃₆, and a NK-1 antagonist, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treatment or prevention of obesity, diabetes or an obesity-related disorder which comprises an effective amount of a cholecystokinin-1 receptor agonist of formula I, II or III and an effective
30 amount of the agent, together or separately. Yet another aspect of the present invention relates to a product containing a therapeutically effective amount of a cholecystokinin-1 receptor agonist of formula I, II or III, or a pharmaceutically acceptable salt thereof; and and a therapeutically effective amount of an agent selected from the group consisting of an insulin sensitizer, an insulin mimetic, a sulfonylurea, an α -glucosidase inhibitor, a HMG-CoA reductase inhibitor, a
35 serotonergic agent, a β 3-adrenoreceptor agonist, a neuropeptide Y1 antagonist, a neuropeptide Y2 agonist, a neuropeptide Y5 antagonist, a pancreatic lipase inhibitor, a cannabinoid CB₁ receptor antagonist or inverse agonist, a melanocortin 4 receptor agonist, a melanin-concentrating

hormone receptor antagonist, a bombesin receptor subtype 3 agonist, a ghrelin receptor antagonist, PYY, PYY₃₋₃₆, and a NK-1 antagonist, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use in obesity, diabetes, or an obesity-related disorder.

5 The compounds of formula I, II and III can be provided in kit. Such a kit typically contains an active compound in dosage forms for administration. A dosage form contains a sufficient amount of active compound such that a beneficial effect can be obtained when administered to a patient during regular intervals, such as 1, 2, 3, 4, 5 or 6 times a day, during the course of 1 or more days. Preferably, a kit contains instructions indicating the use of the dosage
10 form for weight reduction (*e.g.*, to treat obesity) and the amount of dosage form to be taken over a specified time period.

Throughout the instant application, the following terms have the indicated meanings:

The term “alkyl”, as well as other groups having the prefix “alk”, such as alkoxy, alkanoyl, means carbon chains of the designated length which may be in a straight or branched
15 configuration, or combinations thereof. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, 1-methylpropyl, 2-methylpropyl, tert-butyl, n-pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,2-dimethylpropyl, 1,1-dimethylpropyl, 2,2-dimethylpropyl, n-hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 1,1-dimethyl butyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-
20 dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethyl butyl, n-heptyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 1-ethylpentyl, 2-ethylpentyl, 3-ethylpentyl, 4-ethylpentyl, 1-propylbutyl, 2-propylbutyl, 3-propylbutyl, 1,1-dimethylpentyl, 1,2-dimethylpentyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl. 2,4-
25 dimethylpentyl, 3,3-dimethylpentyl, 3,4-dimethylpentyl, 4,4-dimethylpentyl, 1-methyl-1-ethylbutyl, 1-methyl-2-ethylbutyl, 2-methyl-2-ethylbutyl, 1-ethyl-2-methylbutyl, 1-ethyl-3-methylbutyl, 1,1-diethylpropyl, n-octyl, n-nonyl, and the like.

The term “alkenyl” means carbon chains which contain at least one carbon-carbon double bond, and which may be linear or branched or combinations thereof. Examples of alkenyl include vinyl, allyl, isopropenyl, pentenyl, hexenyl, heptenyl, 1-propenyl, 2-butenyl, 2-methyl-2-
30 butenyl, and the like.

The term “alkynyl” means carbon chains which contain at least one carbon-carbon triple bond, and which may be linear or branched or combinations thereof. Examples of alkynyl include ethynyl, propargyl, 3-methyl-1-pentynyl, 2-heptynyl and the like.

The term “alkoxy” means alkyl chains of the designated length which contain at least one
35 ether linkage and which may be linear or branched or combinations thereof. Examples of alkoxy include methoxy, ethoxy, 1-propoxy, 2-propoxy, 1-butoxy, 2-butoxy, methylmethoxy,

methylethoxy, methyl-1-propoxy, methyl-2-propoxy, ethyl-2-methoxy, ethyl-1-methoxy and the like.

The term "halogen" includes fluorine, chlorine, bromine and iodine.

The term "C₁₋₄ alkyliminoyl" means C₁₋₃C(=NH)-.

5 The term "aryl" includes mono- or bicyclic aromatic rings containing only carbon atoms. Examples of aryl include phenyl and naphthyl.

The term "heteroaryl" includes monocyclic aromatic rings that contain from 1 to 4 heteroatoms selected from nitrogen, oxygen and sulfur, and bicyclic heteroaromatic ring systems with at least one aromatic ring that contains from 1 to 4 heteroatoms selected from nitrogen,
10 oxygen and sulfur. Examples thereof include, but are not limited to, pyridinyl, furyl, thienyl, pyrrolyl, oxazolyl, thiophenyl, thiazolyl, isothiazolyl, triazolyl, triazinyl, tetrazolyl, thiadiazolyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, pyrazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, benzimidazolyl, benzofuryl, benzothienyl, indolyl, benzthiazolyl, benzoxazolyl, and the like. In one embodiment of the present invention, heteroaryl is selected
15 from the group consisting of pyridinyl, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, triazolyl, triazinyl, tetrazolyl, thiadiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxathiazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, benzimidazolyl, benzofuryl, benzothienyl, indolyl, benzthiazolyl, and benzoxazolyl. Bicyclic heteroaromatic rings include, but are not limited to, benzothiadiazole, indole, indazole, benzothiophene, benzofuran,
20 benzimidazole, benzisoxazole, benzothiazole, quinoline, 7-azaquinoline, quinazoline, benzotriazole, benzoxazole, isoquinoline, purine, furopyridine, thienopyridine, benzisodiazole, triazolopyrimidine, and 5,6,7,8-tetrahydroquinoline, 1,2,3,4-tetrahydroquinoline; 1,2,3,4-tetrahydro-1,8-naphthyridine; 1-*H*-pyrrolo[2,3-*b*]pyridine; imidazo[1,2-*a*]pyrazine; benzopyrazole; benzodioxole; triazolopyridine; and benzopyrrole.

25 The term "cycloalkyl" includes mono- or bicyclic non-aromatic rings containing only carbon atoms. Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl.

The term "heterocycloalkyl" is intended to include non-aromatic heterocycles containing one to four heteroatoms selected from nitrogen, oxygen and sulfur. Examples of
30 heterocycloalkyls include, but are not limited to, azetidine, piperidine, morpholine, thiamorpholine, pyrrolidine, imidazolidine, tetrahydrofuran, piperazine, 1-thia-4-aza-cyclohexane.

Certain of the above defined terms may occur more than once in the above formula and upon such occurrence each term shall be defined independently of the other; thus for example,
35 NR⁴R⁴ may represent NH₂, NHCH₃, N(CH₃)CH₂CH₃, and the like.

The term "subject" means a mammal. One embodiment of the term "mammal" is a "human," said human being either male or female. The instant compounds are also useful for

treating or preventing obesity and obesity related disorders in cats and dogs. As such, the term “mammal” includes companion animals such as cats and dogs. The term “mammal in need thereof” refers to a mammal who is in need of treatment or prophylaxis as determined by a researcher, veterinarian, medical doctor or other clinician.

5 The term "composition", as in pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients.
10 Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier.

 By a cholecystokinin receptor “agonist” is meant an endogenous or drug substance or compound that can interact with a cholecystokinin receptor and initiate a pharmacological or
15 biochemical response characteristic of cholecystokinin receptor activation. The “agonistic” properties of the compounds of the present invention were measured in the functional assay described below.

 By “binding affinity” is meant the ability of a compound/drug to bind to its biological target, in the the present instance, the ability of a compound of formula I, II and III, to bind to a
20 cholecystokinin receptor. Binding affinities for the compounds of the present invention were measured in the binding assay described below and are expressed as IC_{50} 's.

 “Efficacy” describes the relative intensity of response which different agonists produce even when they occupy the same number of receptors and with the same affinity. Efficacy is the property that describes the magnitude of response. Properties of compounds can be categorized
25 into two groups, those which cause them to associate with the receptors (binding affinity) and those that produce a stimulus (efficacy). The term “efficacy” is used to characterize the level of maximal responses induced by agonists. Not all agonists of a receptor are capable of inducing identical levels of maximal responses. Maximal response depends on the efficiency of receptor coupling, that is, from the cascade of events, which, from the binding of the drug to the receptor,
30 leads to the desired biological effect.

 The functional activities expressed as EC_{50} 's and the “agonist efficacy” for the compounds of the present invention at a particular concentration were measured in the functional assay described below. The CCK1R active and selective agonists of the present invention have an $IC_{50} \leq 1000$ nM, preferred CCK1R active and selective agonists of the present invention have
35 an $IC_{50} < 500$ nM, more preferred CCK1R active and selective agonists of the present invention have an $IC_{50} < 50$ nM, and the most preferred CCK1R active and selective agonists of the present invention have an $IC_{50} < 10$ nM, while having at least a 2-fold selectivity over CCK2R, more

preferably a >10-fold selectivity over CCK2R, and most preferably a > 100-fold selectivity over CCK2R. The CCK1R active and selective agonists of the present invention have an $EC_{50} \leq 1000$ nM, preferred CCK1R active and selective agonists of the present invention have an $EC_{50} < 500$ nM, more preferred CCK1R active and selective agonists of the present invention have an $EC_{50} < 50$ nM, and the most preferred CCK1R active and selective agonists of the present invention have an $EC_{50} < 10$ nM, while having at least a 2-fold selectivity over CCK2R, more preferably a >10-fold selectivity over CCK2R, and most preferably a > 100-fold selectivity over CCK2R.

Compounds of formula I, II and III, may contain one or more asymmetric or chiral centers and can exist in different stereoisomeric forms, such as racemates and racemic mixtures, single enantiomers, enantiomeric mixtures, individual diastereomers and diastereomeric mixtures. All stereoisomeric forms of the intermediates and compounds of the present invention as well as mixtures thereof, including racemic and diastereomeric mixtures, which possess properties useful in the treatment of the conditions discussed herein or are intermediates useful in the preparation of compounds having such properties, form a part of the present invention.

Generally, one of the enantiomers will be more active biologically than the other enantiomer. Racemic mixtures can subsequently be separated into each enantiomer using standard conditions, such as resolution or chiral chromatography. Diastereomeric mixtures may be separated into their individual diastereoisomers on the basis of their physical chemical differences by methods well known to those skilled in the art, such as by chiral chromatography using an optically active stationary phase and/or fractional crystallization from a suitable solvent. Absolute stereochemistry may be determined by X-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration. Enantiomers may be separated by use of a chiral HPLC column and by converting the enantiomeric mixture into a diastereomeric mixture by reaction with an appropriate optically active compound (e.g., chiral auxiliary such as a chiral alcohol or Mosher's acid chloride), separating the diastereoisomers and converting (e.g., hydrolyzing) the individual diastereoisomers to the corresponding pure enantiomers. Alternatively, any stereoisomer of a compound of the general formula I, II and III may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known absolute configuration.

The present invention includes all such isomeric forms of the compounds of formula I, II and III, including the E and Z geometric isomers of double bonds and mixtures thereof. A number of the compounds of the present invention and intermediates therefor exhibit tautomerism and therefore may exist in different tautomeric forms under certain conditions. The term "tautomer" or "tautomeric form" refers to structural isomers of different energies which are interconvertible via a low energy barrier. For example, proton tautomers (also known as prototropic tautomers) include interconversions via migration of a proton, such as keto-enol and

imine-enamine isomerizations. A specific example of a proton tautomer is an imidazole moiety where the hydrogen may migrate between the ring nitrogens. Valence tautomers include interconversions by reorganization of some of the bonding electrons. All such tautomeric forms (e.g., all keto-enol and imine-enamine forms) are within the scope of the invention. The depiction of any particular tautomeric form in any of the structural formulas herein is not intended to be limiting with respect to that form, but is meant to be representative of the entire tautomeric set.

The present invention also encompasses isotopically labeled compounds which are identical to the compounds of Formula (I) or intermediates thereof 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 the intermediates or compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine, iodine, and chlorine, such as 2H , 3H , 11C , 13C , 14C , 13N , 15N , 15O , 17O , 18O , 31P , 32P , 35S , 18F , 123I , 125I and 36Cl , respectively. Compounds of the present invention, prodrugs thereof and pharmaceutically acceptable salts, hydrates and solvates of said compounds and of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of the present invention. Certain isotopically labeled compounds of the present invention (e.g., those labeled with 3H and 14C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., 3H) and carbon-14 (i.e., 14C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., 2H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Positron emitting isotopes such as 15O , 13N , 11C , and 18F are useful for positron emission tomography (PET) studies to examine substrate receptor occupancy. Isotopically labeled compounds of the present invention can generally be prepared by following procedures analogous to those disclosed in the Schemes and/or in the Examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

The compounds of the present invention and intermediates may exist in unsolvated as well as solvated forms with solvents such as water, ethanol, isopropanol and the like, and both solvated and unsolvated forms are included within the scope of the invention. Solvates for use in the methods aspect of the invention should be with pharmaceutically acceptable solvents. It will be understood that the compounds of the present invention include hydrates, solvates, polymorphs, crystalline, hydrated crystalline and amorphous forms of the compounds of the present invention, and pharmaceutically acceptable salts thereof.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and

inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganese salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, lithium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable
5 organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine,
10 lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, TEA, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of formula I, II and III is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, formic,
15 fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, malonic, mucic, nitric, pantoic, pantothenic, phosphoric, propionic, succinic, sulfuric, tartaric, p-toluenesulfonic acid, trifluoroacetic acid, and the like. Particularly preferred are citric, fumaric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids. It will be understood that, as used herein, references to the compounds of formula I, II and
20 III are meant to also include the pharmaceutically acceptable salts, such as the hydrochloride salts and trifluoroacetic acid salts.

Compounds of formula I, II and III are cholecystokinin receptor ligands and as such are useful in the treatment, control or prevention of diseases, disorders or conditions responsive to the modulation of one or more of the cholecystokinin receptors. In particular, the compounds of
25 formula I, II and III act as cholecystokinin-1 receptor agonists useful in the treatment, control or prevention of diseases, disorders or conditions responsive to the activation of the cholecystokinin-1 receptor. Such diseases, disorders or conditions include, but are not limited to, obesity (by reducing food intake, reducing appetite, increasing metabolic rate, increasing satiety, reducing carbohydrate craving, reducing gastric emptying), diabetes mellitus (by enhancing
30 glucose tolerance, decreasing insulin resistance), bulimia nervosa and related eating disorders, dyslipidemia, hypertension, hyperlipidemia, osteoarthritis, cancer, gall stones, cholelithiasis, cholecystitis, gall bladder disease, sleep apnea, depression, anxiety, compulsion, neuroses, irritable bowel syndrome, inflammatory bowel syndrome, constipation, pain, neuroprotective and cognitive and memory enhancement including the treatment of Alzheimer's disease. Such
35 diseases, conditions and disorders also include non-obese overweight conditions and normal weight conditions where weight control or management is desired in order to prevent an obese or overweight condition from developing, or to maintain a healthy weight.

The compounds and compositions of the present invention are useful for the treatment or prevention of disorders associated with excessive food intake, such as obesity and obesity-related disorders. The obesity herein may be due to any cause, whether genetic or environmental.

The obesity-related disorders herein are associated with, caused by, or result from obesity.

5 Examples of obesity-related disorders include overeating, binge eating, bulimia nervosa, hypertension, type 2 diabetes, elevated plasma insulin concentrations, hyperinsulinemia, insulin resistance, glucose intolerance, dyslipidemia, hyperlipidemia, endometrial cancer, breast cancer, prostate cancer, kidney cancer, colon cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, cholecystitis, gallstones, gout, gallbladder disease, abnormal heart rhythms and
10 arrhythmias, myocardial infarction, congestive heart failure, coronary heart disease, angina pectoris, sudden death, stroke, metabolic syndrome, psychological disorders (depression, eating disorders, distorted bodyweight, and low self esteem), and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g. children with acute lymphoblastic leukemia. Further examples of obesity-related
15 disorders are sexual and reproductive dysfunction, such as polycystic ovary disease, infertility, hypogonadism in males and hirsutism in females, gastrointestinal motility disorders, such as obesity-related gastro-esophageal reflux, respiratory disorders, such as obesity-hypoventilation syndrome (Pickwickian syndrome), cardiovascular disorders, inflammation, such as systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower
20 back pain, gallbladder disease, gout, and kidney cancer. Additionally, the present compounds are useful in the treatment of any condition in which it is desirable to lose weight or to reduce food intake. Additionally, the present compounds are useful in the treatment of any condition in which it is desirable to enhance cognition and memory, such as Alzheimer's Disease. The compositions of the present invention are also useful for reducing the risk of secondary outcomes
25 of obesity, such as reducing the risk of left ventricular hypertrophy. Therefore, the present invention provides methods of treatment or prevention of such diseases, conditions and/or disorders modulated by CCK-1 receptor agonists in an animal which comprises administering to the animal in need of such treatment a compound of formula I, II or III, in particular a therapeutically or prophylactically effective amount thereof.

30 Some agonists encompassed by formula I, II and III show highly selective affinity for the cholecystokinin-1 receptor (CCK-1R) relative to cholecystokinin-2 receptor CCK-2R (also known as the CCK-B receptor), which makes them especially useful in the prevention and treatment of obesity, diabetes, and obesity related disorders. Compounds of the present invention are at least 500 fold more selective for the CCK-1 receptor than for the CCK-2 receptor.

35 The term "metabolic syndrome", also known as syndrome X, is defined in the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP-III). E.S. Ford et al., JAMA, vol. 287

(3), Jan. 16, 2002, pp 356-359. Briefly, a person is defined as having metabolic syndrome if the person has three or more of the following symptoms: abdominal obesity, hypertriglyceridemia, low HDL cholesterol, high blood pressure, and high fasting plasma glucose. The criteria for these are defined in ATP-III. The term "diabetes," as used herein, includes both insulin-
5 dependent diabetes mellitus (i.e., IDDM, also known as type I diabetes) and non-insulin-dependent diabetes mellitus (i.e., NIDDM, also known as Type II diabetes). Type I diabetes, or insulin-dependent diabetes, is the result of an absolute deficiency of insulin, the hormone which regulates glucose utilization. Type II diabetes, or insulin-independent diabetes (i.e., non-insulin-dependent diabetes mellitus), often occurs in the face of normal, or even elevated levels of
10 insulin and appears to be the result of the inability of tissues to respond appropriately to insulin. Most of the Type II diabetics are also obese. The compositions of the present invention are useful for treating both Type I and Type II diabetes. The compositions are especially effective for treating Type II diabetes. The compounds or combinations of the present invention are also useful for treating and/or preventing gestational diabetes mellitus.

15 Treatment of diabetes mellitus refers to the administration of a compound or combination of the present invention to treat diabetes. One outcome of treatment may be decreasing the glucose level in a subject with elevated glucose levels. Another outcome of treatment may be improving glycemic control. Another outcome of treatment may be decreasing insulin levels in a subject with elevated insulin levels. Another outcome of treatment may be decreasing plasma
20 triglycerides in a subject with elevated plasma triglycerides. Another outcome of treatment may be lowering LDL cholesterol in a subject with high LDL cholesterol levels. Another outcome of treatment may be increasing HDL cholesterol in a subject with low HDL cholesterol levels. Another outcome may be decreasing the LDL/HDL ratio in a subject in need thereof. Another outcome of treatment may be increasing insulin sensitivity. Another outcome of treatment may be
25 enhancing glucose tolerance in a subject with glucose intolerance. Another outcome of treatment may be decreasing insulin resistance in a subject with increased insulin resistance or elevated levels of insulin. Another outcome may be decreasing triglycerides in a subject with elevated triglycerides. Yet another outcome may be improving LDL cholesterol, non-HDL cholesterol, triglyceride, HDL cholesterol or other lipid analyte profiles. Prevention of diabetes mellitus
30 refers to the administration of a compound or combination of the present invention to prevent the onset of diabetes in a subject at risk thereof.

"Obesity" is a condition in which there is an excess of body fat. The operational definition of obesity is based on the Body Mass Index (BMI), which is calculated as body weight per height in meters squared (kg/m^2). "Obesity" refers to a condition whereby an otherwise
35 healthy subject has a Body Mass Index (BMI) greater than or equal to $30 \text{ kg}/\text{m}^2$, or a condition whereby a subject with at least one co-morbidity has a BMI greater than or equal to $27 \text{ kg}/\text{m}^2$. An "obese subject" is an otherwise healthy subject with a Body Mass Index (BMI) greater than or

equal to 30 kg/m² or a subject with at least one co-morbidity with a BMI greater than or equal to 27 kg/m². A “subject at risk of obesity” is an otherwise healthy subject with a BMI of 25 kg/m² to less than 30 kg/m² or a subject with at least one co-morbidity with a BMI of 25 kg/m² to less than 27 kg/m². The increased risks associated with obesity occur at a lower Body Mass Index (BMI) in Asians. In Asian countries, including Japan, “obesity” refers to a condition whereby a subject with at least one obesity-induced or obesity-related co-morbidity, that requires weight reduction or that would be improved by weight reduction, has a BMI greater than or equal to 25 kg/m². In Asian countries, including Japan, an “obese subject” refers to a subject with at least one obesity-induced or obesity-related co-morbidity that requires weight reduction or that would be improved by weight reduction, with a BMI greater than or equal to 25 kg/m². In Asia-Pacific, a “subject at risk of obesity” is a subject with a BMI of greater than 23 kg/m² to less than 25 kg/m².

As used herein, the term “obesity” is meant to encompass all of the above definitions of obesity.

Obesity-induced or obesity-related co-morbidities include, but are not limited to, diabetes, non-insulin dependent diabetes mellitus - type II (2), impaired glucose tolerance, impaired fasting glucose, insulin resistance syndrome, dyslipidemia, hypertension, hyperuricacidemia, gout, coronary artery disease, myocardial infarction, angina pectoris, sleep apnea syndrome, Pickwickian syndrome, fatty liver; cerebral infarction, cerebral thrombosis, transient ischemic attack, orthopedic disorders, arthritis deformans, lumbodynia, emmeniopathy, and infertility. In particular, co-morbidities include: hypertension, hyperlipidemia, dyslipidemia, glucose intolerance, cardiovascular disease, sleep apnea, diabetes mellitus, and other obesity-related conditions.

Treatment of obesity and obesity-related disorders refers to the administration of the compounds or combinations of the present invention to reduce or maintain the body weight of an obese subject. One outcome of treatment may be reducing the body weight of an obese subject relative to that subject’s body weight immediately before the administration of the compounds or combinations of the present invention. Another outcome of treatment may be preventing body weight regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of treatment may be decreasing the occurrence of and/or the severity of obesity-related diseases. The treatment may suitably result in a reduction in food or calorie intake by the subject, including a reduction in total food intake, or a reduction of intake of specific components of the diet such as carbohydrates or fats; and/or the inhibition of nutrient absorption; and/or the inhibition of the reduction of metabolic rate; and in weight reduction in subjects in need thereof. The treatment may also result in an alteration of metabolic rate, such as an increase in metabolic rate, rather than or in addition to an inhibition of the reduction of metabolic rate; and/or in minimization of the metabolic resistance that normally results from

weight loss. Prevention of obesity and obesity-related disorders refers to the administration of the compounds or combinations of the present invention to reduce or maintain the body weight of a subject at risk of obesity. One outcome of prevention may be reducing the body weight of a subject at risk of obesity relative to that subject's body weight immediately before the
5 administration of the compounds or combinations of the present invention. Another outcome of prevention may be preventing body weight regain of body weight previously lost as a result of diet, exercise, or pharmacotherapy. Another outcome of prevention may be preventing obesity from occurring if the treatment is administered prior to the onset of obesity in a subject at risk of obesity. Another outcome of prevention may be decreasing the occurrence and/or severity of
10 obesity-related disorders if the treatment is administered prior to the onset of obesity in a subject at risk of obesity. Moreover, if treatment is commenced in already obese subjects, such treatment may prevent the occurrence, progression or severity of obesity-related disorders, such as, but not limited to, arteriosclerosis, Type II diabetes, polycystic ovary disease, cardiovascular diseases, osteoarthritis, hypertension, dyslipidemia, insulin resistance, hypercholesterolemia,
15 hypertriglyceridemia, and cholelithiasis.

The terms "administration of" and or "administering" a compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to a subject in need of treatment. The administration of the compounds of the present invention in order to practice the present methods of therapy is carried out by administering a therapeutically
20 effective amount of the compound to a subject in need of such treatment or prophylaxis. The need for a prophylactic administration according to the methods of the present invention is determined via the use of well known risk factors.

The term "therapeutically effective amount" as used herein means the amount of the active compound that will elicit the biological or medical response in a tissue, system, subject,
25 mammal, or human that is being sought by the researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disorder being treated. The novel methods of treatment of this invention are for disorders known to those skilled in the art. The term "prophylactically effective amount" as used herein means the amount of the active compound that will elicit the biological or medical response in a tissue, system, subject,
30 mammal, or human that is being sought by the researcher, veterinarian, medical doctor or other clinician, to prevent the onset of the disorder in subjects as risk for obesity or the disorder. The therapeutically or prophylactically effective amount, or dosage, of an individual compound is determined, in the final analysis, by the physician in charge of the case, but depends on factors
35 such as the exact disease to be treated, the severity of the disease and other diseases or conditions from which the patient suffers, the chosen route of administration, other drugs and treatments which the patient may concomitantly require, and other factors in the physician's judgement.

Administration and Dose Ranges

Any suitable route of administration may be employed for providing a subject or mammal, especially a human with an effective dosage of a compound of the present invention. For example, oral, rectal, topical, parenteral, ocular, pulmonary, nasal, and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, 5 creams, ointments, aerosols, and the like. Preferably the compound of Formula I, II or III is administered orally or topically.

The effective dosage of active ingredient employed may vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. Such dosage may be ascertained readily by a person skilled in the 10 art.

When treating obesity, in conjunction with diabetes and/or hyperglycemia, or alone, generally satisfactory results are obtained when the compound of formula I, II or III is administered at a daily dosage of from about 0.001 milligram to about 50 milligrams per kilogram of animal body weight, preferably given in a single dose or in divided doses two to six 15 times a day, or in sustained release form. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.07 milligrams to about 3500 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response. When treating diabetes mellitus and/or hyperglycemia, as well as other diseases or disorders for which the compound of formula I, II or III is useful, generally satisfactory results are obtained when the compounds of the present 20 invention are administered at a daily dosage of from about 0.001 milligram to about 50 milligram per kilogram of animal body weight, preferably given in a single dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.07 milligrams to about 3500 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response. When treating 25 dyslipidemia, bulimia nervosa, and gallstones satisfactory results are obtained when the compound of formula I, II or III is administered at a daily dosage of from about 0.001 milligram to about 50 milligrams per kilogram of animal body weight, preferably given in a single dose or in divided doses two to six times a day, or in sustained release form. In the case of a 70 kg adult human, the total daily dose will generally be from about 0.07 milligrams to about 3500 30 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

In the case where an oral composition is employed, a suitable dosage range is, e.g. from about 0.01 mg to about 1500 mg of a compound of Formula I, II or III per day, preferably from about 0.1 mg to about 600 mg per day, more preferably from about 0.1 mg to about 100 mg per day. For oral administration, the compositions are preferably provided in the form of tablets 35 containing from 0.01 to 1,000 mg, preferably 0.01, 0.05, 0.1, 0.5, 1, 2.5, 5, 10, 15, 20, 25, 30, 40, 50, 100, 250, 500, 600, 750, 1000, 1250 or 1500 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. For use where a composition

for intranasal administration is employed, intranasal formulations for intranasal administration comprising 0.001-10% by weight solutions or suspensions of the compound of formula I, II or III in an acceptable intranasal formulation may be used. For use where a composition for intravenous administration is employed, a suitable dosage range is from about 0.001 mg to about 50 mg, preferably from 0.01 mg to about 50 mg, more preferably 0.1 mg to 10 mg, of a compound of formula I, II or III per kg of body weight per day. This dosage regimen may be adjusted to provide the optimal therapeutic response. It may be necessary to use dosages outside these limits in some cases. For the treatment of diseases of the eye, ophthalmic preparations for ocular administration comprising 0.001-1% by weight solutions or suspensions of the compound of formula I, II or III in an acceptable ophthalmic formulation may be used.

The magnitude of prophylactic or therapeutic dosage of the compounds of the present invention will, of course, vary depending on the particular compound employed, the mode of administration, the condition being treated and the severity of the condition being treated. It will also vary according to the age, weight and response of the individual patient. Such dosage may be ascertained readily by a person skilled in the art.

A Compound of formula I, II or III may be used in combination with other drugs that are used in the treatment/prevention/suppression or amelioration of the diseases or conditions for which compounds of formula I, II and III are useful. Such other drugs may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of formula I, II or III. When a compound of formula I, II or III is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of Formula I is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of formula I, II or III.

Examples of other active ingredients that may be combined with a compound of formula I, II and III for the treatment or prevention of obesity and/or diabetes, either administered separately or in the same pharmaceutical compositions, include, but are not limited to:

- (a) insulin sensitizers including (i) PPAR γ antagonists such as glitazones (e.g. ciglitazone; darglitazone; englitazone; isaglitazone (MCC-555); pioglitazone; rosiglitazone; troglitazone; tularik; BRL49653; CLX-0921; 5-BTSD), GW-0207, LG-100641, and LY-300512, and the like), and compounds disclosed in WO 97/10813, WO 97/27857, WO 97/28115, WO 97/28137, and WO 97/27847; (iii) biguanides such as metformin and phenformin;
- (b) insulin or insulin mimetics, such as biota, LP-100, novarapid, insulin detemir, insulin lispro, insulin glargine, insulin zinc suspension (lente and ultralente); Lys-Pro insulin, GLP-1 (73-7) (insulintropin); and GLP-1 (7-36)-NH₂;

(c) sulfonylureas, such as acetohexamide; chlorpropamide; diabinese; glibenclamide; glipizide; glyburide; glimepiride; gliclazide; glipentide; gliquidone; glisolamide; tolazamide; and tolbutamide;

(d) α -glucosidase inhibitors, such as acarbose, adiposine; camiglibose; emiglitate; 5 miglitol; voglibose; pradimicin-Q; salbostatin; trestatin, tendamistate, CKD-711; MDL-25,637; MDL-73,945; and MOR 14, and the like;

(e) anti-diabetic agents such as glucagon receptor agonists, glucokinase activators, GPR40 (G-protein coupled receptor 40) also called SNORF 55 such as BG 700, and those disclosed in WO 04/041266, 04/022551, 03/099793; GPR119 (also called RUP3; SNORF 25) 10 such as RUP3, HGPRBMY26, PFI 007, SNORF 25; selective peroxisome proliferator activator receptor modulators (SPPARMs), SCD-1 (stearoyl-CoA desaturase-1) inhibitors, and SGLT inhibitors, and GLP-1 agonists;

(f) cholesterol lowering agents such as (i) HMG-CoA reductase inhibitors (atorvastatin, itavastatin, fluvastatin, lovastatin, pravastatin, rivastatin, rosuvastatin, simvastatin, and other 15 statins), (ii) bile acid absorbers/sequestrants, such as cholestyramine, colestipol, dialkylaminoalkyl derivatives of a cross-linked dextran; Colestid®; LoCholest®, and the like, (ii) nicotinyl alcohol, nicotinic acid or a salt thereof, (iii) proliferator-activater receptor α agonists such as fenofibric acid derivatives (gemfibrozil, clofibrate, fenofibrate and benzafibrate), (iv) inhibitors of cholesterol absorption such as stanol esters, beta-sitosterol, sterol glycosides such as 20 tiqueside; and azetidinones such as ezetimibe, and the like, and (acyl CoA:cholesterol acyltransferase (ACAT)) inhibitors such as avasimibe, and melinamide, (v) anti-oxidants, such as probucol, (vi) vitamin E, and (vii) thymimetics;

(g) PPAR α agonists such as beclofibrate, benzafibrate, ciprofibrate, clofibrate, etofibrate, fenofibrate, and gemfibrozil; and other fibric acid derivatives, such as Atromid®, Lopid® and 25 Tricor®, and the like, and PPAR α agonists as described in WO 97/36579 by Glaxo;

(h) PPAR δ agonists, such as those disclosed in WO97/28149;

(i) PPAR α/δ agonists, such as muraglitazar, and the compounds disclosed in US 6,414,002;

(j) smoking cessation agents, such as a nicotine agonist or a partial nicotine agonist such 30 as varenicline, or a monoamine oxidase inhibitor (MAOI), or another active ingredient demonstrating efficacy in aiding cessation of tobacco consumption; for example, an antidepressant such as bupropion, doxepine, ornortriptyline; or an anxiolytic such as buspirone or clonidine; and

(k) anti-obesity agents, such as (1) growth hormone secretagogues, growth hormone 35 secretagogue receptor agonists/antagonists, such as NN703, hexarelin, MK-0677, SM-130686, CP-424,391, L-692,429, and L-163,255, and such as those disclosed in U.S. Patent Nos. 5,536,716, and 6,358,951, U.S. Patent Application Nos. 2002/049196 and 2002/022637, and

PCT Application Nos. WO 01/56592 and WO 02/32888; (2) protein tyrosine phosphatase-1B (PTP-1B) inhibitors; (3) cannabinoid receptor ligands, such as cannabinoid CB₁ receptor antagonists or inverse agonists, such as rimonabant (Sanofi Synthelabo), AMT-251, and SR-14778 and SR 141716A (Sanofi Synthelabo), SLV-319 (Solvay), BAY 65-2520 (Bayer), and those disclosed in U.S. Patent Nos. 5,532,237, 4,973,587, 5,013,837, 5,081,122, 5,112,820, 5,292,736, 5,624,941, 6,028,084, PCT Application Nos. WO 96/33159, WO 98/33765, WO98/43636, WO98/43635, WO 01/09120, WO98/31227, WO98/41519, WO98/37061, WO00/10967, WO00/10968, WO97/29079, WO99/02499, WO 01/58869, WO 01/64632, WO 01/64633, WO 01/64634, W002/076949, WO 03/007887, WO 04/048317, and WO 05/000809; and EPO Application No. EP-658546, EP-656354, EP-576357; (4) anti-obesity serotonergic agents, such as fenfluramine, dexfenfluramine, phentermine, and sibutramine; (5) β -adrenoreceptor agonists, such as AD9677/TAK677 (Dainippon/Takeda), CL-316,243, SB 418790, BRL-37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, Trecadrine, Zeneca D7114, SR 59119A, and such as those disclosed in U.S. Patent Application Nos. 5,705,515, and US 5,451,677 and PCT Patent Publications WO94/18161, WO95/29159, WO97/46556, WO98/04526 and WO98/32753, WO 01/74782, and WO 02/32897; (6) pancreatic lipase inhibitors, such as orlistat (Xenical®), Triton WR1339, RHC80267, lipstatin, tetrahydrolipstatin, teasaponin, diethylumbelliferyl phosphate, and those disclosed in PCT Application No. WO 01/77094; (7) neuropeptide Y1 antagonists, such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI-264879A, and those disclosed in U.S. Patent No. 6,001,836, and PCT Patent Publication Nos. WO 96/14307, WO 01/23387, WO 99/51600, WO 01/85690, WO 01/85098, WO 01/85173, and WO 01/89528; (8) neuropeptide Y5 antagonists, such as GW-569180A, GW-594884A, GW-587081X, GW-548118X, FR226928, FR 240662, FR252384, 1229U91, GI-264879A, CGP71683A, LY-377897, PD-160170, SR-120562A, SR-120819A and JCF-104, and those disclosed in U.S. Patent Nos. 6,057,335; 6,043,246; 6,140,354; 6,166,038; 6,180,653; 6,191,160; 6,313,298; 6,335,345; 6,337,332; 6,326,375; 6,329,395; 6,340,683; 6,388,077; 6,462,053; 6,649,624; and 6,723,847, hereby incorporated by reference in their entirety; European Patent Nos. EP-01010691, and EP-01044970; and PCT International Patent Publication Nos. WO 97/19682, WO 97/20820, WO 97/20821, WO 97/20822, WO 97/20823, WO 98/24768; WO 98/25907; WO 98/25908; WO 98/27063, WO 98/47505; WO 98/40356; WO 99/15516; WO 99/27965; WO 00/64880, WO 00/68197, WO 00/69849, WO 01/09120, WO 01/14376; WO 01/85714, WO 01/85730, WO 01/07409, WO 01/02379, WO 01/02379, WO 01/23388, WO 01/23389, WO 01/44201, WO 01/62737, WO 01/62738, WO 01/09120, WO 02/22592, WO 0248152, and WO 02/49648; WO 02/094825; WO 03/014083; WO 03/10191; WO 03/092889; WO 04/002986; and WO 04/031175; (9) melanin-concentrating hormone (MCH) receptor antagonists, such as those disclosed in WO 01/21577 and WO 01/21169; (10) melanin-concentrating hormone 1 receptor (MCH1R) antagonists, such as T-

226296 (Takeda), and those disclosed in PCT Patent Application Nos. WO 01/82925, WO 01/87834, WO 02/051809, WO 02/06245, WO 02/076929, WO 02/076947, WO 02/04433, WO 02/51809, WO 02/083134, WO 02/094799, WO 03/004027, and Japanese Patent Application Nos. JP 13226269, and JP 2004-139909; (11) melanin-concentrating hormone 2 receptor (MCH2R) agonist/antagonists; (12) orexin-1 receptor antagonists, such as SB-334867-A, and those disclosed in PCT Patent Application Nos. WO 01/96302, WO 01/68609, WO 02/51232, and WO 02/51838; (13) serotonin reuptake inhibitors such as fluoxetine, paroxetine, and sertraline, and those disclosed in U.S. Patent Application No. 6,365,633, and PCT Patent Application Nos. WO 01/27060 and WO 01/162341; (14) melanocortin agonists, such as Melanotan II, CHIR86036 (Chiron), ME-10142, and ME-10145 (Melacure), CHIR86036 (Chiron); PT-141, and PT-14 (Palatin); (15) other MC4R (melanocortin 4 receptor) agonists, such as those disclosed in: US Patent Nos. 6,410,548; 6,294,534; 6,350,760; 6,458,790; 6,472,398; 6,376,509; and 6,818,658; US Patent Publication No. US2002/0137664; US2003/0236262; US2004/009751; US2004/0092501; and PCT Application Nos. WO 99/64002; WO 00/74679; WO 01/70708; WO 01/70337; WO 01/74844; WO 01/91752; WO 01/991752; WO 02/15909; WO 02/059095; WO 02/059107; WO 02/059108; WO 02/059117; WO 02/067869; WO 02/068387; WO 02/068388; WO 02/067869; WO 02/11715; WO 02/12166; WO 02/12178; WO 03/007949; WO 03/009847; WO 04/024720; WO 04/078716; WO 04/078717; WO 04/087159; WO 04/089307; and WO 05/009950; (16) 5HT-2 agonists; (17) 5HT2C (serotonin receptor 2C) agonists, such as BVT933, DPCA37215, WAY161503, R-1065, and those disclosed in U.S. Patent No. 3,914,250, and PCT Application Nos. WO 02/36596, WO 02/48124, WO 02/10169, WO 01/66548, WO 02/44152, WO 02/51844, WO 02/40456, and WO 02/40457; (18) galanin antagonists; (19) CCK agonists; (20) other CCK-1 (cholecystokinin –A) agonists, such as AR-R 15849, GI 181771, JMV-180, A-71378, A-71623 and SR146131, and those disclosed in U.S. Patent No. 5,739,106; (21) GLP-1 agonists; (22) corticotropin-releasing hormone agonists; (23) histamine receptor-3 (H3) modulators; (24) histamine receptor-3 (H3) antagonists/inverse agonists, such as hioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate, clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), and those described and disclosed in PCT Application No. WO 02/15905, and O-[3-(1H-imidazol-4-yl)propanol]-carbamates (Kiec-Kononowicz, K. et al., *Pharmazie*, 55:349-55 (2000)), piperidine-containing histamine H3-receptor antagonists (Lazewska, D. et al., *Pharmazie*, 56:927-32 (2001)), benzophenone derivatives and related compounds (Sasse, A. et al., *Arch. Pharm.(Weinheim)* 334:45-52 (2001)), substituted N-phenylcarbamates (Reidemeister, S. et al., *Pharmazie*, 55:83-6 (2000)), and proxifan derivatives (Sasse, A. et al., *J. Med. Chem.* 43:3335-43 (2000)); (25) β -hydroxy steroid dehydrogenase-1 inhibitors (β -HSD-1); (26) PDE (phosphodiesterase) inhibitors, such as theophylline, pentoxifylline, zaprinast, sildenafil, amrinone, milrinone, cilostamide, rolipram, and cilomilast; (27) phosphodiesterase-3B (PDE3B) inhibitors; (28) NE

(norepinephrine) transport inhibitors, such as GW 320659, despiramine, talsupram, and nomifensine; (29) ghrelin receptor antagonists, such as those disclosed in PCT Application Nos. WO 01/87335, and WO 02/08250; (30) leptin, including recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen); (31) leptin derivatives, such as those disclosed in U.S. Patent Nos. 5,552,524, 5,552,523, 5,552,522, 5,521,283, and PCT International Publication Nos. WO 96/23513, WO 96/23514, WO 96/23515, WO 96/23516, WO 96/23517, WO 96/23518, WO 96/23519, and WO 96/23520; (32) BRS3 (bombesin receptor subtype 3) agonists such as [D-Phe6,beta-Ala11,Phe13,Nle14]Bn(6-14) and [D-Phe6,Phe13]Bn(6-13)propylamide, and those compounds disclosed in Pept. Sci. 2002 Aug; 8(8): 461-75); (33) CNTF (Ciliary neurotrophic factors), such as GI-181771 (Glaxo-SmithKline), SR146131 (Sanofi Synthelabo), butabindide, PD170,292, and PD 149164 (Pfizer); (34) CNTF derivatives, such as axokine (Regeneron), and those disclosed in PCT Application Nos. WO 94/09134, WO 98/22128, and WO 99/43813; (35) monoamine reuptake inhibitors, such as sibutramine, and those disclosed in U.S. Patent Nos. 4,746,680, 4,806,570, and 5,436,272, U.S. Patent Publication No. 2002/0006964 and PCT Application Nos. WO 01/27068, and WO 01/62341; (36) UCP-1 (uncoupling protein-1), 2, or 3 activators, such as phytanic acid, 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl]benzoic acid (TTNPB), retinoic acid, and those disclosed in PCT Patent Application No. WO 99/00123; (37) thyroid hormone β agonists, such as KB-2611 (KaroBioBMS), and those disclosed in PCT Application No. WO 02/15845, and Japanese Patent Application No. JP 2000256190; (38) FAS (fatty acid synthase) inhibitors, such as Cerulenin and C75; (39) DGAT1 (diacylglycerol acyltransferase 1) inhibitors; (40) DGAT2 (diacylglycerol acyltransferase 2) inhibitors; (41) ACC2 (acetyl-CoA carboxylase-2) inhibitors; (42) glucocorticoid antagonists; (43) acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al., Obesity Research, 9:202-9 (2001); (44) dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, valine pyrrolidide, NVP-DPP728, LAF237, P93/01, TSL 225, TMC-2A/2B/2C, FE 999011, P9310/K364, VIP 0177, SDZ 274-444 and sitagliptin; and the compounds disclosed in US Patent No. US 6,699,871, which is incorporated herein by reference; and International Patent Application Nos. WO 03/004498; WO 03/004496; EP 1 258 476; WO 02/083128; WO 02/062764; WO 03/000250; WO 03/002530; WO 03/002531; WO 03/002553; WO 03/002593; WO 03/000180; and WO 03/000181; (46) dicarboxylate transporter inhibitors; (47) glucose transporter inhibitors; (48) phosphate transporter inhibitors; (49) Metformin (Glucophage®); and (50) Topiramate (Topimax®); and (50) peptide YY, PYY 3-36, peptide YY analogs, derivatives, and fragments such as BIM-43073D, BIM-43004C (Olitvak, D.A. et al., Dig. Dis. Sci. 44(3):643-48 (1999)), and those disclosed in US 5,026,685, US 5,604,203, US 5,574, 010, US 5, 696,093, US 5,936,092, US 6,046, 162, US 6,046,167, US, 6,093,692, US 6,225,445, U.S. 5,604,203, US 4,002,531, US 4, 179,337, US 5,122,614, US 5,349,052, US 5,552,520, US 6, 127,355, WO 95/06058, WO

98/32466, WO 03/026591, WO 03/057235, WO 03/027637, and WO 2004/066966, which are incorporated herein by reference; (51) Neuropeptide Y2 (NPY2) receptor agonists such NPY3-36, N acetyl [Leu(28,31)] NPY 24-36, TASP-V, and cyclo-(28/32)-Ac-[Lys28-Glu32]-(25-36)-pNPY; (52) Neuropeptide Y4 (NPY4) agonists such as pancreatic peptide (PP) as described in
5 Batterham et al., J. Clin. Endocrinol. Metab. 88:3989-3992 (2003), and other Y4 agonists such as 1229U91; (54) cyclo-oxygenase-2 inhibitors such as etoricoxib, celecoxib, valdecoxib, parecoxib, lumiracoxib, BMS347070, tiracoxib or JTE522, ABT963, CS502 and GW406381, and pharmaceutically acceptable salts thereof; (55) Neuropeptide Y1 (NPY1) antagonists such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI-264879A and those disclosed in
10 U.S. Patent No. 6,001,836; and PCT Application Nos. WO 96/14307, WO 01/23387, WO 99/51600, WO 01/85690, WO 01/85098, WO 01/85173, and WO 01/89528; (56) Opioid antagonists such as nalmefene (Revex ®), 3-methoxynaltrexone, naloxone, naltrexone, and those disclosed in: PCT Application No. WO 00/21509; (57) 11 β HSD-1 (11-beta hydroxy steroid dehydrogenase type 1) inhibitors such as BVT 3498, BVT 2733, and those disclosed in WO
15 01/90091, WO 01/90090, WO 01/90092, and US Patent No. US 6,730,690 and US Publication No. US 2004-0133011, which are incorporated by reference herein in their entirety; and (58) aminorex; (59) ampechloral; (60) amphetamine; (61) benzphetamine; (62) chlorphentermine; (63) clobenzorex; (64) cloforex; (65) clominorex; (66) clortermine; (67) cyclexedrine; (68) dextroamphetamine; (69) diphemethoxidine, (70) N-ethylamphetamine; (71) fenbutrazate; (72)
20 fenisorex; (73) fenproporex; (74) fludorex; (75) fluminorex; (76) furfurylmethylamphetamine; (77) levamfetamine; (78) levophacetoperane; (79) mefenorex; (80) metamfepramone; (81) methamphetamine; (82) norpseudoephedrine; (83) pentorex; (84) phendimetrazine; (85) phenmetrazine; (86) picilorex; (87) phytopharm 57; (88) zonisamide, (89) neuromedin U and analogs or derivatives thereof, (90) oxyntomodulin and analogs or derivatives thereof, and (91)
25 Neurokinin-1 receptor antagonists (NK-1 antagonists) such as the compounds disclosed in: U.S. Patent Nos. 5,162,339, 5,232,929, 5,242,930, 5,373,003, 5,387,595, 5,459,270, 5,494,926, 5,496,833, and 5,637,699; and (92) Qnexa.

Specific compounds of use in combination with a compound of the present invention include: simvastatin, mevastatin, ezetimibe, atorvastatin, sitagliptin, metformin, sibutramine,
30 orlistat, Qnexa, topiramate, naltrexone, bupriopion, phentermine, and losartan, losartan with hydrochlorothiazide. Specific CB1 antagonists/inverse agonists of use in combination with a compound of the present invention include: those described in WO03/077847, including: *N*-[3-(4-chlorophenyl)-2(*S*)-phenyl-1(*S*)-methylpropyl]-2-(4-trifluoromethyl-2-pyrimidyloxy)-2-methylpropanamide, *N*-[3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide, *N*-[3-(4-chlorophenyl)-2-(5-chloro-3-pyridyl)-1-methylpropyl]-2-(5-trifluoromethyl-2-pyridyloxy)-2-methylpropanamide, and
35 pharmaceutically acceptable salts thereof; as well as those in WO05/000809, which includes the

following: 3-{1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}-3-(3,5-difluorophenyl)-2,2-dimethylpropanenitrile, 1-{1-[1-(4-chlorophenyl)pentyl]azetidin-3-yl}-1-(3,5-difluorophenyl)-2-methylpropan-2-ol. 3-((S)-(4-chlorophenyl){3-[(1S)-1-(3,5-difluorophenyl)-2-hydroxy-2-methylpropyl]azetidin-1-yl}methyl)benzotrile, 3-((S)-(4-chlorophenyl){3-[(1S)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)benzotrile, 3-((4-chlorophenyl){3-[1-(3,5-difluorophenyl)-2,2-dimethylpropyl]azetidin-1-yl}methyl)benzotrile, 3-((1S)-1-{1-[(S)-(3-cyanophenyl)(4-cyanophenyl)methyl]azetidin-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzotrile, 3-[(S)-(4-chlorophenyl)(3-[(1S)-2-fluoro-1-[3-fluoro-5-(4H-1,2,4-triazol-4-yl)phenyl]-2-methylpropyl]azetidin-1-yl)methyl]benzotrile, and 5-((4-chlorophenyl){3-[(1S)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}methyl)thiophene-3-carbonitrile, and pharmaceutically acceptable salts thereof; as well as: 3-[(S)-(4-chlorophenyl)(3-[(1S)-2-fluoro-1-[3-fluoro-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl]azetidin-1-yl)methyl]benzotrile, 3-[(S)-(4-chlorophenyl)(3-[(1S)-2-fluoro-1-[3-fluoro-5-(1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl]azetidin-1-yl)methyl]benzotrile, 3-[(S)-(3-[(1S)-1-[3-(5-amino-1,3,4-oxadiazol-2-yl)-5-fluorophenyl]-2-fluoro-2-methylpropyl]azetidin-1-yl)(4-chlorophenyl)methyl]benzotrile, 3-[(S)-(4-cyanophenyl)(3-[(1S)-2-fluoro-1-[3-fluoro-5-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl]azetidin-1-yl)methyl]benzotrile, 3-[(S)-(3-[(1S)-1-[3-(5-amino-1,3,4-oxadiazol-2-yl)-5-fluorophenyl]-2-fluoro-2-methylpropyl]azetidin-1-yl)(4-cyanophenyl)methyl]benzotrile, 3-[(S)-(4-cyanophenyl)(3-[(1S)-2-fluoro-1-[3-fluoro-5-(1,3,4-oxadiazol-2-yl)phenyl]-2-methylpropyl]azetidin-1-yl)methyl]benzotrile, 3-[(S)-(4-chlorophenyl)(3-[(1S)-2-fluoro-1-[3-fluoro-5-(1,2,4-oxadiazol-3-yl)phenyl]-2-methylpropyl]azetidin-1-yl)methyl]benzotrile, 3-[(1S)-1-(1-[(S)-(4-cyanophenyl)[3-(1,2,4-oxadiazol-3-yl)phenyl]-methyl]azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzotrile, 5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-1H-tetrazole, 5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-1-methyl-1H-tetrazole, 5-(3-{1-[1-(diphenylmethyl)azetidin-3-yl]-2-fluoro-2-methylpropyl}-5-fluorophenyl)-2-methyl-2H-tetrazole, 3-[(4-chlorophenyl)(3-{2-fluoro-1-[3-fluoro-5-(2-methyl-2H-tetrazol-5-yl)phenyl]-2-methylpropyl]azetidin-1-yl)methyl]benzotrile, 3-[(4-chlorophenyl)(3-{2-fluoro-1-[3-fluoro-5-(1-methyl-1H-tetrazol-5-yl)phenyl]-2-methylpropyl]azetidin-1-yl)methyl]benzotrile, 3-[(4-cyanophenyl)(3-{2-fluoro-1-[3-fluoro-5-(1-methyl-1H-tetrazol-5-yl)phenyl]-2-methylpropyl]azetidin-1-yl)methyl]benzotrile, 3-[(4-cyanophenyl)(3-{2-fluoro-1-[3-fluoro-5-(2-methyl-2H-tetrazol-5-yl)phenyl]-2-methylpropyl]azetidin-1-yl)methyl]benzotrile, 5-{3-[(S)-3-[(1S)-1-(3-bromo-5-fluorophenyl)-2-fluoro-2-methylpropyl]azetidin-1-yl}(4-chlorophenyl)methyl]phenyl}-1,3,4-oxadiazol-2(3H)-one, 3-[(1S)-1-(1-[(S)-(4-chlorophenyl)[3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]methyl]azetidin-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzotrile, 3-[(1S)-1-(1-

{(S)-(4-cyanophenyl)[3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]methyl} azetid-3-yl)-
 2-fluoro-2-methylpropyl]-5-fluorobenzonitrile, 3-[(1S)-1-(1-((S)-(4-cyanophenyl)[3-(1,3,4-
 oxadiazol-2-yl)phenyl]methyl}azetid-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile, 3-
 [(1S)-1-(1-((S)-(4-chlorophenyl)[3-(1,3,4-oxadiazol-2-yl)phenyl]methyl}azetid-3-yl)-2-fluoro-
 5 2-methylpropyl]-5-fluorobenzonitrile, 3-((1S)-1-{1-[(S)-[3-(5-amino-1,3,4-oxadiazol-2-
 yl)phenyl](4-chlorophenyl)methyl]azetid-3-yl}-2-fluoro-2-methylpropyl)-5-fluorobenzonitrile,
 3-((1S)-1-{1-[(S)-[3-(5-amino-1,3,4-oxadiazol-2-yl)phenyl](4-cyanophenyl)methyl]azetid-3-
 yl}-2-fluoro-2-methylpropyl)-5-fluorobenzonitrile, 3-[(1S)-1-(1-((S)-(4-cyanophenyl)[3-(1,2,4-
 oxadiazol-3-yl)phenyl]methyl}azetid-3-yl)-2-fluoro-2-methylpropyl]-5-fluorobenzonitrile, 3-
 10 [(1S)-1-(1-((S)-(4-chlorophenyl)[3-(1,2,4-oxadiazol-3-yl)phenyl]methyl}azetid-3-yl)-2-fluoro-
 2-methylpropyl]-5-fluorobenzonitrile, 5-[3-((S)-(4-chlorophenyl){3-[(1S)-1-(3,5-difluorophenyl)-
 2-fluoro-2-methylpropyl] azetid-1-yl}methyl)phenyl]-1,3,4-oxadiazol-2(3H)-one, 5-[3-((S)-(4-
 chlorophenyl){3-[(1S)-1-(3,5-difluorophenyl)-2-fluoro-2-methylpropyl]azetid-1-
 yl}methyl)phenyl]-1,3,4-oxadiazol-2(3H)-one, 4-((S)-{3-[(1S)-1-(3,5-difluorophenyl)-2-fluoro-
 15 2-methylpropyl]azetid-1-yl}[3-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)phenyl]methyl)-
 benzonitrile, and pharmaceutically acceptable salts thereof.

Specific NPY5 antagonists of use in combination with a compound of the present
 invention include: 3-oxo-N-(5-phenyl-2-pyrazinyl)-spiro[isobenzofuran-1(3H),4'-piperidine]-1'-
 carboxamide, 3-oxo-N-(7-trifluoromethylpyrido[3,2-b]pyridin-2-yl)spiro-[isobenzofuran-
 20 1(3H),4'-piperidine]-1'-carboxamide, N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro-
 [isobenzofuran-1(3H),4'-piperidine]-1'-carboxamide, trans-3'-oxo-N-(5-phenyl-2-
 pyrimidinyl)spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide, trans-3'-oxo-N-[1-(3-
 quinolyl)-4-imidazolyl]spiro[cyclohexane-1,1'(3'H)-isobenzofuran]-4-carboxamide, trans-3-oxo-
 N-(5-phenyl-2-pyrazinyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide,
 25 trans-N-[5-(3-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-azaisobenzofuran-1(3H),1'-
 cyclohexane]-4'-carboxamide, trans-N-[5-(2-fluorophenyl)-2-pyrimidinyl]-3-oxospiro[5-
 azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, trans-N-[1-(3,5-difluorophenyl)-4-
 imidazolyl]-3-oxospiro[7-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, trans-3-oxo-
 N-(1-phenyl-4-pyrazolyl)spiro[4-azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide,
 30 trans-N-[1-(2-fluorophenyl)-3-pyrazolyl]-3-oxospiro[6-azaisobenzofuran-1(3H),1'-cyclohexane]-
 4'-carboxamide, trans-3-oxo-N-(1-phenyl-3-pyrazolyl)spiro[6-azaisobenzofuran-1(3H),1'-
 cyclohexane]-4'-carboxamide, trans-3-oxo-N-(2-phenyl-1,2,3-triazol-4-yl)spiro[6-
 azaisobenzofuran-1(3H),1'-cyclohexane]-4'-carboxamide, and pharmaceutically acceptable salts
 and esters thereof.

35 Specific ACC-1/2 inhibitors of use in combination with a compound of the present
 invention include: 1'-[(4,8-dimethoxyquinolin-2-yl)carbonyl]-6-(1H-tetrazol-5-yl)spiro[chroman-
 2,4'-piperidin]-4-one; (5-{1'-[(4,8-dimethoxyquinolin-2-yl)carbonyl]-4-oxospiro[chroman-2,4'-

5 piperidin]-6-yl}-2*H*-tetrazol-2-yl)methyl pivalate; 5-{1'-[(8-cyclopropyl-4-methoxyquinolin-2-yl)carbonyl]-4-oxospiro[chroman-2,4'-piperidin]-6-yl}nicotinic acid; 1'-(8-methoxy-4-morpholin-4-yl-2-naphthoyl)-6-(1*H*-tetrazol-5-yl)spiro[chroman-2,4'-piperidin]-4-one; and 1'-[(4-ethoxy-8-ethylquinolin-2-yl)carbonyl]-6-(1*H*-tetrazol-5-yl)spiro[chroman-2,4'-piperidin]-4-one; and pharmaceutically acceptable salts and esters thereof.

Specific MCH1R antagonist compounds of use in combination with a compound of the present invention include: 1-{4-[(1-ethylazetid-3-yl)oxy]phenyl}-4-[(4-fluorobenzyl)oxy]pyridin-2(1*H*)-one, 4-[(4-fluorobenzyl)oxy]-1-{4-[(1-isopropylazetid-3-yl)oxy]phenyl}pyridin-2(1*H*)-one, 1-[4-(azetid-3-yloxy)phenyl]-4-[(5-chloropyridin-2-yl)methoxy]pyridin-2(1*H*)-one, 4-[(5-chloropyridin-2-yl)methoxy]-1-{4-[(1-ethylazetid-3-yl)oxy]phenyl}pyridin-2(1*H*)-one, 4-[(5-chloropyridin-2-yl)methoxy]-1-{4-[(1-propylazetid-3-yl)oxy]phenyl}pyridin-2(1*H*)-one, and 4-[(5-chloropyridin-2-yl)methoxy]-1-(4-[(2*S*)-1-ethylazetid-2-yl]methoxy)phenylpyridin-2(1*H*)-one, or a pharmaceutically acceptable salt thereof.

15 Specific DP-IV inhibitors of use in combination with a compound of the present invention are selected from 7-[(3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine. In particular, the compound of formula I is favorably combined with 7-[(3*R*)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-tetrahydro-1,2,4-triazolo[4,3-*a*]pyrazine, and pharmaceutically acceptable salts thereof.

20 Specific H3 (histamine H3) antagonists/inverse agonists of use in combination with a compound of the present invention include: those described in WO05/077905, including: 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-2-ethylpyrido[2,3-*d*]-pyrimidin-4(3*H*)-one, 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one, 2-ethyl-3-(4-{3-[(3*S*)-3-methylpiperidin-1-yl]propoxy}phenyl)pyrido[2,3-*d*]pyrimidin-4(3*H*)-one 2-methyl-3-(4-{3-[(3*S*)-3-methylpiperidin-1-yl]propoxy}phenyl)pyrido[4,3-*d*]pyrimidin-4(3*H*)-one, 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-2,5-dimethyl-4(3*H*)-quinazolinone, 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-2-methyl-5-trifluoromethyl-4(3*H*)-quinazolinone, 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-5-methoxy-2-methyl-4(3*H*)-quinazolinone, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-5-fluoro-2-methyl-4(3*H*)-quinazolinone, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-7-fluoro-2-methyl-4(3*H*)-quinazolinone, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-6-methoxy-2-methyl-4(3*H*)-quinazolinone, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-6-fluoro-2-methyl-4(3*H*)-quinazolinone, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-8-fluoro-2-methyl-4(3*H*)-quinazolinone, 3-{4-[(1-cyclopentyl-4-piperidinyl)oxy]phenyl}-2-methylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one, 3-{4-[(1-cyclobutylpiperidin-4-yl)oxy]phenyl}-6-fluoro-2-methylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one, 3-{4-[(1-cyclobutyl-4-piperidinyl)oxy]phenyl}-2-ethylpyrido[4,3-*d*]pyrimidin-4(3*H*)-one, 6-

methoxy-2-methyl-3-{4-[3-(1-piperidiny)propoxy]phenyl}pyrido[3,4-d]pyrimidin-4(3H)-one, 6-methoxy-2-methyl-3-{4-[3-(1-pyrrolidiny)propoxy]phenyl}pyrido[3,4-d]pyrimidin-4(3H)-one, 2,5-dimethyl-3-{4-[3-(1-pyrrolidiny)propoxy]phenyl}-4(3H)-quinazolinone, 2-methyl-3-{4-[3-(1-pyrrolidiny)propoxy]phenyl}-5-trifluoromethyl-4(3H)-quinazolinone, 5-fluoro-2-methyl-3-
 5 {4-[3-(1-piperidiny)propoxy]phenyl}-4(3H)-quinazolinone, 6-methoxy-2-methyl-3-{4-[3-(1-piperidiny)propoxy]phenyl}-4(3H)-quinazolinone, 5-methoxy-2-methyl-3-(4-{3-[(3S)-3-methylpiperidin-1-yl]propoxy}phenyl)-4(3H)-quinazolinone, 7-methoxy-2-methyl-3-(4-{3-[(3S)-3-methylpiperidin-1-yl]propoxy}phenyl)-4(3H)-quinazolinone, 2-methyl-3-(4-{3-[(3S)-3-methylpiperidin-1-yl]propoxy}phenyl)pyrido[2,3-d]pyrimidin-4(3H)-one, 5-fluoro-2-methyl-3-
 10 (4-{3-[(2R)-2-methylpyrrolidin-1-yl]propoxy}phenyl)-4(3H)-quinazolinone, 2-methyl-3-(4-{3-[(2R)-2-methylpyrrolidin-1-yl]propoxy}phenyl)pyrido[4,3-d]pyrimidin-4(3H)-one, 6-methoxy-2-methyl-3-(4-{3-[(2R)-2-methylpyrrolidin-1-yl]propoxy}phenyl)-4(3H)-quinazolinone, 6-methoxy-2-methyl-3-(4-{3-[(2S)-2-methylpyrrolidin-1-yl]propoxy}phenyl)-4(3H)-quinazolinone, and pharmaceutically acceptable salts thereof.

15 Specific CCK1R agonists of use in combination with a compound of the present invention include: 3-(4-{[1-(3-ethoxyphenyl)-2-(4-methylphenyl)-1*H*-imidazol-4-yl]carbonyl}-1-piperazinyl)-1-naphthoic acid; 3-(4-{[1-(3-ethoxyphenyl)-2-(2-fluoro-4-methylphenyl)-1*H*-imidazol-4-yl]carbonyl}-1-piperazinyl)-1-naphthoic acid; 3-(4-{[1-(3-ethoxyphenyl)-2-(4-fluorophenyl)-1*H*-imidazol-4-yl]carbonyl}-1-piperazinyl)-1-naphthoic acid; 3-(4-{[1-(3-ethoxyphenyl)-2-(2,4-difluorophenyl)-1*H*-imidazol-4-yl]carbonyl}-1-piperazinyl)-1-naphthoic
 20 acid; and 3-(4-{[1-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-(4-fluorophenyl)-1*H*-imidazol-4-yl]carbonyl}-1-piperazinyl)-1-naphthoic acid; and pharmaceutically acceptable salts thereof.

Specific MC4R agonists of use in combination with a compound of the present invention
 25 include: 1) (5*S*)-1'-{[(3*R*,4*R*)-1-*tert*-butyl-3-(2,3,4-trifluorophenyl)piperidin-4-yl]carbonyl}-3-chloro-2-methyl-5-[1-methyl-1-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethyl]-5*H*-spiro[furo[3,4-*b*]pyridine-7,4'-piperidine]; 2) (5*R*)-1'-{[(3*R*,4*R*)-1-*tert*-butyl-3-(2,3,4-trifluorophenyl)piperidin-4-yl]carbonyl}-3-chloro-2-methyl-5-[1-methyl-1-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethyl]-5*H*-spiro[furo[3,4-*b*]pyridine-7,4'-piperidine]; 3) 2-(1'-{[(3*S*,4*R*)-1-*tert*-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-chloro-2-methyl-5*H*-spiro[furo[3,4-*b*]pyridine-7,4'-piperidin]-5-yl)-2-methylpropanenitrile; 4) 1'-{[(3*S*,4*R*)-1-*tert*-butyl-4-(2,4-difluorophenyl)pyrrolidin-3-yl]carbonyl}-3-chloro-2-methyl-5-[1-methyl-1-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethyl]-5*H*-spiro[furo[3,4-*b*]pyridine-7,4'-piperidine]; 5) *N*-[(3*R*,4*R*)-3-(3-chloro-2-methyl-5-[1-methyl-1-(1-methyl-1*H*-1,2,4-triazol-5-yl)ethyl]-1'*H*,5*H*-spiro[furo-[3,4-*b*]pyridine-7,4'-piperidin]-1'-yl]carbonyl)-4-(2,4-difluorophenyl)-cyclopentyl]-*N*-methyltetrahydro-2*H*-
 35 pyran-4-amine; 6) 2-[3-chloro-1'-((1*R*,2*R*)-2-(2,4-difluorophenyl)-4-[methyl(tetrahydro-2*H*-

pyran-4-yl)amino]-cyclopentyl}-carbonyl)-2-methyl-5*H*-spiro[furo[3,4-*b*]pyridine-7,4'-piperidin]-5-yl]-2-methyl-propane-nitrile; and pharmaceutically acceptable salts thereof.

Examples of other anti-obesity agents that can be employed in combination with a compound of formula I, II and III are disclosed in "Patent focus on new anti-obesity agents," Exp. Opin. Ther. Patents, 10: 819-831 (2000); "Novel anti-obesity drugs," Exp. Opin. Invest. Drugs, 9: 1317-1326 (2000); and "Recent advances in feeding suppressing agents: potential therapeutic strategy for the treatment of obesity," Exp. Opin. Ther. Patents, 11: 1677-1692 (2001). The role of neuropeptide Y in obesity is discussed in Exp. Opin. Invest. Drugs, 9: 1327-1346 (2000). Cannabinoid receptor ligands are discussed in Exp. Opin. Invest. Drugs, 9: 1553-1571 (2000).

The instant invention also includes administration of a single pharmaceutical dosage formulation which contains both the CCK-1R ligand or agonist in combination with a second active ingredient, as well as administration of each active agent in its own separate pharmaceutical dosage formulation. Where separate dosage formulations are used, the individual components of the composition can be administered at essentially the same time, i.e., concurrently, or at separately staggered times, i.e. sequentially prior to or subsequent to the administration of the other component of the composition. The instant invention is therefore to be understood to include all such regimes of simultaneous or alternating treatment, and the terms "administration" and "administering" are to be interpreted accordingly. Administration in these various ways are suitable for the present compositions as long as the beneficial pharmaceutical effect of the combination of the CCK-1R ligand or agonist and the second active ingredient is realized by the patient at substantially the same time. Such beneficial effect is preferably achieved when the target blood level concentrations of each active ingredient are maintained at substantially the same time. It is preferred that the combination of the CCK-1R ligand or agonist and the second active ingredient be co-administered concurrently on a once-a-day dosing schedule; however, varying dosing schedules, such as the CCK-1R ligand or agonist once a day and the second active ingredient once, twice or more times per day or the CCK-1R ligand or agonist three times a day and the second active ingredient once, twice or more times per day, is also encompassed herein. A single oral dosage formulation comprised of both a CCK-1R ligand or agonist and a second active ingredient is preferred. A single dosage formulation will provide convenience for the patient, which is an important consideration especially for patients with diabetes or obese patients who may be in need of multiple medications.

The compounds in the combinations of the present invention may be administered separately, therefore the invention also relates to combining separate pharmaceutical compositions into a kit form. The kit, according to this invention, comprises two separate pharmaceutical compositions: a first unit dosage form comprising a prophylactically or therapeutically effective amount of the cholecystokinin-1 receptor agonist, or a pharmaceutically

acceptable salt or ester thereof, and a pharmaceutically acceptable carrier or diluent in a first unit dosage form, and a second unit dosage form comprising a prophylactically or therapeutically effective amount of the second active ingredient or drug, or a pharmaceutically acceptable salt or ester thereof, and a pharmaceutically acceptable carrier or diluent in a second unit dosage form.

5 In one embodiment, the kit further comprises a container. Such kits are especially suited for the delivery of solid oral forms such as tablets or capsules. Such a kit preferably includes a number of unit dosages. Such kits can include a card having the dosages oriented in the order of their intended use. An example of such a kit is a "blister pack". Blister packs are well known in the packaging industry and are widely used for packaging pharmaceutical unit dosage forms. If
10 desired, a memory aid can be provided, for example in the form of numbers, letters, or other markings or with a calendar insert, designating the days or time in the treatment schedule in which the dosages can be administered.

Another aspect of the present invention provides pharmaceutical compositions which comprise a compound of formula I, II or III, as an active ingredient or a pharmaceutically
15 acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic bases or acids and organic bases or acids.

The compositions include compositions suitable for oral, rectal, topical, parenteral
20 (including subcutaneous, intramuscular, and intravenous), ocular (ophthalmic), pulmonary (nasal or buccal inhalation), or nasal administration, although the most suitable route in any given case will depend on the nature and severity of the conditions being treated and on the nature of the active ingredient. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

25 In practical use, the compound of formula I, II or III can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual
30 pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixirs and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, hard and
35 soft capsules and tablets, with the solid oral preparations being preferred over the liquid preparations.

Because of their ease of administration, tablets and capsules represent the typical oral dosage unit form, in which case solid pharmaceutical carriers are typically employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques. Such compositions and preparations should contain at least 0.1 percent of active compound. The percentage of active compound in these compositions may, of course, be varied and may conveniently be between about 2 percent to about 60 percent of the weight of the unit. The amount of active compound in such therapeutically useful compositions is such that an effective dosage will be obtained. The active compounds can also be administered intranasally as, for example, liquid drops or spray. The tablets, pills, capsules, and the like may also contain a binder such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil. Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

The Compound of formula I, II or III may also be administered parenterally. Solutions or suspensions of these active compounds can be prepared in water suitably mixed with a surfactant such as hydroxy-propylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils.

The compounds of formula I, II and III of the present invention can be prepared according to the procedures of the following Schemes and Examples, using appropriate materials and are further exemplified by the following specific examples. Moreover, by utilizing the procedures described herein, one of ordinary skill in the art can readily prepare additional compounds of the present invention claimed herein. The compounds illustrated in the examples are not, however, to be construed as forming the only genus that is considered as the invention. The Examples further illustrate details for the preparation of the compounds of the present invention. Those

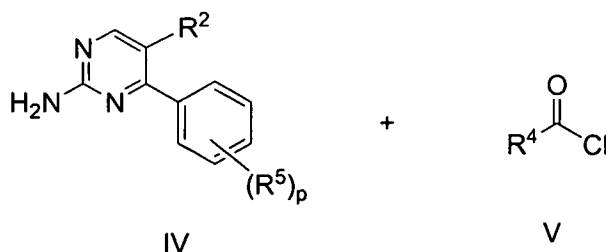
skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds. The instant compounds are generally isolated in the form of their pharmaceutically acceptable salts, such as those described previously hereinabove. The free amine bases corresponding to the isolated salts
5 can be generated by neutralization with a suitable base, such as aqueous sodium hydrogencarbonate, sodium carbonate, sodium hydroxide, and potassium hydroxide, and extraction of the liberated amine free base into an organic solvent followed by evaporation. The amine free base isolated in this manner can be further converted into another pharmaceutically acceptable salt by dissolution in an organic solvent followed by addition of the appropriate acid
10 and subsequent evaporation, precipitation, or crystallization. All temperatures are degrees Celsius unless otherwise noted. Mass spectra (MS) were measured by electron-spray ion-mass spectroscopy.

The phrase "standard peptide coupling reaction conditions" means coupling a carboxylic acid with an amine using an acid activating agent such as EDC, DCC, and BOP in an inert
15 solvent such as dichloromethane in the presence of a catalyst such as HOBT. The use of protecting groups for the amine and carboxylic acid functionalities to facilitate the desired reaction and minimize undesired reactions is well documented. Conditions required to remove protecting groups are found in standard textbooks such as Greene, T, and Wuts, P. G. M.,
Protective Groups in Organic Synthesis, John Wiley & Sons, Inc., New York, NY, 1991. CBZ
20 and BOC are commonly used protecting groups in organic synthesis, and their removal conditions are known to those skilled in the art. For example, CBZ may be removed by catalytic hydrogenation in the presence of a noble metal or its oxide such as palladium on activated carbon in a protic solvent such as methanol or ethanol. In cases where catalytic hydrogenation is
25 contraindicated due to the presence of other potentially reactive functionalities, removal of CBZ groups can also be achieved by treatment with a solution of hydrogen bromide in acetic acid or by treatment with a mixture of TFA and dimethylsulfide. Removal of BOC protecting groups is carried out with a strong acid, such as trifluoroacetic acid, hydrochloric acid, or hydrogen chloride gas, in a solvent such as methylene chloride, methanol, or ethyl acetate.

Abbreviations Used in the Description of the Preparation of the Compounds of the
30 Present Invention: Ac is acetyl, BOC (Boc) is t-butyloxycarbonyl, BOP is benzotriazol-1-ylxytris(dimethylamino)- phosphonium hexafluorophosphate, Bn is benzyl, Bu is butyl, *tert*-Bu is tertiary butyl, calc. or calc'd is Calculated, celite is Celite™ diatomaceous earth, CBZ (Cbz) is benzyloxycarbonyl, c-hex is cyclohexyl, c-pen is cyclopentyl, c-pro is cyclopropyl, DCC is dicyclohexylcarbodiimide, DEAD is diethyl azodicarboxylate, DIEA is diisopropyl-ethylamine,
35 DMAP is 4-dimethylaminopyridine, DMF is *N,N*-dimethylformamide, DMSO is dimethyl sulfoxide, dppf is 1,1'-bis(diphenylphosphino)ferrocene, EDC is 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, eq is equivalent(s), ES-MS and ESI-MS are electron spray

ion-mass spectroscopy, Et is ethyl, EtOAc is ethyl acetate, g is gram(s), h or hr is hour(s), HATU is *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate, HMPA is hexamethyl phosphoramidate, HOAc is acetic acid, HOAT is 1-hydroxy-7-azabenzotriazole, HOBT or HOBT is 1-hydroxybenzotriazole, HPLC is high performance liquid chromatography, LC/MS or LC-MS is liquid chromatography mass spectrum, LDA is lithium diisopropylamide, CCK-*xR* is cholecystokinin receptor (*x* being a number), L is liter, Me is methyl, MeOH is methanol, MF is molecular formula, min is minutes, mg is milligram(s), mL is milliliter, mmol is millimole(s), MPLC is medium pressure liquid chromatography, MS is mass spectrum, Ms is methane sulfonyl, MTBE is tert-butyl methyl ether, *N* is normal, NaHMDS is sodium hexamethyl disilazide, NaOtBu is sodium *tert*-butoxide, NMM is *N*-Methylmorpholine, NMO is *N*-Methylmorpholine-*N*-oxide, OTf is trifluoromethanesulfonyl, Pd₂(dba)₃ is tris(dibenzylideneacetone) dipalladium (0), Ph is phenyl, Phe is phenyl alanine, Pr is propyl, *i*Pr is isopropyl, prep. is prepared, PyBOP is benzotriazol-1-yloxytripyrrolidine-phosphonium hexafluorophosphate, PyBrop is bromo-tris-pyrrolidino-phosphonium hexafluoro-phosphate, r.t. or rt is room temperature, SCF CO₂ S is super critical fluid carbon dioxide, TBAF is tetrabutylammonium fluoride, TEA or Et₃N is triethylamine, Tf is triflate or trifluoromethanesulfonate, TFA is trifluoroacetic acid, THF is tetrahydrofuran, TIPS is triisopropylsilyl, TBDMS is *tert*-butyldimethylsilyl, TBDPS is *tert*-butyldiphenylsilyl, and TLC is thin-layer chromatography.

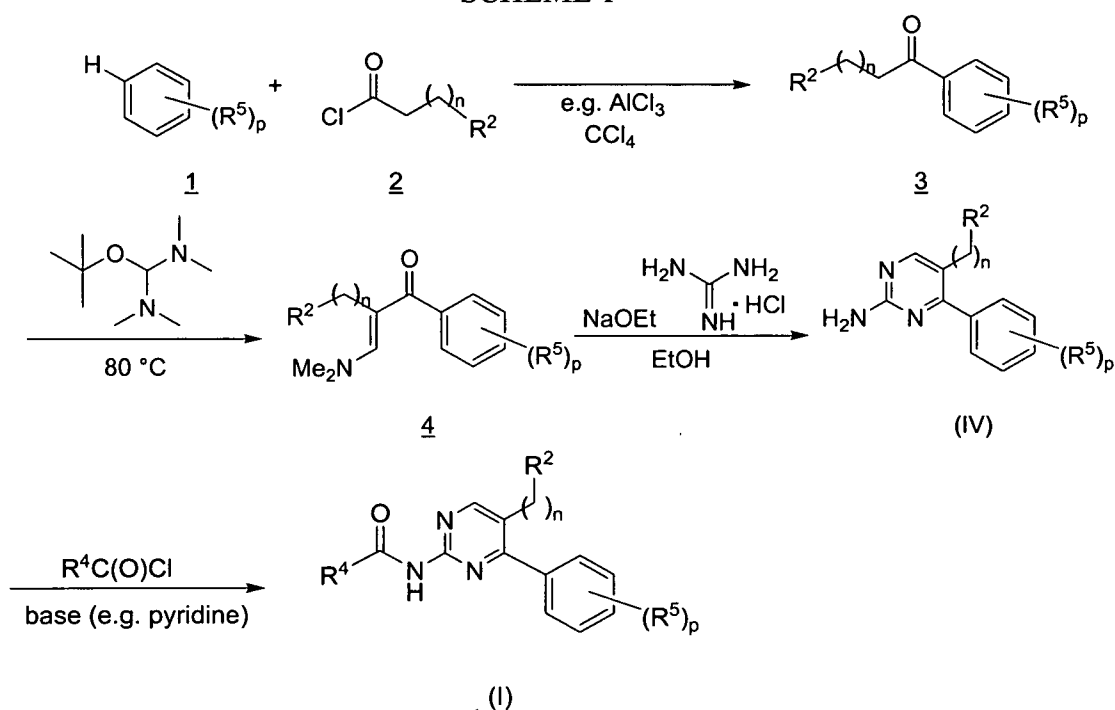
Reaction Schemes 1-3 illustrate the methods employed in the synthesis of the compounds of the present invention of formula I, II and III. All substituents are as defined above unless indicated otherwise. The synthesis of the novel compounds of formula I, II and III which are the subject of this invention may be accomplished by one or more of several similar routes. The compounds of the present invention can be prepared from aminopyrimidines such as those of formula IV and a substituted aryl or heteroaryl carboxylic acid chloride such as V followed by additional modifications. The preparation of these intermediates is described in the following Schemes, wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ are as defined above.



Intermediates of formula IV may be conveniently prepared by a variety of methods familiar to those skilled in the art. One method utilizes a Friedel-Crafts acylation to prepare an aryl ketone of general formula 3 that is subsequently elaborated to IV. The requisite aryl ketone

3 can be prepared using a procedure described in US 6,380,230. Friedel-Crafts donor 1 is treated with an appropriately substituted acyl chloride 2 in the presence of a Lewis acid such as AlCl₃ or FeCl₃ preferably in a halogenated solvent, for example CCl₄, to afford aryl ketone 3. Using a procedure analogous to that described by Wasserman, H.; et. al. in *J. Org. Chem.* 1985, 50, 3573-3580, and references therein, this ketone is then reacted with *tert*-butoxy-bis(dimethylamino)methane (Bredereck's reagent) to give enamine 4. Condensation of 4 with the free base of guanidinium hydrochloride followed by cyclization in the presence of sodium methoxide affords the requisite aminopyrimidine IV. The aminopyrimidine is ultimately reacted with an appropriately substituted aryl or heteroaryl acid chloride in the presence of a base such as pyridine or triethylamine to deliver compounds of the general structure I, wherein R¹ is phenyl and R³ is hydrogen (Scheme 1).

SCHEME 1

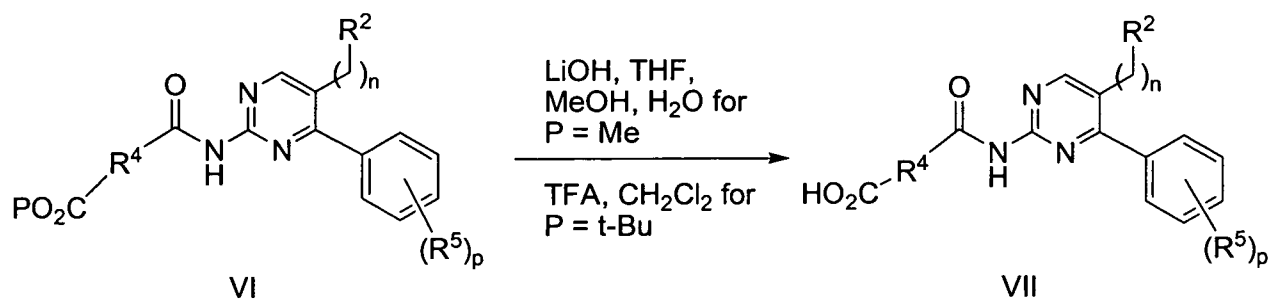


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In cases where R⁴ possesses an attached carboxylate ester, the carboxylic acid functionality can be unmasked at the end of the synthesis using a variety of known procedures (Scheme 2). In the case of protecting group P = Me, lithium, sodium, or potassium hydroxide or potassium trimethylsilanolate can be used to cleave the ester. When P = *tert*-Bu, an acid such as trifluoroacetic acid or hydrochloric acid in a solvent such as methylene chloride can be employed.

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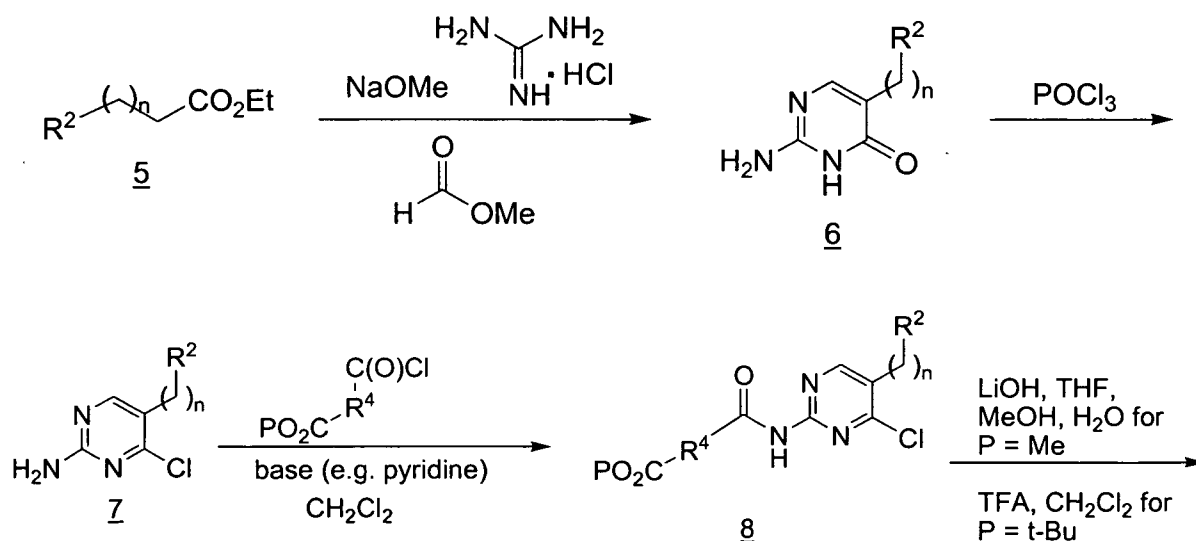
SCHEME 2



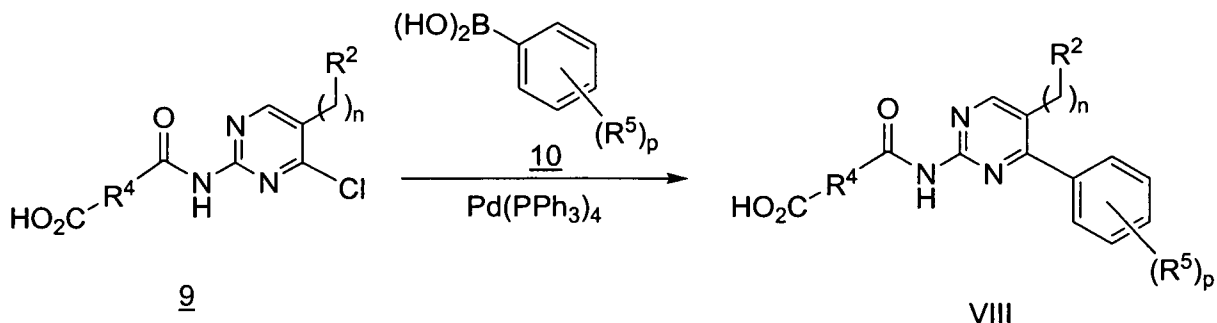
Compounds of the general structure I can also be prepared by the route outlined in Scheme 2 which is adapted from Stoss, P., et. al. in *J. Heterocyclic Chem.* 1991, 28, 231-236.

- 5 Treatment of an appropriately substituted ester 5 with guanidinium hydrochloride, methyl formate, and sodium methoxide in DMF gives pyrimidinone 6. This is chlorinated with, for example, phosphorus oxychloride to give chloropyrimidine 7. The chloropyrimidine is then reacted with an ester-substituted aryl or heteroaryl acid chloride ($\text{PO}_2\text{C}-\text{R}^4-\text{C}(\text{O})\text{Cl}$) in the presence of a base such as pyridine in a solvent such as CH_2Cl_2 to furnish pyrimidine amide 8.
- 10 After cleavage of the ester functionality to the carboxylic acid 9, a palladium-catalyzed cross coupling reaction with an appropriately substituted aryl boronic acid 10 affords VIII (Scheme 3).

SCHEME 3



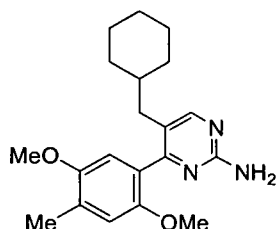
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The compounds of formula I may be purified from unwanted side products, if necessary, by recrystallization, trituration, preparative thin layer chromatography, flash chromatography on silica gel, such as with a Biotage® apparatus, or HPLC. Compounds that are purified by HPLC
 5 may be isolated as the corresponding salt. Purification of intermediates is achieved in the same manner.

In some cases the order of carrying out the foregoing reaction schemes may be varied to facilitate the reaction or to avoid unwanted reaction products. The following examples are provided so that the invention might be more fully understood. These examples are illustrative
 10 only and should not be construed as limiting the invention in any way.

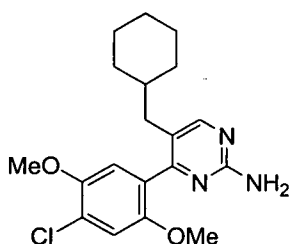
INTERMEDIATE 1



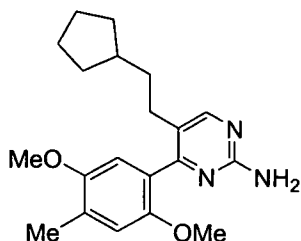
5-(Cyclohexylmethyl)-4-(2,5-dimethoxy-4-methylphenyl)pyrimidin-2-amine 3-Cyclohexyl-1-
 15 (2,5-dimethoxy-4-methylphenyl)propan-1-one (5.0 g, 17 mmol, prepared according to a procedure from US 6,380,230) was heated at 80 °C with neat *tert*-butoxy-*bis*(dimethylamino)methane (5.3 mL, 26 mmol) for 24 h, then the reaction mixture was cooled to ambient temperature to afford a crude solution of 2-(cyclohexylmethyl)-1-(2,5-dimethoxy-4-methylphenyl)-3-(dimethylamino)prop-2-en-1-one. Meanwhile, guanidinium hydrochloride (3.3
 20 g, 34 mmol) was added in one portion to a solution of sodium ethoxide (4.7 g, 69 mmol) in dry ethanol (110 mL) and the resulting suspension was stirred at ambient temperature for 0.5 h to afford the guanidine free base. The free base solution was then added to the above 2-(cyclohexylmethyl)-1-(2,5-dimethoxy-4-methylphenyl)-3-(dimethylamino)prop-2-en-1-one and the reaction mixture was heated at reflux for 4 h, then cooled to ambient temperature and
 25 concentrated *in vacuo*. The resulting residue was partitioned between saturated aqueous ammonium chloride (100 mL) and ethyl acetate (100 mL). The organic layer was removed and

the aqueous layer was extracted with ethyl acetate (2 x 75 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue was purified by recrystallization from 150 mL of 10:1 hexanes/ethyl acetate to give the title compound as a flocculent white solid. ¹H NMR (CDCl₃): δ 8.14 (s, 1 H), 6.76 (s, 1 H), 6.67 (s, 1 H), 5.07 (br s, 2 H), 3.79 (s, 3 H), 3.70 (s, 3 H), 2.27 (s, 3 H), 2.23-2.22 (d, *J* = 7.1 Hz, 2 H), 1.60-1.48 (m, 5 H), 1.27-1.20 (m, 1 H), 1.11-1.03 (m, 3 H), 0.75-0.69 (m, 2 H); LC/MS 441.1 (M+1).

INTERMEDIATE 2



10 4-(4-Chloro-2,5-dimethoxyphenyl)-5-(cyclohexylmethyl)pyrimidin-2-amine. 1-(4-Chloro-2,5-dimethoxyphenyl)-3-cyclohexylpropan-1-one (1.4 g, 4.5 mmol, prepared according to a procedure from US 6,380,230) was heated at 80 °C with neat *tert*-butoxy-*bis*(dimethylamino)methane (1.1 mL, 5.4 mmol) for 24 h then the reaction mixture was cooled to ambient temperature to afford a crude solution of 1-(4-chloro-2,5-dimethoxyphenyl)-2-
15 (cyclohexylmethyl)-3-(dimethylamino)prop-2-en-1-one. Meanwhile, guanidinium hydrochloride (0.65 g, 6.8 mmol) was added in one portion to a solution of sodium ethoxide (1.2 g, 18 mmol) in dry ethanol (50 mL) and the resulting suspension was stirred at ambient temperature for 20 min to afford the guanidine free base. The free base solution was added to the above 1-(4-chloro-2,5-dimethoxyphenyl)-2-(cyclohexylmethyl)-3-(dimethylamino)prop-2-en-1-one dissolved in 15 mL
20 of ethanol and the reaction mixture was heated at reflux for 4 h, then cooled to ambient temperature and concentrated *in vacuo*. The resulting residue was partitioned between saturated aqueous ammonium chloride (100 mL) and ethyl acetate (150 mL). The organic layer was removed and the aqueous layer was extracted with ethyl acetate (2 x 150 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated
25 *in vacuo*. The resulting residue was purified by flash chromatography on a Biotage Horizon ® system (silica gel, 10% ethyl acetate in hexanes to 80% ethyl acetate in hexanes gradient) to give the title compound as a white solid. LC/MS 362.1 (M+1).

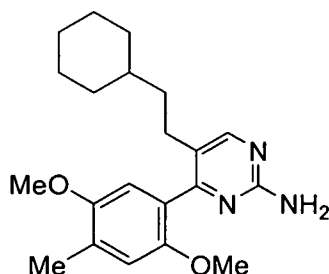
INTERMEDIATE 3

5 5-(2-Cyclopentylethyl)-4-(2,5-dimethoxy-4-methylphenyl)pyrimidin-2-amine. 4-Cyclopentyl-1-(2,5-dimethoxy-4-methylphenyl)butan-1-one (0.21 g, 0.71 mmol, prepared according to a procedure from US 6,380,230) was heated at 70 °C with neat *tert*-butoxy-

10 *bis*(dimethylamino)methane (0.22 mL, 1.1 mmol) for 14 h then the reaction mixture was cooled to ambient temperature to afford a crude solution of 4-cyclopentyl-1-(2,5-dimethoxy-4-methylphenyl)-2-[(dimethylamino)methylene]butan-1-one. Meanwhile, guanidinium hydrochloride (0.17 g, 1.8 mmol) was added in one portion to a solution of sodium ethoxide

15 (0.22 g, 3.2 mmol) in dry ethanol (3.6 mL) and the resulting suspension was stirred at ambient temperature for 1 h to afford the guanidine free base. The free base solution was added to the above 4-cyclopentyl-1-(2,5-dimethoxy-4-methylphenyl)-2-[(dimethylamino)methylene]butan-1-one and the reaction mixture was heated at 75 °C for 24 h, then cooled to ambient temperature and concentrated *in vacuo*. The resulting residue was partitioned between saturated aqueous ammonium chloride (100 mL) and ethyl acetate (100 mL). The organic layer was removed and the aqueous layer was extracted with ethyl acetate (1 x 75 mL). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on a Biotage Horizon ® system (silica gel, 30% ethyl acetate in hexanes to 70% ethyl acetate in hexanes gradient) to give the title

20 compound as a white solid. LC/MS 342.2 (M+1).

INTERMEDIATE 4

25 5-(2-Cyclohexylethyl)-4-(2,5-dimethoxy-4-methylphenyl)pyrimidin-2-amine. 4-Cyclohexyl-1-(2,5-dimethoxy-4-methylphenyl)butan-1-one (4.5 g, 15 mmol, prepared according to a procedure from US 6,380,230) was heated at 80 °C with neat *tert*-butoxy-*bis*(dimethylamino)methane (4.6

mL, 22 mmol) for 16 h then the reaction mixture was cooled to ambient temperature to afford a crude solution of 4-cyclohexyl-1-(2,5-dimethoxy-4-methylphenyl)-2-
[(dimethylamino)methylene]butan-1-one. Meanwhile, guanidinium hydrochloride (2.8 g, 30
mmol) was added in one portion to a solution of sodium ethoxide (4.0 g, 59 mmol) in 92 mL of
5 dry ethanol and the resulting suspension was stirred at ambient temperature for 0.5 h to afford the
guanidine free base. The free base solution was added to the above 4-cyclohexyl-1-(2,5-
dimethoxy-4-methylphenyl)-2-[(dimethylamino)methylene]butan-1-one and the reaction mixture
was heated at reflux for 4 h, then cooled to ambient temperature and concentrated *in vacuo*. The
10 resulting residue was partitioned between saturated aqueous ammonium chloride (200 mL) and
ethyl acetate (150 mL). The organic layer was removed and the aqueous layer was extracted with
ethyl acetate (2 x 150 mL). The combined organic extracts were washed with brine, dried over
magnesium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by
recrystallization from 220 mL of 2:1 hexanes/ethyl acetate. LC/MS 356.0 (M+1).

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INTERMEDIATE 5

4-Chloro-5-(cyclohexylmethyl)pyrimidin-2-amine



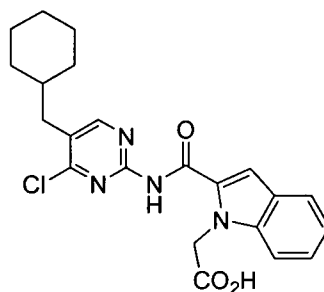
Step A: 2-Amino-5-(cyclohexylmethyl)pyrimidin-4(3H)-one. To a solution of ethyl
cyclohexanepropionate (29.4 mL, 150 mmol) in 15 mL of *N,N*-dimethylformamide was added
20 sodium methoxide (10.8 g, 200 mmol). The resulting suspension was cooled in an ice bath and
methyl formate (6.16 mL, 100 mmol) was added dropwise. The bath was removed and the
mixture was stirred rapidly at ambient temperature for 0.5 h. To the resulting suspension was
added a solution of guanidine hydrochloride (9.55 g, 100 mmol) in 35 mL of methanol, and the
reaction mixture was heated at reflux overnight. During this period additional methanol (25 mL)
25 was added to improve stirring. Next, the reaction mixture was cooled to ambient temperature
and poured into water, and the pH of the solution was adjusted to pH 7 with concentrated
hydrochloric acid while rapidly stirring. The mixture was then cooled in an ice bath and filtered.
The solids were washed sequentially with water (50 mL) and diethyl ether (50 mL), and finally
dried *in vacuo* to give the title compound. LC/MS 208.2 (M+1).

30 Step B: 4-Chloro-5-(cyclohexylmethyl)pyrimidin-2-amine. To a suspension of the product from
Step A (1.00 g, 4.82 mmol) in 8 mL of acetonitrile was added phosphorus oxychloride (1.12 mL,
12.1 mmol) and the resulting mixture was heated at reflux for 5 h. Additional acetonitrile (3 mL)
was added to improve stirring. The pale yellow solution was then cooled to ambient temperature

and allowed to stand overnight. Next, the reaction mixture was added slowly to a rapidly stirred mixture of ice and water. Additional ice was added as necessary to maintain the temperature at or below 5 °C. The mixture was made basic by the dropwise addition of concentrated aqueous ammonium hydroxide while continuing to cool by the addition of solid ice. The resulting mixture was then diluted with water and sequentially extracted with chloroform (3 x 100 mL) and ethyl acetate (3 x 100 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Flash chromatography of the resulting crude product on a Biotage Horizon ® system (silica gel, 30% ethyl acetate in hexanes then 50% ethyl acetate in hexanes gradient) gave the title compound as a white solid. ¹H NMR (CDCl₃): δ 8.01 (s, 1 H), 5.20 (br s, 2 H), 2.42 (d, *J* = 7.1 Hz, 2 H), 1.72-1.66 (comp, 5 H), 1.57-1.49 (m, 1 H), 1.26-1.10 (m, 3 H), 0.99-0.92 (m, 2H). LC/MS 226.1 (M+1).

INTERMEDIATE 6

[2-({[4-Chloro-5-(cyclohexylmethyl)pyrimidin-2-yl]amino}carbonyl)-1*H*-indol-1-yl]acetic acid



15

Step A: Methyl [2-({[4-chloro-5-(cyclohexylmethyl)pyrimidin-2-yl]amino}carbonyl)-1*H*-indol-1-yl]acetate. To a solution of 1-(2-methoxy-2-oxoethyl)-1*H*-indole-2-carboxylic acid (0.78 g, 3.3 mmol), prepared according to a procedure from US 6,380,230) in 5 mL dichloromethane containing *N,N*-dimethylformamide (0.017 mL, 0.22 mmol) was added oxalyl chloride (1.7 mL, 3.3 mmol, 2.0 M in dichloromethane). The resulting solution was stirred at ambient temperature for 2 h. Next, this mixture was added to a pre-prepared solution of Intermediate 3 (0.50 g, 2.2 mmol) and pyridine (0.72 mL, 8.9 mmol) in 5 mL of dichloromethane. After 24 h at ambient temperature the resulting reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on a Biotage Horizon ® system (silica gel, 100% hexanes to 50% ethyl acetate in hexanes gradient) to give the title compound as a white solid. LC/MS 441.1 (M+1).

Step B: [2-({[4-Chloro-5-(cyclohexylmethyl)pyrimidin-2-yl]amino}carbonyl)-1*H*-indol-1-yl]acetic acid.

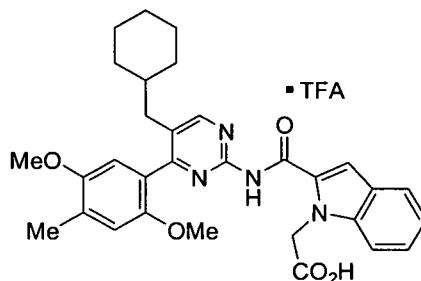
To a cooled (-10 °C) solution of the compound from Step A (130 mg, 0.30 mmol) in 2.5 mL of anhydrous tetrahydrofuran was added potassium trimethylsilanolate (90% tech. grade, 92 mg, 0.65 mmol) in one portion. The reaction mixture was stirred at -10 °C for 2 h and then at

30

ambient temperature overnight. The mixture was cooled in an ice bath, diluted with water, and then acidified with 1 *N* hydrochloric acid. The bath was removed and the aqueous mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give the title compound, which was used without further purification. ¹H NMR (CDCl₃): δ 9.27 (br s, 1 H), 8.35 (s, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.40-7.35 (comp, 2 H), 7.26 (s, 1 H), 7.20 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1 H), 5.36 (s, 2H), 2.53 (d, *J* = 7.1 Hz, 2 H), 1.71-1.64 (comp, 5 H), 1.61-1.54 (m, 1 H), 1.20-1.14 (comp, 3 H), 1.02-0.95 (comp, 2 H); LC/MS 427.3 (M+1).

EXAMPLE 1

[2-({[5-(Cyclohexylmethyl)-4-(2,5-dimethoxy-4-methylphenyl)pyrimidin-2-yl]amino}carbonyl)-1*H*-indol-1-yl]acetic acid, trifluoroacetic acid salt



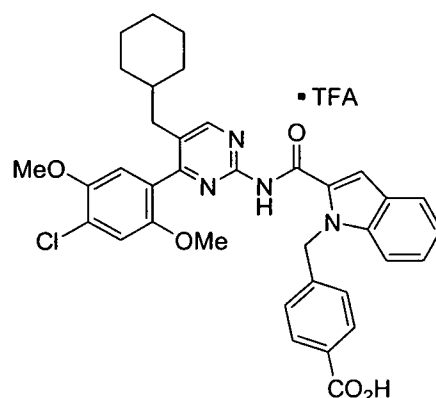
Step A: Methyl [2-({[5-(cyclohexylmethyl)-4-(2,5-dimethoxy-4-methylphenyl)pyrimidin-2-yl]amino}carbonyl)-1*H*-indol-1-yl]acetate. To a solution of 1-(2-methoxy-2-oxoethyl)-1*H*-indole-2-carboxylic acid (88 mg, 0.38 mmol, prepared according to a procedure from US 6,380,230) in 0.75 mL dichloromethane containing *N,N*-dimethylformamide (1 drop) was added oxalyl chloride (0.033 mL, 0.38 mmol). The resulting solution was stirred at ambient temperature for 2 h. Next, this mixture was added to a pre-prepared solution of Intermediate 1 (65 mg, 0.19 mmol) and pyridine (0.10 mL, 1.2 mmol) in 1.1 mL of dichloromethane. After 24 h at ambient temperature the resulting reaction mixture was concentrated *in vacuo* and the resulting residue was purified by flash chromatography on a Biotage Horizon ® system (silica gel, 100% hexanes to 70% ethyl acetate in hexanes gradient) to give the title compound as a white solid. LC/MS 557.6 (M+1).

Step B: [2-({[5-(Cyclohexylmethyl)-4-(2,5-dimethoxy-4-methylphenyl)pyrimidin-2-yl]amino}carbonyl)-1*H*-indol-1-yl]acetic acid, trifluoroacetic acid salt. To a solution of the product of Step A (100 mg, 0.18 mmol) in 2 mL of 4:1 methanol/tetrahydrofuran was added 1 *N* aqueous lithium hydroxide (0.22 mL, 0.22 mmol). After stirring for 24 h at ambient temperature the reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in a mixture of 1 mL of *N,N*-dimethylformamide and 0.2 mL of acetic acid and purified by reverse phase HPLC (gradient 10-80% acetonitrile/water containing 0.1% trifluoroacetic acid). The pure

fractions were lyophilized to give the title compound as a yellow solid. ¹H NMR (DMSO-d₆): δ 10.98 (s, 1 H), 8.56 (s, 1 H), 7.67 (d, *J* = 7.8 Hz, 1 H), 7.59 (d, *J* = 8.0 Hz, 1 H), 7.57 (s, 1 H), 7.30 (t, *J* = 7.1 Hz, 1 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 6.98 (s, 1 H), 6.81 (s, 1 H), 5.31 (s, 2 H), 3.71 (s, 3 H), 3.67 (s, 3 H), 2.31 (d, *J* = 7.1 Hz, 2 H), 2.23 (s, 3 H), 1.55 (m, 3 H), 1.44-1.42 (m, 2 H), 1.31 (m, 1 H), 1.04 (m, 3 H), 0.74 (m, 2 H); LC/MS 543.2 (M+1).

EXAMPLE 2

4-{{2-({[4-(4-Chloro-2,5-dimethoxyphenyl)-5-(cyclohexylmethyl)pyrimidin-2-yl]amino}carbonyl)-1*H*-indol-1-yl]methyl}benzoic acid, trifluoroacetic acid salt



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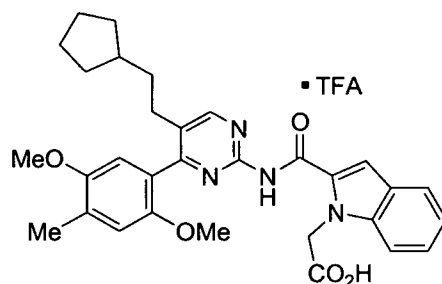
Step A: Methyl 4-{{2-({[4-(4-chloro-2,5-dimethoxyphenyl)-5-(cyclohexylmethyl)pyrimidin-2-yl]amino}carbonyl)-1*H*-indol-1-yl]methyl}benzoate. To a solution of 1-[4-(methoxycarbonyl)benzyl]-1*H*-indole-2-carboxylic acid (190 mg, 0.61 mmol, prepared according to a procedure from US 6,380,230) in 1.3 mL dichloromethane containing *N,N*-dimethylformamide (1 drop) was added a solution of oxalyl chloride in dichloromethane (2.0 M, 0.33 mL, 0.66 mmol). The resulting solution was stirred at ambient temperature for 2 h. Next, this mixture was added to a pre-prepared solution of Intermediate 2 (100 mg, 0.28 mmol) and pyridine (0.13 mL, 1.7 mmol) in 0.2 mL of dichloromethane. After 24 h at ambient temperature the resulting reaction mixture was concentrated *in vacuo* and the resulting residue was purified by flash chromatography on a Biotage Horizon ® system (silica gel, 10% ethyl acetate in hexanes to 70% ethyl acetate in hexanes gradient) to give the title compound as a white solid.

Step B: 4-{{2-({[4-(4-Chloro-2,5-dimethoxyphenyl)-5-(cyclohexylmethyl)pyrimidin-2-yl]amino}carbonyl)-1*H*-indol-1-yl]methyl}benzoic acid, trifluoroacetic acid salt. To a solution of the product of Step A (164 mg, 0.25 mmol) in 1.3 mL of tetrahydrofuran was added potassium trimethylsilylanolate (technical grade (90%), 89 mg, 0.63 mmol). After stirring for 24 h at ambient temperature the reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in 1 mL of *N,N*-dimethylformamide and the resulting solution was acidified with 6 *N* hydrochloric acid then purified by reverse phase HPLC (gradient 40-100% acetonitrile/water containing 0.1% trifluoroacetic acid). The pure fractions were lyophilized to give the title

compound as a yellow solid. ¹H NMR (DMSO-d₆): δ 11.09 (s, 1 H), 8.57 (s, 1 H), 7.80 (d, *J* = 7.7 Hz, 2 H), 7.70 (d, *J* = 7.8 Hz, 1 H), 7.54 (s, 1 H), 7.50 (d, *J* = 8.4 Hz, 1 H), 7.27 (t, *J* = 7.5 Hz, 1 H), 7.25 (s, 1 H), 7.14-7.11 (m, 3 H), 7.03 (m, 1 H), 5.93 (s, 2 H), 3.73, (s, 3 H), 3.69 (s, 3 H), 2.28 (m, 2 H), 1.54 (m, 3 H), 1.43-1.41 (m, 2 H), 1.28 (m, 1 H), 1.03 (m, 3 H), 0.74-0.72 (m, 2 H); LC/MS 638.8 (M+1).

EXAMPLE 3

[2-({[5-(2-Cyclopentylethyl)-4-(2,5-dimethoxy-4-methylphenyl)pyrimidin-2-yl]amino}carbonyl)-1*H*-indol-1-yl]acetic acid, trifluoroacetic acid salt



10

To a solution of 1-(2-methoxy-2-oxoethyl)-1*H*-indole-2-carboxylic acid (23 mg, 0.10 mmol), prepared according to a procedure from US 6,380,230) in 0.5 mL dichloromethane containing *N,N*-dimethylformamide (1 drop) was added a solution of oxalyl chloride in dichloromethane (2.0 M, 0.056 mL, 0.11 mmol). The resulting solution was stirred at ambient temperature for 1 h. Next, this mixture was added to a pre-prepared solution of Intermediate 3 (20 mg, 0.059 mmol) and pyridine (0.028 mL, 0.35 mmol) in 0.1 mL of dichloromethane. After 17 h at ambient temperature the resulting reaction mixture was concentrated *in vacuo*. The resulting residue was redissolved in 1 mL of tetrahydrofuran then potassium trimethylsilanolate (technical grade (90%), 75 mg, 0.53 mmol) was added and the resulting suspension was heated at 50 °C. After 1 h the reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The resulting residue was dissolved in 1 mL of *N,N*-dimethylformamide and the resulting solution was acidified with trifluoroacetic acid then purified by reverse phase HPLC (gradient 40-100% acetonitrile/water containing 0.1% trifluoroacetic acid). The pure fractions were lyophilized to give the title compound as a yellow solid. ¹H NMR (DMSO-d₆): δ 10.99 (s, 1 H), 8.61 (s, 1 H), 7.67 (d, *J* = 7.7 Hz, 1 H), 7.58 (d, *J* = 8.2 Hz, 1 H), 7.58 (s, 1 H), 7.30 (dd, *J* = 8.2, 7.3 Hz, 1 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 6.99 (s, 1 H), 6.82 (s, 1 H), 5.31 (s, 2 H), 3.71, (s, 3 H), 3.68 (s, 3 H), 2.42 (t, *J* = 7.8 Hz, 2 H), 2.23 (s, 3 H), 1.60-1.36 (m, 9 H), 0.90-0.87 (m, 2 H); LC/MS 543.2 (M+1).

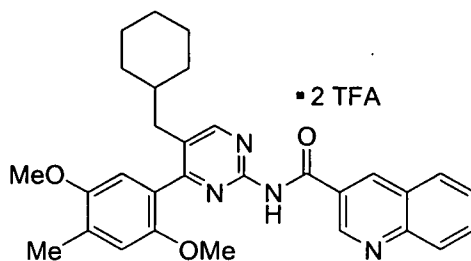
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EXAMPLE 4

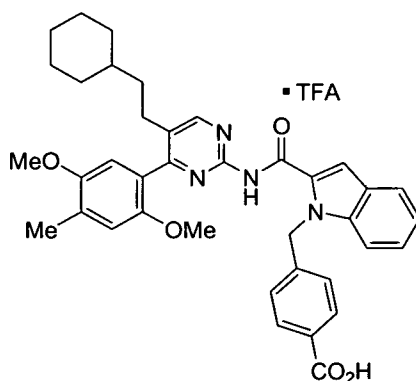
N-[5-(Cyclohexylmethyl)-4-(2,5-dimethoxy-4-methylphenyl)pyrimidin-2-yl]quinoline-3-carboxamide, *bis* trifluoroacetic acid salt



Quinoline-3-carboxylic acid (20 mg, 0.12 mmol) was heated at reflux in 1 mL of thionyl chloride for 1 h. The resulting solution was cooled to ambient temperature and concentrated *in vacuo* to give solid quinoline-3-carbonyl chloride. Intermediate 1 (20 mg, 0.059 mmol) was added to the crude acid chloride followed by pyridine (0.5 mL). After 3 h at ambient temperature the reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in 1 mL of *N,N*-dimethylformamide and the resulting solution was purified by reverse phase HPLC (gradient 40-100% acetonitrile/water containing 0.1% trifluoroacetic acid). The pure fractions were lyophilized to give the title compound as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 11.35 (s, 1 H), 9.31 (br s, 1 H), 8.97 (br s, 1 H), 8.60 (s, 1 H), 8.12-8.09 (m, 2 H), 7.90 (dd, *J* = 8.3, 6.8 Hz, 1 H), 7.71 (dd, *J* = 8.0, 7.1 Hz, 1 H), 6.98 (s, 1 H), 6.77 (s, 1 H), 3.69 (s, 3 H), 3.67 (s, 3 H), 2.33-2.32 (m, 2 H), 2.22 (s, 3 H), 1.55-1.30 (m, 6 H), 1.04 (m, 3 H), 0.74 (m, 2 H); LC/MS 497.2 (M+1).

EXAMPLE 5

15 4-[[2-({[5-(2-Cyclohexylethyl)-4-(2,5-dimethoxy-4-methylphenyl)pyrimidin-2-yl]amino}carbonyl)-1*H*-indol-1-yl]methyl]benzoic acid, trifluoroacetic acid salt

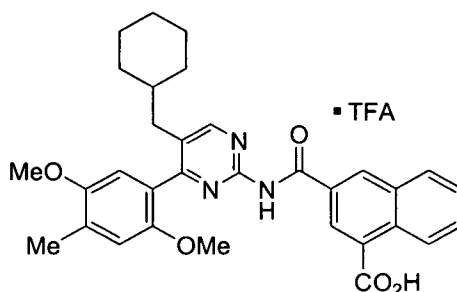


To a solution of 1-[4-(methoxycarbonyl)benzyl]-1*H*-indole-2-carboxylic acid (35 mg, 0.11 mmol, prepared according to a procedure from US 6,380,230) in 1 mL of dichloromethane containing *N,N*-dimethylformamide (1 drop) was added a solution of oxalyl chloride in dichloromethane (2.0 M, 0.059 mL, 0.12 mmol). The resulting solution was stirred at ambient temperature for 2 h. Next, this mixture was added to a previously prepared solution of Intermediate 4 (20 mg, 0.056 mmol) and pyridine (0.18 mL, 0.23 mmol) in 0.5 mL of dichloromethane. After 18 h at ambient temperature the resulting reaction mixture was

concentrated *in vacuo*. The resulting residue was redissolved in 1.5 mL of tetrahydrofuran then potassium trimethylsilanolate (technical grade (90%), 36 mg, 0.28 mmol) was added and the resulting suspension was heated at 50 °C. After 0.5 h the reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The resulting residue was dissolved in 1 mL of *N,N*-dimethylformamide and the resulting solution was acidified with trifluoroacetic acid then purified by reverse phase HPLC (gradient 40-100% acetonitrile/water containing 0.1% trifluoroacetic acid). The pure fractions were lyophilized to give the title compound as a yellow solid. ¹H NMR (DMSO-*d*₆): δ 11.03 (s, 1 H), 8.57 (s, 1 H), 7.78 (d, *J* = 8.3 Hz, 2 H), 7.70 (d, *J* = 8.0 Hz, 1 H), 7.52 (s, 1 H), 7.49 (d, *J* = 8.5 Hz, 1 H), 7.26 (t, *J* = 8.0 Hz, 1 H), 7.14-7.11 (m, 3 H), 6.97 (s, 1 H), 6.73 (s, 1 H), 5.93 (s, 2 H), 3.65 (s, 3 H), 3.63 (s, 3 H), 2.40 (t, *J* = 7.7 Hz, 2 H), 2.21 (s, 3 H), 1.54-1.45 (m, 5 H), 1.29-1.25 (m, 2 H), 1.11-0.98 (m, 4 H), 0.74-0.67 (m, 2 H); LC/MS 633.3 (M+1).

EXAMPLE 6

3-({[5-(Cyclohexylmethyl)-4-(2,5-dimethoxy-4-methylphenyl)pyrimidin-2-yl]amino}carbonyl)-1-naphthoic acid, trifluoroacetic acid salt



Step A: Methyl 3-cyano-1-naphthoate. A flask containing methyl 3-bromo-1-naphthoate (100 mg, 0.38 mmol), *tetrakis*(triphenylphosphine)palladium (44 mg, 0.038 mmol), and zinc cyanide (49 mg, 0.42 mmol) was flushed with N₂ for 5 minutes then 1.2 mL of *N,N*-dimethylformamide was added. The resulting solution was heated at 70 °C for 3 h, then cooled to ambient temperature and poured into brine. The aqueous mixture was extracted with ethyl acetate (3 x 10 mL) and the combined extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on a Biotage Horizon ® system (silica gel, 100% hexanes to 10% ethyl acetate in hexanes gradient) to give the title compound as a white solid.

Step B: Dimethyl naphthalene-1,3-dicarboxylate. The product from Step A was suspended in 1.1 mL of ethanol in a microwave vial then aqueous sodium hydroxide (6.25 *N*, 0.30 ml, 1.9 mmol) was added. The resulting mixture was heated in a microwave reactor at 180°C for 20 min, then cooled to ambient temperature and concentrated *in vacuo*. The resulting residue was partitioned between 6 *N* aqueous hydrochloric acid (10 mL) and ethyl acetate (10 mL). The

organic layer was removed and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined extracts were washed with brine, dried over magnesium sulfate, filtered and concentrated *in vacuo*. The resulting residue was dissolved in a mixture of 4 mL of diethyl ether and 1 mL of methanol and the resulting solution was treated with excess of a solution of

5 trimethylsilyldiazomethane. The excess reagent was quenched with acetic acid and the mixture was concentrated *in vacuo* to give the title compound as a white solid. LC/MS 245.2 (M+1).

Step C: 4-(Methoxycarbonyl)-2-naphthoic acid. The product from Step B (50 mg, 0.21 mmol) was dissolved in 0.5 mL of tetrahydrofuran and the resulting solution was cooled to 0 °C.

Aqueous sodium hydroxide (1 N, 0.21 mL, 0.21 mmol) was added and the reaction mixture was

10 allowed to warm to ambient temperature. Methanol (10 drops) was added until the turbidity cleared and the solution was stirred at ambient temperature for 24 h then concentrated *in vacuo*.

The residue was partitioned between 6 N aqueous hydrochloric acid (5 mL) and ethyl acetate (5 mL). The organic layer was removed and the aqueous layer was extracted with ethyl acetate (4 x

15 5 mL). The combined organic extracts were dried over magnesium sulfate, filtered and

concentrated. The resulting residue was dissolved in 1 mL of *N,N*-dimethylformamide and the resulting solution was then purified by reverse phase HPLC (gradient 10-100% acetonitrile/water containing 0.1% trifluoroacetic acid). The pure fractions were combined and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were washed with brine, dried over

20 magnesium sulfate, filtered and concentrated to give the title compound contaminated with circa 10% of the other acid regioisomer. LC/MS 230.9 (M+1).

Step D: Methyl 3-({[5-(cyclohexylmethyl)-4-(2,5-dimethoxy-4-methylphenyl)pyrimidin-2-yl]amino}carbonyl)-1-naphthoate. To a solution of the acid from Step C (23 mg, 0.098 mmol) in 1.5 mL of dichloromethane containing *N,N*-dimethylformamide (1 drop) was added a solution of oxalyl chloride in dichloromethane (2.0 M, 0.053 mL, 0.11 mmol). The resulting solution was

25 stirred at ambient temperature for 0.5 h. Next, this mixture was added to a pre-prepared solution of Intermediate 1 (28 mg, 0.082 mmol) and pyridine (0.04 mL, 0.49 mmol) in 0.2 mL of dichloromethane. After 14 h at ambient temperature the resulting reaction mixture was concentrated *in vacuo*. The resulting residue was dissolved in 2 mL of 15% ethanol in hexanes and purified by normal phase HPLC (Chiralcel OD column, eluting with 15% ethanol in

30 hexanes). The appropriate fractions were combined and concentrated to give the regioisomerically pure title compound as a white solid. LC/MS 554.2 (M+1).

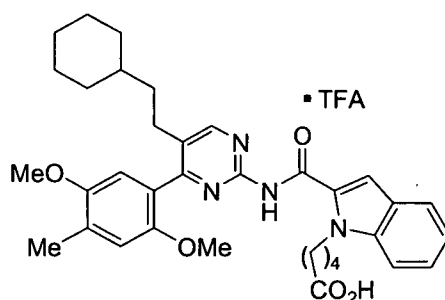
Step E: 3-({[5-(Cyclohexylmethyl)-4-(2,5-dimethoxy-4-methylphenyl)pyrimidin-2-yl]amino}carbonyl)-1-naphthoic acid, trifluoroacetic acid salt. To a solution of the methyl ester from Step D (10 mg, 0.018 mmol) in 2 mL of tetrahydrofuran was added potassium

35 trimethylsilylanolate (technical grade (90%), 20 mg, 0.14 mmol) and the resulting suspension was heated at 50 °C. After 1 h the reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The resulting residue was dissolved in 1 mL of *N,N*-dimethylformamide

and the resulting solution was acidified with trifluoroacetic acid then purified by reverse phase HPLC (gradient 40-100% acetonitrile/water containing 0.1% trifluoroacetic acid). The pure fractions were lyophilized to give the title compound as a yellow solid. ¹H NMR (DMSO-d₆): δ 11.27 (s, 1 H), 8.89 (d, *J* = 8.7 Hz, 1 H), 8.83 (s, 1 H), 8.60-8.59 (m, 2 H), 8.13 (d, *J* = 8.2 Hz, 1 h), 7.76 (t, *J* = 7.1 Hz, 1 H), 7.67 (t, *J* = 7.3 Hz, 1 H), 6.98 (s, 1 H), 6.76 (s, 1 H), 3.68 (s, 3 H), 3.67 (s, 3 H), 2.33 (br d, *J* = 6.8 Hz, 2 H), 2.22 (s, 3 H), 1.55-1.30 (m, 6 H), 1.04-1.03 (m, 3 H), 0.74-0.72 (m, 2 H). LC/MS 540.3 (M+1).

EXAMPLE 7

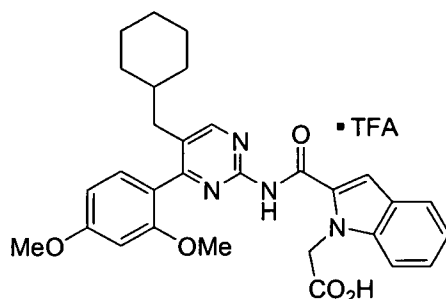
10 5-[2-({[5-(2-Cyclohexylethyl)-4-(2,5-dimethoxy-4-methylphenyl)pyrimidin-2-yl]amino}carbonyl)-1*H*-indol-1-yl]pentanoic acid, trifluoroacetic acid salt



To a solution of 1-(5-methoxy-5-oxopentyl)-1*H*-indole-2-carboxylic acid (34 mg, 0.12 mmol, prepared according to a procedure from US 6,380,230) in 0.4 mL of dichloromethane containing *N,N*-dimethylformamide (1 drop) was added a solution of oxalyl chloride in dichloromethane (2.0 M, 0.068 mL, 0.14 mmol). The resulting solution was stirred at ambient temperature for 1 h. Next, this mixture was added to a previously prepared solution of Intermediate 4 (20 mg, 0.056 mmol) and pyridine (0.027 mL, 0.34 mmol) in 0.2 mL of dichloromethane. After 2 h at ambient temperature the resulting reaction mixture was concentrated *in vacuo*. The resulting residue was redissolved in 1 mL of tetrahydrofuran then potassium trimethylsilanolate (technical grade (90%), 66 mg, 0.46 mmol) was added and the resulting suspension was heated at 50 °C. After 0.5 h the reaction mixture was cooled to ambient temperature and concentrated *in vacuo*. The resulting residue was dissolved in 1 mL of *N,N*-dimethylformamide and the resulting solution was acidified with trifluoroacetic acid then purified by reverse phase HPLC (gradient 40-100% acetonitrile/water containing 0.1% trifluoroacetic acid). The pure fractions were lyophilized to give the title compound as a yellow solid. ¹H NMR (DMSO-d₆): δ 10.95 (s, 1 H), 8.60 (s, 1 H), 7.65 (d, *J* = 8.0 Hz, 1 H), 7.57 (d, *J* = 8.5 Hz, 1 H), 7.42 (s, 1 H), 7.30 (t, *J* = 7.3 Hz, 1 H), 7.10 (d, *J* = 7.6 Hz, 1 H), 6.99 (s, 1 H), 6.79 (s, 1 H), 4.55 (t, *J* = 7.0 Hz, 2 H), 3.70 (s, 3 H), 3.68 (s, 3 H), 2.43 (t, *J* = 7.6 Hz, 2 H), 2.23 (s, 3 H), 2.20 (t, *J* = 7.6 Hz, 2 H), 1.71 (p, *J* = 7.6 Hz, 2 H), 1.55-1.47 (m, 7 H), 1.29 (q, *J* = 6.6 Hz, 2 H), 1.13-1.00 (m, 4 H), 0.75-0.69 (m, 2 H). LC/MS 599.4 (M+1).

EXAMPLE 8

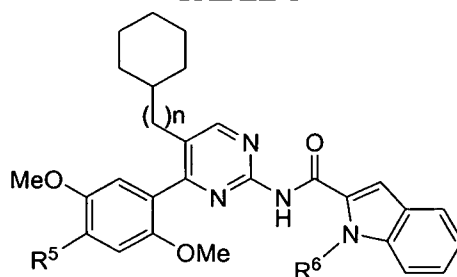
[2-({[5-(Cyclohexylmethyl)-4-(2,4-dimethoxyphenyl)pyrimidin-2-yl]amino}carbonyl)-1H-indol-1-yl]acetic acid, trifluoroacetic acid salt



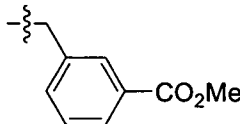
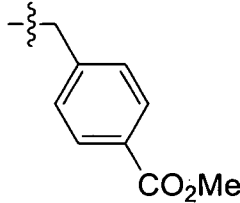
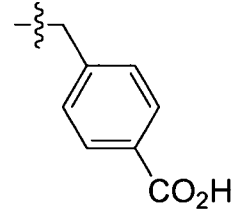
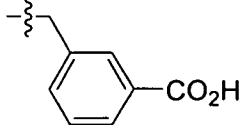
To a mixture of Intermediate 4 (20 mg, 0.047 mmol), 2,4-dimethoxyphenylboronic acid (10 mg, 0.056 mmol), and *tetrakis*(triphenylphosphine)palladium (2.0 mg, 0.0017 mmol) that had been purged for 5 minutes with a stream of dry nitrogen was added *N,N*-dimethylformamide (0.8 mL) and 2M aqueous sodium carbonate (0.070 mL, 0.14 mmol). The resulting solution was heated at 90 °C for 1.5 h then cooled to ambient temperature. Trifluoroacetic acid (0.02 mL) was added and the resulting mixture was purified directly by reverse phase HPLC (gradient 20-90% acetonitrile/water containing 0.1% trifluoroacetic acid). The pure fractions were lyophilized to give the title compound as a yellow solid. LC/MS 529.4 (M+1).

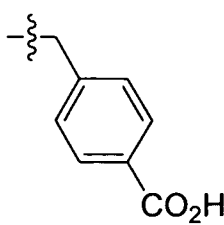
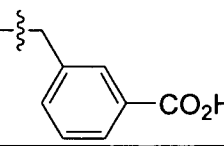
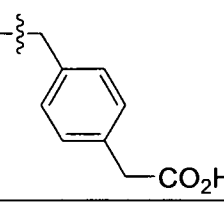
Following essentially the procedures outlined for Examples 1-8, Examples 9-41 in Table 1 were prepared.

TABLE 1



Example	n	R ⁵	R ⁶	MS (M+1)
9	2	Cl	- ξ -Me	533.4
10	2	Cl	- ξ -CH ₂ CO ₂ Me	591.7
11	2	Cl	- ξ -CH ₂ CO ₂ H	577.6
12	1	Cl	- ξ -Me	519.4
13	1	Cl	- ξ -CH ₂ CO ₂ Me	577.2

14	1	Cl	$\text{-}\overset{\xi}{\text{C}}\text{-CH}_2\text{CO}_2\text{H}$	563.2
15	1	Cl		653.5
16	1	Cl		653.5
17	1	Me	$\text{-}\overset{\xi}{\text{C}}\text{-CH}_2\text{CO}_2\text{Me}$	557.6
18	1	Cl	$\text{-}\overset{\xi}{\text{C}}\text{-(CH}_2\text{)}_2\text{CO}_2\text{Me}$	591.4
19	1	Me	$\text{-}\overset{\xi}{\text{C}}\text{-(CH}_2\text{)}_2\text{CO}_2\text{Me}$	571.6
20	1	Cl	$\text{-}\overset{\xi}{\text{C}}\text{-(CH}_2\text{)}_2\text{CO}_2\text{H}$	577.6
21	1	Me	$\text{-}\overset{\xi}{\text{C}}\text{-(CH}_2\text{)}_2\text{CO}_2\text{H}$	557.6
22	2	Cl	$\text{-}\overset{\xi}{\text{C}}\text{-(CH}_2\text{)}_2\text{CO}_2\text{Me}$	605.4
23	2	Cl	$\text{-}\overset{\xi}{\text{C}}\text{-(CH}_2\text{)}_2\text{CO}_2\text{H}$	591.5
24	1	Me		619.0
25	1	Me		619.2

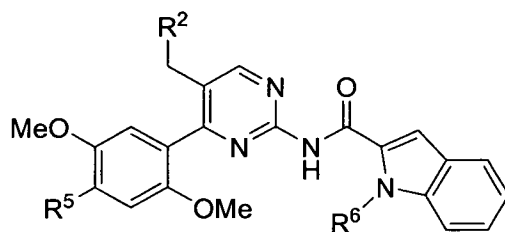
26	2	Me		633.3
27	2	Me		633.3
28	2	Me	$\xi\text{-CH}_2\text{CO}_2\text{H}$	557.4
29	2	Me	$\xi\text{-(CH}_2)_2\text{CO}_2\text{H}$	571.4
30	2	Me	$\xi\text{-(CH}_2)_4\text{CO}_2\text{H}$	
31	2	Me	$\xi\text{-(CH}_2)_3\text{CO}_2\text{H}$	585.1
32	2	Me	$\xi\text{-H}$	499.3
33	2	Cl	$\xi\text{-(CH}_2)_4\text{CO}_2\text{H}$	619.1
34	2	Me		647.3
35	2	F	$\xi\text{-CH}_2\text{CO}_2\text{H}$	561.3
36	2	Br	$\xi\text{-CH}_2\text{CO}_2\text{H}$	621.2
37	2	F	$\xi\text{-(CH}_2)_4\text{CO}_2\text{H}$	603.4
38	2	Br	$\xi\text{-(CH}_2)_4\text{CO}_2\text{H}$	662.9
39	2	Me	$\xi\text{-(CH}_2)_5\text{CO}_2\text{H}$	613.1

40	2	Br		678.1
41	2	Me		571.3

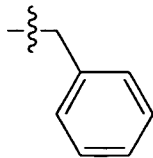
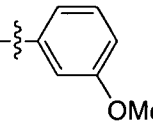

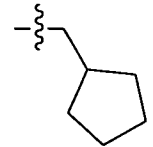
Following essentially the procedures outlined for Examples 1-8, Examples 42-51 in Table 2 were prepared.

TABLE 2

5

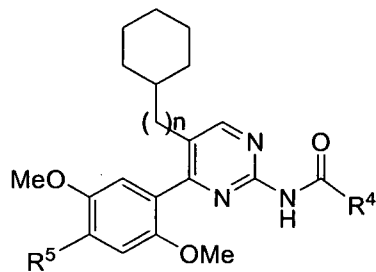


Example	R ⁵	R ⁶	R ²	MS (M+1)
42	Cl	-ξ-Me		505.5
43	Cl	-ξ-CH ₂ CO ₂ Me		563.2
44	Cl	-ξ-CH ₂ CO ₂ H		549.1
45	Cl	-ξ-(CH ₂) ₂ CO ₂ Me		577.4
46	Cl	-ξ-CH ₂ CO ₂ Me		591.6
47	Cl	-ξ-CH ₂ CO ₂ H		577.3

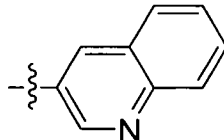
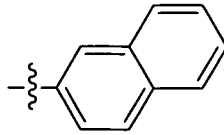
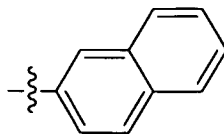
48	Me	$-\text{CH}_2-\text{(CH}_2\text{)}_4\text{CO}_2\text{H}$		593.3
49	Me	$-\text{CH}_2-\text{(CH}_2\text{)}_5\text{CO}_2\text{H}$		623.1
50	Me	$-\text{CH}_2-\text{(CH}_2\text{)}_5\text{CO}_2\text{H}$		623.1
51	Me	$-\text{CH}_2-\text{(CH}_2\text{)}_2\text{CO}_2\text{H}$		557.2

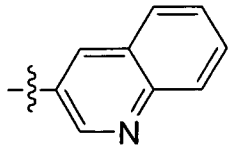
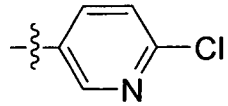
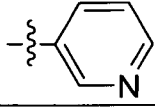
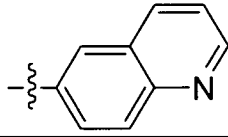
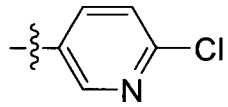
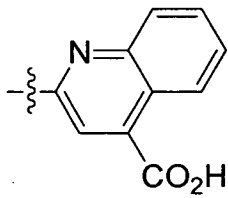
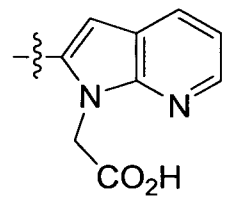
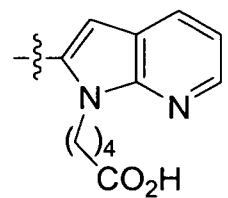
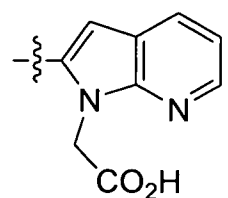
Following essentially the procedures outlined for Examples 1-8, Examples 52-64 in Table 3 were prepared.

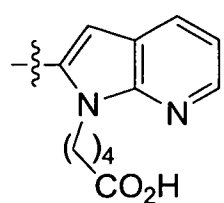
TABLE 3



5

<u>Example</u>	<u>n</u>	<u>R⁵</u>	<u>R⁴</u>	<u>MS (M+1)</u>
52	1	Me		497.2
53	1	Me		496.1
54	2	Me		510.4

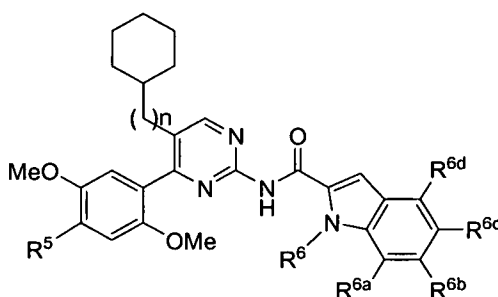
55	2	Me		511.4
56	1	Me		481.3
57	1	Me		447.3
58	1	Me		497.2
59	2	Me		495.2
60	1	Me		541.2
61	1	Me		544.2
62	1	Me		586.3
63	2	Me		558.3

64	2	Me		600.2
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Following essentially the procedures outlined for Examples 1-8, Examples 65-67 in Table 4 were prepared.

TABLE 4

5



Example	n	R ⁵	R ⁶	R ^{6a}	R ^{6b}	R ^{6c}	R ^{6d}	MS (M+1)
65	1	Me	-CH ₂ CO ₂ Me	Me	H	Me	H	585.5
66	1	Me	-CH ₂ CO ₂ H	H	H	H	Cl	577.3
67	1	Me	-CH ₂ CO ₂ H	H	H	Cl	H	577.3

BIOLOGICAL ASSAYS

10 A. Cholecystokinin-1 Receptor (CCK1R) and Cholecystokinin-2 Receptor (CCK2R) Binding Assays

Cells were cultured to confluence and harvested by aspirating culture medium and rinsed twice with 1x PBS without Mg⁺⁺ and Ca⁺⁺. 3 mL of Cell Dissociate Solution was added to each T-175 flask until all cells dissociated and then an additional 15ml 1x PBS without Mg⁺⁺ and Ca⁺⁺ was added to each flask. Dissociated cells were collected in a centrifuge tube by centrifuging at 1000 rpm for 10 min. The cell pellet was homogenized at 4°C using a Polytron (setting 40, 20 stokes) in about 10 mL / T175 flask membrane preparation buffer (10mM Tris pH 7.4, 0.01mM

Pefabloc, 10 μ M phosphoramidon and 40 μ g/mL Bacitracin). After centrifugation at 2200 rpm (1000 x g) for 10 min at 4°C, the supernatant was transferred to a clean centrifuge tube and spun at 18,000 rpm (38,742xg) for 15 min. at 4°C. Membranes were resuspended with the above membrane preparation buffer (1000 μ l per T-175 flask), homogenized, aliquoted, quickly frozen in liquid nitrogen and stored at -80°C. The specific binding of 125 I-Bolton Hunter-CCK-8S to CCK1R or CCK2R was measured by filtration binding assay in 96 well plate format. 0.5 μ g membrane/well in binding buffer (50 mM Tris pH 7.4, 5 mM MgCl₂, 200 μ g/mL Bacitracin and protease inhibitor cocktail) was mixed with agonists in 1% DMSO (final concentration) and 0.1 nM 125 I-Bolton Hunter-CCK-8S was added. After incubation for 1-2 hrs at room temperature, membrane-bound 125 I-Bolton Hunter-CCK8S was separated from the free 125 I-Bolton Hunter-CCK8S by filtering through GF/C filters presoaked in 0.2% BSA solution. The filters were washed with ice-cold washing buffer (50 mM Tris pH 7.4, 10 mM MgCl₂, 2 mM EDTA and 0.04% Tween 20). The radioactivity was determined by adding 30 μ l of microscintillant/well after each plate was dried at room temperature overnight or placed at 55°C for 30 mins. A Packard Top Count was then used to read each filter plate. The data in cpms was plotted vs. the log molar concentration of receptor ligand (compound). The IC₅₀ was reported as the inflection point of the resulting sigmoidal curve. The maximum inhibition observed at the highest compound concentration was reported for compounds which do not generate a curve.

B. Cell Culture of Cholecystokinin-1 Receptor (CCK1R) and Cholecystokinin-2 Receptor (CCK2R) Cell Lines Stable CHO cell lines expressing the human CCK1R and CCK2R cDNA and stable HEK293 cell lines expressing the human CCK2R cDNA were generated using standard cell biology techniques. One CCK1R clone identified as CHO_WT23 was used for both FLIPR and IP3 functional and binding assays. One CCK2R clone called CHO_B101 was used for FLIPR functional assays and another CCK2R clone, CHO_hCCK2R, was used for IP3 functional assays. Both WT23 and B101 cells were routinely cultured in T175 flasks in Iscoves Modified Dulbecco's Medium (Invitrogen #12440-046) supplemented with 10% FBS (cat# SH30070.03, Hyclone, Logan, Utah), 1X HT Supplement (0.1mM Sodium Hypoxanthine and 16 μ M Thymidine), 100 units/mL Pennicillin-G and 100 μ g/mL Streptomycin, 2mM L-Glutamine and 1mg/mL Geneticin. hCCK2R/CHO/Flip-in cells were routinely cultured in T175 flasks in F-12 Nutrient Mixture (Ham) supplemented with 10% FBS (cat# SH30070.03, Hyclone, Logan, Utah), 100 units/mL Pennicillin-G and 100 μ g/mL Streptomycin, 2mM L-Glutamine and 150 μ g/mL Hygromycin. One Hek293 hCCK2R clone identified as Hek293_hCCK2R#37 was used for binding assays. Hek293_hCCK2R#37 cells were routinely cultured in T175 flasks in Dulbecco's Modified Eagle Medium, with high glucose (Invitrogen Cat # 11965-084) supplemented with 10% FBS (cat# SH30070.03, Hyclone, Logan, Utah), 25 mM of HEPES Buffer Solution (Invitrogen cat#15630-080), 500 μ g/mL Geneticin (Invitrogen cat# 10131-027) and 200 μ g/mL Hygromycin. Cells were grown as attached monolayers in tissue culture flasks

under appropriate media in an incubator at 37 °C with 5% CO₂. Cells were passed 1:5 for CHO_WT23, B101 and CHO_hCCK2R cells and 1:3 for HEK 293_hCCK2R#37 twice a week. Cell culture media, antibiotics, Fetal Bovine Serum were all from Invitrogen Technologies Inc. unless otherwise specified.

5 C. Cholecystokinin-1 Receptor (CCK1R) and Cholecystokinin-2 Receptor (CCK2R) Functional Assays

1) FLIPR (Fluometric Imaging Plate Reader, Molecular Devices, Sunnyvale, CA)

CHO_WT23 and B101 cells cultured as described above were detached with Trypsin-EDTA and 20µl volume of cells were seeded in 384 well plate at 62,500 cells/mL. The cells grew overnight at 37 °C with 5% CO₂ in a humidified atmosphere. On the day of the assay, the cells were loaded with 20µl/well of No-wash assay buffer (HBSS, 0.1% BSA, 20mM HEPES, 2.5mM Probenecid and 1.6mM TR40 Quenching Solution) containing 8µM Fluo-4 AM in the dark at room temperature for 1.5 hrs. Agonists were dissolved in DMSO and diluted into assay buffer. 13.3 µl/well of 4X concentration of agonist solution was added to cells while measuring fluorescence. The EC₅₀ for activation of the CCK1R or CCK2R receptor was reported as the inflection point of the resulting sigmoidal curve.

2) Inositol Phosphate SPA assay (IP3) to measure IP3 accumulation

This functional assay was performed in a 96-well format. On the first day, 75µl of CHO cells at 62,500/mL were plated on poly-D-lysine plates. On the afternoon of the next day, the plates were aspirated, and the cells were washed with PBS w/o Mg⁺⁺, Ca⁺⁺. Next 150µl of ³H-inositol labeling media, Inositol-free DMEM media ICN #1642954 supplemented with 10% FBS, 1X pen/strep/glutamine to which ³H-myo-inositol (NEN #NET114A) was added, 1mCi/mL, 25Ci/mmol diluted 1:150 in loading medium (final specific radioactivity of 1 µCi/150 µl). After 18 hours of labeling, 5 µl 300 mM LiCl was added to the wells, mixed, and incubated for 20 minutes at 37°C, then 1.5µl DMSO of 200X compounds were added to wells and incubated for an additional 90 minutes at 37°C. Plates were aspirated, and then the reaction was terminated and cells were lysed with the addition of 60 µl 10 mM formic acid for 60 minutes at room temperature. 20µl of lysate was transferred to clear-bottom Opti-plates which contained RNA binding YSi SPA-beads (Amersham RPNQ0013) that were suspended in 10% glycerol at 1 mg beads/ 70 µl of solution and dispensed at 70 µl per well. After mixing, the plates sit at room temperature for 2hrs and were then counted using a Wallac Microbeta reader. The EC₅₀ for activation of the CCK1F or CCK2R receptor was calculated from the titration curve of the compounds.

D. In-vivo overnight food intake and body weight in C57 Lean Male Mice

35 Methods: Male C57 mice, approximately 8 weeks old (weighing approximately 25g) were individually housed and acclimated for several days prior to testing. Mice were orally dosed (PO; n=8) with either vehicle controls (10% Tween- water) or CCK1R agonists (various doses).

A known CB1 inverse agonist, AM251 (3mg/kg) was used as the positive control for inter- and intra-experimental control. CCK1R agonists were dosed (PO) approximately 60-120 minutes prior to the onset of the dark cycle. Overnight food intake (g) and body weight (g) (\pm SEM) were collected and analyzed. All data were presented as mean \pm SEM (n=8). Statistical significance was calculated using Student's *t-test* to determine whether compared the groups were statistically distinct. Differences were considered significant when $p < 0.05$.

Compounds useful in the present invention decrease overnight food intake by at least 10% and/or decrease body weight overnight by at least 1% relative to placebo.

E. Mouse Gallbladder Emptying Assay for CCK-1R Binding Specificity

Methods: Male CD-1 mice, approximately 7-8 weeks old (weighing 25g) were housed (8 mice per cage), and fasted for 18 hours with *ad lib* access to water. Mice were orally dosed (PO; n=8) with either vehicle controls (10% Tween- water) or CCK1R agonists (various doses) for 4h. After 4h, mice were deeply anesthetized with CO₂ inhalant; blood samples were drawn via cardiac puncture and stored at -20°C (for future assays). Gall bladders were isolated, removed and weighed. Gallbladder weights were normalized to body weight (g/kg) and compared to vehicle control group. The entire assay typically required approximately 30-40 minutes for tissue collection. All data were presented as mean \pm SEM (n=8) and Statistical significance was calculated using Student's *t-test* to determine whether compared the groups were statistically distinct. Differences were considered significant when $p < 0.05$.

The compounds of the present invention, including the compounds of Examples 1-67, were tested and found to bind to the cholecystinin-1 receptor, and were found to have IC₅₀ values \leq 1000 nM. The compounds of the present invention, including the compounds of Examples 1-67, were also tested in the functional assay and found to activate the cholecystinin-1 receptor with EC₅₀ values \leq 1000 nM.

EXAMPLES OF PHARMACEUTICAL COMPOSITIONS

As a specific embodiment of an oral composition of a composition of the present invention, 5 mg of Example 1 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gelatin capsule.

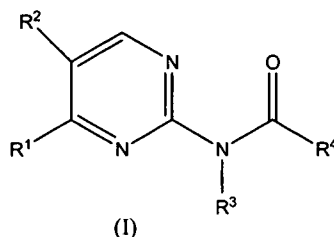
As another specific embodiment of an oral composition of a compound of the present invention, 2.5 mg of Example 1 is formulated with sufficient finely divided lactose to provide a total amount of 580 to 590 mg to fill a size O hard gelatin capsule.

While the invention has been described and illustrated in reference to certain preferred embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the preferred doses as set forth hereinabove

may be applicable as a consequence of variations in the responsiveness of the subject or mammal being treated obesity, diabetes and obesity-related disorders, or for other indications for the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compound selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the embodiments of the present invention. It is intended, therefore, that the invention be limited only by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A compound of formula I:



5

or a pharmaceutically acceptable salt thereof; wherein

R^1 is phenyl, unsubstituted or substituted with 1-5 substituents selected from R^5 ;

10 R^2 is selected from the group consisting of:

- (1) $-(CH_2)_mC_3$ -gcycloalkyl,
- (2) $-(CH_2)_mC_3$ -gheterocycloalkyl,
- (3) $-(CH_2)_q$ aryl, and
- (4) $-(CH_2)_q$ heteroaryl,

15 wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with one to five substituents selected from halogen, OH, $-C_{1-6}$ alkyl, and $-C_{1-6}$ alkoxy;

R^3 is selected from the group consisting of:

- (1) hydrogen, and
- (2) $-C_{1-6}$ alkyl,

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wherein alkyl is unsubstituted or substituted with one to five substituents selected from halogen and -OH;

R^4 is a mono- or bi-cyclic ring selected from the group consisting of:

- (1) $-C_3$ -gcycloalkyl,
- (2) $-C_3$ -gheterocycloalkyl,
- (3) aryl, and
- (4) heteroaryl,

25

wherein cycloalkyl, heterocycloalkyl, aryl and heteroaryl are unsubstituted or substituted with
30 one to five substituents selected from R^6 ;

each R^5 is independently selected from the group consisting of:

- (1) $-(CH_2)_n$ halogen,

- (2) $-(\text{CH}_2)_n\text{OR}^7$,
- (3) $-(\text{CH}_2)_n\text{NR}^3\text{R}^3$,
- (4) $-(\text{CH}_2)_n\text{SC}_{1-6}\text{alkyl}$, and
- (5) $-\text{C}_{1-6}\text{alkyl}$,

5 wherein alkyl and $-(\text{CH}_2)_n$ are unsubstituted or substituted with one to five substituents selected from halogen, OH, $-\text{C}_{1-6}\text{alkyl}$, and $-\text{C}_{1-6}\text{alkoxy}$;

each R^6 is independently selected from the group consisting of:

- (1) $-(\text{CH}_2)_n\text{halogen}$,
- 10 (2) $-(\text{CH}_2)_n\text{CN}$,
- (3) $-\text{C}_{1-6}\text{alkyl}$,
- (4) $-\text{C}_{2-6}\text{alkenyl}$,
- (5) $-(\text{CH}_2)_n\text{C}_{2-8}\text{heterocycloalkyl}$,
- (6) $-(\text{CH}_2)_n\text{C}_{3-8}\text{cycloalkyl}$,
- 15 (7) $-(\text{CH}_2)_n\text{aryl}$,
- (8) $-(\text{CH}_2)_n\text{heteroaryl}$,
- (9) $-(\text{CH}_2)_n\text{OR}^7$,
- (10) $-(\text{CH}_2)_n\text{COR}^7$,
- (11) $-(\text{CH}_2)_n\text{CO}_2\text{R}^7$,
- 20 (12) $-(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^7\text{R}^7$,
- (13) $-(\text{CH}_2)_n\text{CONR}^7\text{COR}^7$,
- (14) $-(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^7(\text{CH}_2)_n\text{CO}_2\text{R}^7$,
- (15) $-(\text{CH}_2)_n\text{C}(\text{O})\text{NR}^7\text{CH}(\text{CO}_2\text{R}^7)_2$,
- (16) $-(\text{CH}_2)_n\text{NR}^7\text{R}^7$,
- 25 (17) $-(\text{CH}_2)_n\text{NR}^7\text{C}(\text{O})\text{NR}^7\text{R}^7$,
- (18) $-(\text{CH}_2)_n\text{NR}^7\text{C}(\text{O})\text{R}^7$,
- (19) $-(\text{CH}_2)_n\text{OC}(\text{O})\text{NR}^7\text{R}^7$,
- (20) $-(\text{CH}_2)_n\text{NR}^7\text{CO}_2\text{R}^7$,
- (21) $-(\text{CH}_2)_n\text{NR}^7\text{SO}_2\text{R}^7$,
- 30 (22) $-(\text{CH}_2)_n\text{SO}_2\text{NR}^7\text{R}^7$,
- (23) $-(\text{CH}_2)_n\text{SO}_2\text{R}^7$,
- (24) $-(\text{CH}_2)_n\text{SO}_3\text{H}$, and
- (25) $-(\text{CH}_2)_n\text{PO}_{2-3}\text{R}^7$,

35 wherein alkyl, alkenyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and $(\text{CH}_2)_n$ are unsubstituted or substituted with one to five substituents selected from R^8 ;

each R^7 is independently selected from the group consisting of:

- (1) hydrogen,
- (2) $-(\text{CH}_2)_n\text{OH}$,
- (3) $-\text{C}_{1-6}\text{alkyl}$,
- (4) $-(\text{CH}_2)_n\text{C}_{2-8}\text{heterocycloalkyl}$,
- 5 (5) $-(\text{CH}_2)_n\text{C}_{3-8}\text{cycloalkyl}$,
- (6) $-(\text{CH}_2)_n\text{aryl}$, and
- (7) $-(\text{CH}_2)_n\text{heteroaryl}$,

wherein alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, and $(\text{CH}_2)_n$ are unsubstituted or substituted with one to five substituents selected from R^8 ;

10

each R^8 is independently selected from the group consisting of:

- (1) oxo,
- (2) $-(\text{CH}_2)_n\text{halogen}$,
- (3) $-\text{C}_{1-6}\text{alkyl}$,
- 15 (4) $-\text{C}_{1-6}\text{alkoxy}$,
- (5) $-(\text{CH}_2)_{0-1}\text{OH}$,
- (6) $-(\text{CH}_2)_n\text{CN}$,
- (7) $-(\text{CH}_2)_n\text{CF}_3$,
- (8) $-(\text{CH}_2)_n\text{SO}_3\text{H}$,
- 20 (9) $-(\text{CH}_2)_n\text{CO}_2\text{H}$,
- (10) $-(\text{CH}_2)_n\text{CO}_2\text{C}_{1-6}\text{alkyl}$, and
- (11) $-(\text{CH}_2)_n\text{CO}_2\text{C}_{2-6}\text{alkene}$;

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each n is independently 0, 1, 2, 3, 4, 5, 6, 7 or 8;

each m is independently 0, 1, 2, 3, or 4;

30

each p is independently 0, 1, 2, 3, 4 or 5; and

each q is independently 1, 2, 3, or 4.

2. The compound of Claim 1 wherein R^1 is phenyl substituted with 1-5 substituents selected from R^5 ; or a pharmaceutically acceptable salt thereof.

35

3. The compound of Claim 1 wherein R^2 is selected from the group consisting of: $-(\text{CH}_2)_m\text{cycloalkyl}$, and $-(\text{CH}_2)_q\text{aryl}$, wherein cycloalkyl, aryl, and (CH_2) are unsubstituted or substituted with one to five substituents selected from halogen, OH, $-\text{C}_{1-6}\text{alkyl}$, and $-\text{C}_{1-6}\text{alkoxy}$; or a pharmaceutically acceptable salt thereof.

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4. The compound of Claim 1 wherein R^2 is selected from the group consisting of: $-(\text{CH}_2)_{0-2}\text{cyclohexyl}$, $-(\text{CH}_2)_{0-2}\text{cyclopentyl}$, $-(\text{CH}_2)_{0-2}\text{cycloheptyl}$, and $-(\text{CH}_2)_{1-2}\text{phenyl}$, wherein R^2

is unsubstituted or substituted with one to five substituents selected from halogen, OH, -C₁₋₆alkyl, and -C₁₋₆alkoxy; or a pharmaceutically acceptable salt thereof.

5 5. The compound of Claim 1 wherein R³ is hydrogen; or a pharmaceutically acceptable salt thereof.

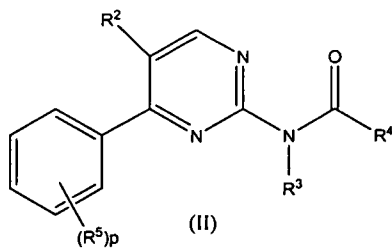
10 6. The compound of Claim 1 wherein R⁴ is a mono- or bicyclic ring selected from the group consisting of: aryl, and heteroaryl, wherein aryl and heteroaryl are unsubstituted or substituted with one to five substituents selected from R⁶; or a pharmaceutically acceptable salt thereof.

15 7. The compound of Claim 1 wherein R⁴ is selected from the group consisting of: phenyl, naphthalene, 1,2,3,4-tetrahydroquinoline, quinoline, 7-azaquinoline, indole, 1*H*-pyrrolo[2,3-*b*]pyridine, and pyridine, wherein R⁴ is unsubstituted or substituted with one to five substituents selected from R⁶; or a pharmaceutically acceptable salt thereof.

20 8. The compound of Claim 1 wherein R⁵ is independently selected from the group consisting of: -(CH₂)_nhalogen, -(CH₂)_nOR⁷, and -C₁₋₆alkyl, wherein alkyl and -(CH₂)_n are unsubstituted or substituted with one to five substituents selected from halogen, OH, -C₁₋₆alkyl, and -C₁₋₆alkoxy; or a pharmaceutically acceptable salt thereof.

25 9. The compound of Claim 1 wherein R⁶ is independently selected from the group consisting of: -(CH₂)_nhalogen, -C₁₋₆alkyl, -(CH₂)_nphenyl, -(CH₂)_nCO₂R⁷, and -(CH₂)_nC(O)NR⁷(CH₂)_nCO₂R⁷, wherein alkyl, phenyl, and (CH₂)_n are unsubstituted or substituted with one to five substituents selected from R⁸; or a pharmaceutically acceptable salt thereof.

10. The compound of Claim 1 of formula II:



30 or a pharmaceutically acceptable salt thereof; wherein

R² is selected from the group consisting of:

(1) -(CH₂)₁₋₂cyclohexyl, and

(2) $-(CH_2)_{1-2}$ cyclopentyl,

wherein R^2 is unsubstituted or substituted with one to five substituents selected from halogen, OH, $-C_{1-6}$ alkyl, and $-C_{1-6}$ alkoxy;

5 R^3 is hydrogen;

R^4 is selected from the group consisting of: quinoline, indole, and naphthalene, wherein R^4 is unsubstituted or substituted with one to five substituents selected from R^6 ;

10 R^5 is independently selected from the group consisting of: Cl, Br, F, I, $-OCH_3$ and $-CH_3$, wherein $-OCH_3$ and $-CH_3$ are unsubstituted or substituted with one to five substituents selected from halogen, OH, $-C_{1-6}$ alkyl, and $-C_{1-6}$ alkoxy; and

R^6 is independently selected from the group consisting of: $-(CH_2)_n$ halogen, $-C_{1-6}$ alkyl, $-(CH_2)_n$ phenyl, $-(CH_2)_nCO_2R^7$, and $-(CH_2)_nC(O)NR^7(CH_2)_nCO_2R^7$, wherein alkyl, phenyl, and $-(CH_2)_n$ are unsubstituted or substituted with one to five substituents selected from R^8 .

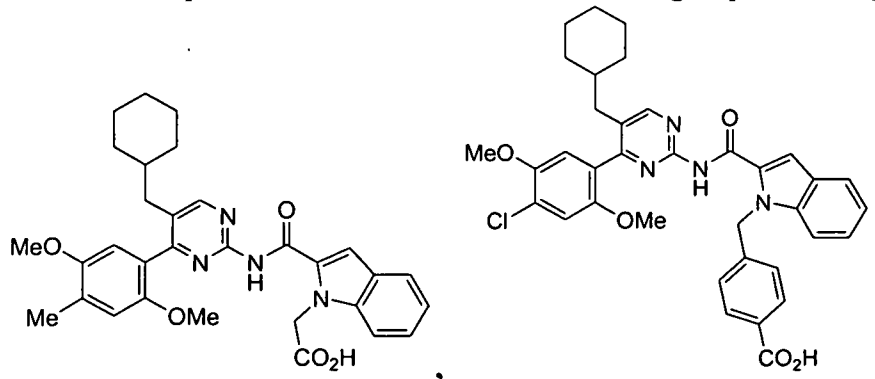
11. The compound of Claim 10 wherein R^6 is $-(CH_2)_{0-5}CO_2H$, or a substituent containing $-(CH_2)_{0-5}CO_2H$, or pharmaceutically acceptable salt thereof.

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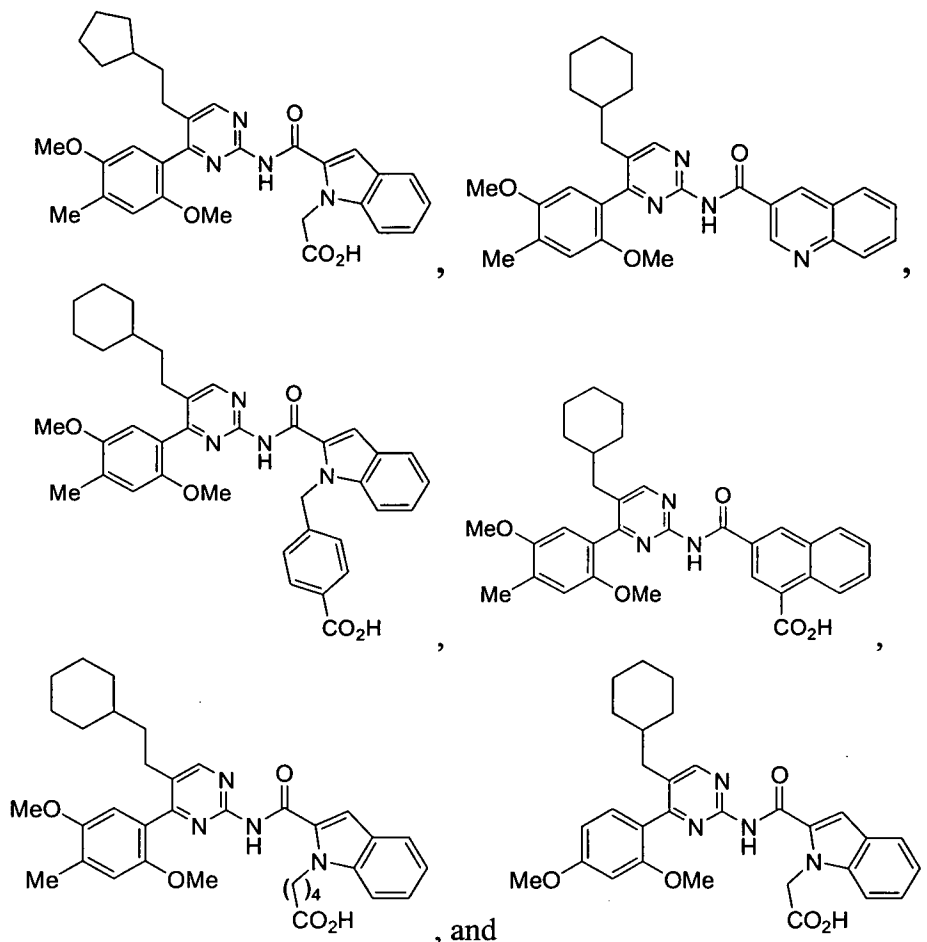
12. The compound of Claim 10 wherein R^4 is selected from the group consisting of: quinoline and indole, wherein R^4 is unsubstituted or substituted with one to five substituents selected from R^6 , or pharmaceutically acceptable salt thereof.

25 13. The compound of Claim 10 wherein R^4 is indole, wherein indole is unsubstituted or substituted with one to five substituents selected from R^6 , or pharmaceutically acceptable salt thereof.

14. The compound of Claim 10 selected from the group consisting of:



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or a pharmaceutically acceptable salt thereof.

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15. The compound of Claim 13 wherein the pharmaceutically acceptable salt thereof is a mono- or di-trifluoroacetic acid salt.

16. A composition which comprises a compound of Claim 1, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

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17. A compound according to Claim 1, or a pharmaceutically acceptable salt thereof, for use in medicine.

18. The use of a compound according to Claim 1, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament useful for the treatment or prevention of a disease mediated by the cholecystinin-1 receptor in a subject in need thereof.

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19. The use according to Claim 18 wherein the disease mediated by the cholecystinin-1 receptor is selected from the group consisting of obesity, diabetes mellitus, or an obesity-related disorder.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 08/00866

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/505

USPC - 514/275

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)

USPC: 514/275

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/49, 252.14, 252.18, 256, 269, 274 (see search terms below) and 514/\$ (unrestricted Key Word Searches)

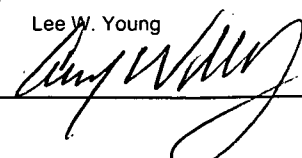
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPTO PubWEST, Google, WIPO, Wikipedia, PAIR Search Terms Used: phenyl, cyclohexyl, pyrimidine, indole, etc.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,958,934 A (Berger et al.) 28 September 1999 (28.09.1999) col 1, ln 50 to col 6, ln 25	1-19
Y	US 5,869,519 A (Karanewsky et al.) 09 February 1999 (09.02.1999) col 2, ln 30 to col 4, ln 40	1-19
Y	US 4,933,324 A (Shashoua) 12 June 1990 (12.06.1990) abstract	1-19
A	US 4,731,363 A (Hamilton et al.) 15 March 1988 (15.03.1988)	1-19

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:	"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
"A" document defining the general state of the art which is not considered to be of particular relevance	"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
"E" earlier application or patent but published on or after the international filing date	"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
"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)	"&" document member of the same patent family
"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	

Date of the actual completion of the international search 10 April 2008 (10.04.2008)	Date of mailing of the international search report 09 MAY 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young  PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774