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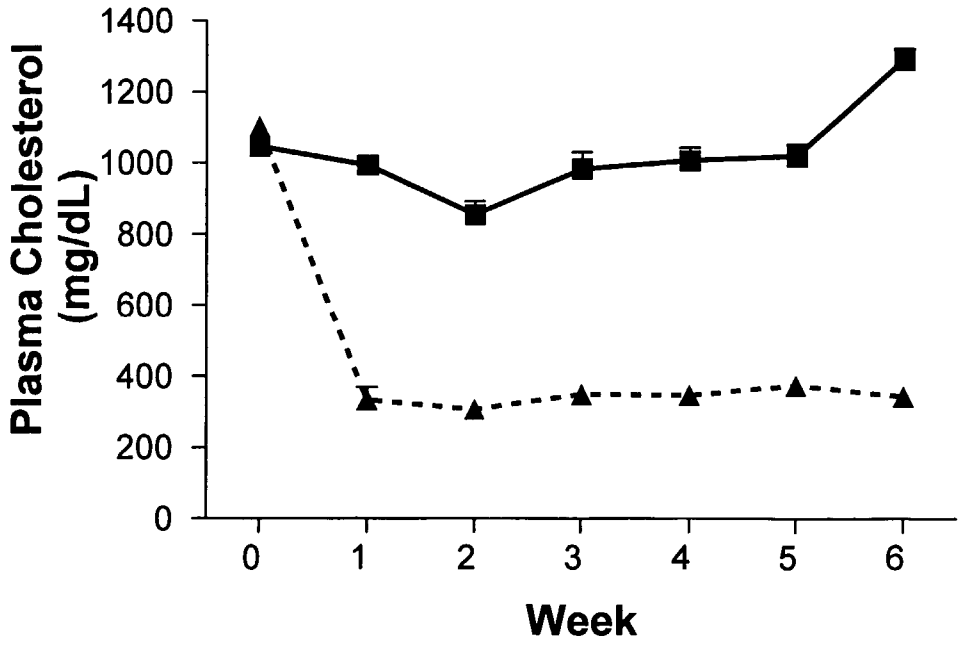
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(54) Title: AZEPINOINDOLE DERIVATIVES AS PHARMACEUTICAL AGENTS



(57) Abstract: Compounds, compositions and methods for modulating the activity of receptors are provided. In particular, compounds and compositions are provided for modulating the activity of receptors and for the treatment, prevention, or amelioration of one or more symptoms of disease or disorder directly or indirectly related to the activity of the receptors.

WO 2005/056554 A2

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AZEPINOINDOLE DERIVATIVES AS PHARMACEUTICAL AGENTS

FIELD OF THE INVENTION

Compounds, compositions and methods are provided for modulating the activity of receptors and for the treatment, prevention, or amelioration of one or more symptoms of disease or disorder related to the activity of the receptors.

BACKGROUND OF THE INVENTION

Nuclear Receptors

Nuclear receptors are a superfamily of regulatory proteins that are structurally and functionally related and are receptors for, *e.g.*, steroids, retinoids, vitamin D and thyroid hormones (see, *e.g.*, Evans (1988) *Science 240*:889-895). These proteins bind to cis-acting elements in the promoters of their target genes and modulate gene expression in response to ligands for the receptors.

Nuclear receptors can be classified based on their DNA binding properties (see, *e.g.*, Evans, *supra* and Glass (1994) *Endocr. Rev. 15*:391-407). For example, one class of nuclear receptors includes the glucocorticoid, estrogen, androgen, progestin and mineralocorticoid receptors which bind as homodimers to hormone response elements (HREs) organized as inverted repeats (see, *e.g.*, Glass, *supra*). A second class of receptors, including those activated by retinoic acid, thyroid hormone, vitamin D_3, fatty acids/peroxisome proliferators (*i.e.*, peroxisome proliferator activated receptor (PPAR)) and ecdysone, bind to HREs as heterodimers with a common partner, the retinoid X receptors (*i.e.*, RXRs, also known as the 9-cis retinoic acid receptors; see, *e.g.*, Levin *et al.* (1992) *Nature 355*:359-361 and Heyman *et al.* (1992) *Cell 68*:397-406).

RXRs are unique among the nuclear receptors in that they bind DNA as a homodimer and are required as a heterodimeric partner for a number of additional nuclear receptors to bind DNA (see, *e.g.*, Mangelsdorf *et al.* (1995) *Cell 83*:841-850). The latter receptors, termed the class II nuclear receptor subfamily, include many which are established or implicated as important regulators of gene expression. There are three RXR genes (see, *e.g.*, Mangelsdorf *et al.* (1992) *Genes Dev. 6*:329-344), coding for RXRα, -ß, and -γ, all of which are able to heterodimerize with any of the class II receptors, although there appear to be preferences for distinct RXR subtypes by partner receptors *in vivo* (see, *e.g.*, Chiba *et al.* (1997) *Mol. Cell. Biol. 17*:3013-

3020). In the adult liver, RXRα is the most abundant of the three RXRs (see, *e.g.*, Mangelsdorf *et al.* (1992) *Genes Dev. 6*:329-344), suggesting that it might have a prominent role in hepatic functions that involve regulation by class II nuclear receptors. See also, Wan *et al.* (2000) *Mol. Cell. Biol 20*:4436-4444.

Orphan Nuclear Receptors

Included in the nuclear receptor superfamily of regulatory proteins are nuclear receptors for whom the ligand is known and those which lack known ligands. Nuclear receptors falling in the latter category are referred to as orphan nuclear receptors. The search for activators for orphan receptors has led to the discovery of previously unknown signaling pathways (see, *e.g.*, Levin *et al.*, (1992), *supra* and Heyman *et al.*, (1992), *supra*). For example, it has been reported that bile acids, which are involved in physiological processes such as cholesterol catabolism, are ligands for the farnesoid X receptor (*infra*).

Since it is known that products of intermediary metabolism act as transcriptional regulators in bacteria and yeast, such molecules may serve similar functions in higher organisms (see, *e.g.*, Tomkins (1975) *Science 189*:760-763 and O'Malley (1989) *Endocrinology 125*:1119-1120). For example, one biosynthetic pathway in higher eukaryotes is the mevalonate pathway, which leads to the synthesis of cholesterol, bile acids, porphyrin, dolichol, ubiquinone, carotenoids, retinoids, vitamin D, steroid hormones and farnesylated proteins.

Farnesoid X Receptor

The farnesoid X receptor (originally isolated as RIP14 (retinoid X receptor-interacting protein-14), see, *e.g.*, Seol *et al.* (1995) *Mol. Endocrinol. 9*:72-85) is a member of the nuclear hormone receptor superfamily and is primarily expressed in the liver, kidney and intestine (see, *e.g.*, Seol *et al., supra* and Forman *et al.* (1995) *Cell 81*:687-693). It functions as a heterodimer with the retinoid X receptor (RXR) and binds to response elements in the promoters of target genes to regulate gene transcription. The farnesoid X receptor-RXR heterodimer binds with highest affinity to an inverted repeat-1 (IR-1) response element, in which consensus receptor-binding hexamers are separated by one nucleotide. The farnesoid X receptor is part of an interrelated process, in that the receptor is activated by bile acids (the end product of cholesterol metabolism) (see, *e.g.*, Makishima *et al.* (1999) *Science 284*:1362-1365, Parks *et al.* (1999) *Science 284*:1365-1368, Wang *et al.* (1999) *Mol. Cell. 3*:543-553),

which serve to inhibit cholesterol catabolism. See also, Urizar *et al.* (2000) *J. Biol. Chem. 275*:39313-39317.

Nuclear Receptors and Disease

Nuclear receptor activity, including the farnesoid X receptor and/or orphan nuclear receptor activity, has been implicated in a variety of diseases and disorders, including, but not limited to, hyperlipidemia and hypercholesterolemia, and complications thereof, including without limitation coronary artery disease, angina pectoris, carotid artery disease, strokes, cerebral arteriosclerosis and xanthoma, (see, *e.g.*, International Patent Application Publication No. WO 00/57915), osteoporosis and vitamin deficiency (see, *e.g.*, U.S. Patent No. 6,316,5103), hyperlipoproteinemia (see, *e.g.*, International Patent Application Publication No. WO 01/60818), hypertriglyceridemia, lipodystrophy, peripheral occlusive disease, ischemic stroke, hyperglycemia and diabetes mellitus (see, *e.g.*, International Patent Application Publication No. WO 01/82917), disorders related to insulin resistance including the cluster of disease states, conditions or disorders that make up "Syndrome X" such as glucose intolerance, an increase in plasma triglyceride and a decrease in high-density lipoprotein cholesterol concentrations, hypertension, hyperuricemia, smaller denser low-density lipoprotein particles, and higher circulating levels of plasminogen activator inhibitor-1, atherosclerosis and gallstones (see, *e.g.*, International Patent Application Publication No. WO 00/37077), disorders of the skin and mucous membranes (see, *e.g.*, U.S. Patent Nos. 6,184,215 and 6,187,814, and International Patent Application Publication No. WO 98/32444), obesity, acne (see, *e.g.*, International Patent Application Publication No. WO 00/49992), and cancer, cholestasis, Parkinson's disease and Alzheimer's disease (see, *e.g.*, International Patent Application Publication No. WO 00/17334).

The activity of nuclear receptors, including the farnesoid X receptor and/or orphan nuclear receptors, has been implicated in physiological processes including, but not limited to, triglyceride metabolism, catabolism, transport or absorption, bile acid metabolism, catabolism, transport, absorption, re-absorption or bile pool composition, cholesterol metabolism, catabolism, transport, absorption, or re-absorption. The modulation of cholesterol 7α-hydroxylase gene (CYP7A1) transcription (see, *e.g.*, Chiang *et al.* (2000) *J. Biol. Chem. 275*:10918-10924), HDL metabolism (see, *e.g.*, Urizar *et al.* (2000) *J. Biol. Chem. 275*:39313-39317), hyperlipidemia, cholestasis, and increased cholesterol efflux and increased expression

of ATP binding cassette transporter protein (ABC1) (see, *e.g.*, International Patent Application Publication No. WO 00/78972) are also modulated or otherwise affected by the farnesoid X receptor.

Thus, there is a need for compounds, compositions and methods of modulating the activity of nuclear receptors, including the farnesoid X receptor and/or orphan nuclear receptors. Such compounds are useful in the treatment, prevention, or amelioration of one or more symptoms of diseases or disorders in which nuclear receptor activity is implicated.

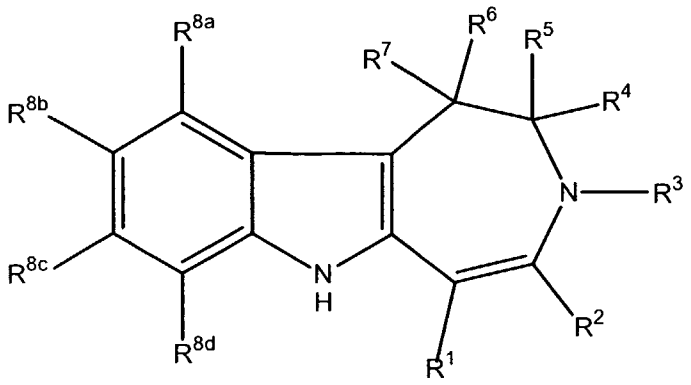
Commonly owned US Patent Application No. 60/383,574, entitled "Azepinoindole and pyridoindole modulators of nuclear receptors," filed May 24, 2002, to Martin et al., and US Patent Application No.10/447,302, filed May 27, 2003, to Martin et al., entitled "Azepinoindole and pyridoindole modulators of nuclear receptors," which are hereby incorporated by reference in their entirety, disclose novel compounds that bind to the farnesoid X receptor.

The present inventors have identified a novel class of such compounds that exhibit extremely high affinity for the farnesoid X receptor, and high potency in vivo. Unexpectedly such compounds show the ability to reduce both plasma trigylceride and cholesterol levels in normal and hyperlipidemic animal models.

SUMMARY OF THE INVENTION

Compounds for use in pharmaceutical compositions and methods for modulating the activity of nuclear receptors are provided. In particular, compounds for use in compositions and methods for modulating the farnesoid X receptor, and/or orphan nuclear receptors, are provided. In one embodiment, the compounds provided herein are agonists of the farnesoid X receptor. In another embodiment, the compounds provided herein are antagonists of the farnesoid X receptor. In another embodiment, the compounds provided herein are inverse agonists, partial agonists or partial antagonists of the farnesoid X receptor. Agonists that exhibit low efficacy are, in certain embodiments, antagonists.

In one embodiment, the compounds for use in the compositions and methods provided herein have formula (I):



(I)

or a pharmaceutically acceptable derivative thereof; wherein:

R^1 is $-C(J)OR^{14}$, $-C(J)SR^{14}$ and $-C(J)N(R^{15})R^{16}$;

J is O, S or NR^{17};

R^2 is hydrogen, halo or optionally substituted alkyl;

R^3 is $-C(O)R^9$;

R^4, R^5, R^6 and R^7 are together selected from a), b), c), d), e) or f) below:

a) R^4 and R^5 are each independently selected from hydrogen or halo; and R^6 and R^7 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$, and $-R^{21}-SC(J)R^{10}$; or R^6 and R^7, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene;

b) R^4 and R^5 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; or R^4 and R^5, together with the carbon atom to which they are attached, form an optionally

substituted cycloalkyl, optionally substituted heterocyclyl, an optionally substituted cycloalkenyl ring, an optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene; and R^6 and R^7 are each independently selected from hydrogen or halo; or

c) R^4 and R^6 are each independently selected from hydrogen or halo; and R^5 and R^7 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$;

d) R^4 is hydrogen or halo; R^5 is selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; and R^6 and R^7 are each independently selected from a group consisting of hydrogen, halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; or R^6 and R^7, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene;

e) R^4 and R^5 are each independently selected from a group consisting of hydrogen, halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl,

optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; or R^4 and R^5, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene; R^6 is hydrogen or halo; and R^7 is selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$;

f) R^4 and R^5 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; or R^4 and R^5, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, an optionally substituted cycloalkenyl ring, an optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene; and R^6 and R^7 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$, and $-R^{21}-SC(J)R^{10}$; or R^6 and R^7, together with the carbon

atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene;

R^{8a}, R^{8b}, R^{8c} and R^{8d} are each independently selected from the group consisting of hydrogen, halo, pseudohalo, cyano, azido, amidino, guanidino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-R^{21}-OR^{22}$, $-R^{21}-SR^{22}$, $-R^{21}-N(R^{23})(R^{24})$, $-R^{21}-C(J)R^{22}$, $-R^{21}-C(J)OR^{22}$, $-R^{21}-C(J)SR^{22}$, $-R^{21}-C(J)N(R^{23})(R^{24})$, $-R^{21}-N(R^{25})S(O)_2R^{26}$ and $-R^{21}-S(O)_2N(R^{23})(R^{24})$;

R^9 is selected from the group consisting of optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heteroaryl and optionally substituted heterocyclyl;

each R^{10} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-OR^{11}$, $-SR^{11}$ and $-N(R^{12})(R^{13})$;

R^{11}, R^{12} and R^{13} are each independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, and optionally substituted heteroaralkyl; or R^{12} and R^{13}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

each R^{14} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted

aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-OR^{18}$, $-SR^{18}$ and $-N(R^{19})(R^{20})$;

R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-OR^{18}$, $-SR^{18}$ and $-N(R^{19})(R^{20})$;

or R^{15} and R^{16}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl ring or an optionally substituted heteroaryl ring;

R^{17} is hydrogen, optionally substituted alkyl, optionally substituted substituted alkenyl or optionally substituted alkynyl;

each R^{18} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, and optionally substituted heteroaralkyl;

each R^{19} and R^{20} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, and optionally substituted heteroaralkyl; or

R^{19} and R^{20}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

each R^{21} is independently a direct bond or an alkylene;

each R^{22} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally

substituted heteroaryl, optionally substituted heteroaralkyl, -R^{21}-OR^{32}, -R^{21}-SR^{32}, -R^{21}-$N(R^{33})(R^{34})$, -R^{21}-$C(J)R^{32}$, -R^{21}-$C(J)OR^{32}$, -R^{21}-$C(J)SR^{32}$, and -R^{21}-$C(J)N(R^{33})(R^{34})$;

R^{23} and R^{24} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, -R^{21}-OR^{32}, -R^{21}-SR^{32}, -R^{21}-$N(R^{33})(R^{34})$, -R^{21}-$C(J)R^{32}$, -R^{21}-$C(J)OR^{32}$, -R^{21}-$C(J)SR^{32}$ and -R^{21}-$C(J)N(R^{33})(R^{34})$;

or R^{23} and R^{24}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

each R^{25} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

each R^{26} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; and

each R^{32} is each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; and

R^{33} and R^{34} are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted

cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; or

R^{33} and R^{34}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl.

Such compounds can bind to the farnesoid X receptor with high affinity and modulate it's activity. Typically such compounds exhibit an EC50 or IC 50 of less than 0.5 μM, and in certain embodiments, less than about 250 nM, 100 nM or 50 nM.

Also of interest are any pharmaceutically-acceptable derivatives, including salts, esters, enol ethers, enol esters, solvates, hydrates and prodrugs of the compounds described herein. Pharmaceutically-acceptable salts, include, but are not limited to, amine salts, such as but not limited to *N,N'*-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, *N*-methylglucamine, procaine, *N*-benzylphenethylamine, 1-*para*-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc, aluminum, and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochloride and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates.

Pharmaceutical compositions formulated for administration by an appropriate route and means containing effective concentrations of one or more of the compounds provided herein, or pharmaceutically acceptable derivatives thereof, that deliver amounts effective for the treatment, prevention, or amelioration of one or more symptoms of diseases or disorders that are modulated or otherwise affected by nuclear receptor activity, including the farnesoid X receptor and/or orphan nuclear receptor activity, or in which nuclear receptor activity, including the farnesoid X receptor and/or orphan nuclear receptor activity, is implicated, are also provided. The effective amounts and concentrations are effective for ameliorating any of the symptoms of any of the diseases or disorders.

Methods for treatment, prevention, or amelioration of one or more symptoms of diseases or disorders mediated by or in which nuclear receptor activity,

including the farnesoid X receptor and/or orphan nuclear receptor activity, is implicated, are provided. Such methods include methods of treatment, prevention and amelioration of one or more symptoms of hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, or cardiovascular disorders, using one or more of the compounds provided herein, or pharmaceutically acceptable derivatives thereof.

Methods of modulating the activity of nuclear receptors, including the farnesoid X receptor and/or orphan nuclear receptors, using the compounds and compositions provided herein are also provided. The compounds and compositions provided herein are active in assays that measure the activity of nuclear receptors, including the farnesoid X receptor and/or orphan nuclear receptors, including the assays provided herein. These methods include inhibiting and up-regulating the activity of nuclear receptors, including the farnesoid X receptor and/or orphan nuclear receptors.

Methods of reducing cholesterol levels in a subject in need thereof by administration of one or more compounds or compositions provided herein are also provided.

Methods of modulating cholesterol metabolism using the compounds and compositions provided herein are provided.

Methods of treating, preventing, or ameliorating one or more symptoms of diseases or disorders which are affected by cholesterol, triglyceride, or bile acid levels by administration of one or more of the compounds and compositions provided herein are also provided.

Methods of reducing plasma cholesterol levels and of directly or indirectly modulating cholesterol metabolism, catabolism, synthesis, absorption, re-absorption, secretion or excretion are provided through administering the claimed compounds and compositions provided herein.

Methods of reducing plasma triglyceride levels and of directly or indirectly modulating triglyceride metabolism, catabolism, synthesis, absorption, re-

absorption, secretion or excretion are provided through administering the claimed compounds and compositions provided herein.

Methods of reducing bile acid levels and of directly or indirectly modulating bile acid metabolism, catabolism, synthesis, absorption, re-absorption, secretion, excretion, or bile acid pool composition are provided through administering the claimed compounds and compositions provided herein.

Methods of treatment, prevention, or amelioration of one or more symptoms of a disease or disorder affecting cholesterol, triglyceride, or bile acid levels, or any combination thereof, are provided using the compounds and compositions provided herein.

Methods are provided for the treatment, prevention, or amelioration of one or more symptoms of, as well as treating the complications of, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, dyslipidemia and lipodystrophy.

Methods are also provided for the treatment, prevention, or amelioration of one or more symptoms of atherosclerosis, atherosclerotic disease, atherosclerotic disease events and atherosclerotic cardiovascular diseases.

Additionally, the instant invention also provides a method for preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event comprising the administration of a prophylactically effective amount of a compound or composition of the present invention to a patient at risk for such an event. The patient may already have atherosclerotic disease at the time of administration, or may be at risk for developing it.

In another aspect, the method of this invention also serves to remove cholesterol from tissue deposits such as atherosclerotic plaques or xanthomas in a patient with atherosclerotic disease manifest by clinical signs such as angina, claudication, bruits, one that has suffered a myocardial infarction or transient ischemic attack, or one diagnosed by angiography, sonography or MRI.

Methods of treatment, prevention, or amelioration of one or more of the symptoms of diabetes mellitus, as well as treating the complications of diabetes mellitus, are also provided using the compounds and compositions provided herein.

Methods of treatment, prevention, or amelioration of one or more of the symptoms of insulin insensitivity or resistance as well as treating the complications of insulin insensitivity or resistance are also provided using the compounds and compositions provided herein.

Methods of treatment, prevention, or amelioration of one or more of the symptoms of hyperglycemia as well as treating the complications of hyperglycemia are also provided using the compounds and compositions provided herein.

Methods of treatment, prevention, or amelioration of any disorders related to diabetes, hyperglycemia or insulin resistance including the cluster of disease states, conditions or disorders that make up "Syndrome X" are provided.

Additionally the instant invention also provides a method for preventing or reducing the risk of developing hyperglycemia, insulin resistance or diabetes in a patient, comprising the administration of a prophylactically effective amount of a compound or composition of the present invention to a patient at risk for such an event.

Further provided herein are methods for the treatment, prevention, or amelioration of one or more symptoms of cholestasis, as well as for the treatment of the complications of cholestasis by administering a compound or composition provided herein.

Accordingly, compounds or compositions provided herein may be used for the treatment, prevention, or amelioration of one or more symptoms of intrahepatic or extrahepatic cholestasis, including without limitation, biliary artesia, obstetric cholestasis, neonatal cholestasis, drug induced cholestasis, cholestasis arising from Hepatitis C infection, chronic cholestatic liver disease such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).

Further provided by this invention are methods for treating obesity, as well as treating the complications of obesity, by administering a compound or composition of the present invention.

Also contemplated herein is combination therapy using more or more compounds or compositions provided herein, or a pharmaceutically acceptable derivative thereof, in combination with one or more of the following: antihyperlipidemic agents, plasma HDL-raising agents, antihypercholesterolemic agents, cholesterol biosynthesis inhibitors (such as HMG CoA reductase inhibitors, such as lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rivastatin), acyl-coenzyme A: cholesterol acytransferase (ACAT) inhibitors, probucol, raloxifene, nicotinic acid, niacinamide, cholesterol absorption inhibitors, bile acid sequestrants (such as anion exchange resins, or quaternary amines (*e.g.*, cholestyramine or colestipol)), low density lipoprotein receptor inducers, clofibrate, fenofibrate, benzofibrate, cipofibrate, gemfibrizol, vitamin B_6, vitamin B_{12}, anti-oxidant vitamins, β-blockers, anti-diabetes agents, angiotensin II antagonists, angiotensin converting enzyme inhibitors, platelet

aggregation inhibitors, fibrinogen receptor antagonists, LXR α or β agonists, antagonists or partial agonists, aspirin or fibric acid derivatives. The compound or composition provided herein, or pharmaceutically acceptable derivative thereof, is administered simultaneously with, prior to, or after administration of one or more of the above agents. Pharmaceutical compositions containing a compound provided herein and one or more of the above agents are also provided.

In practicing the methods, effective amounts of the compounds or compositions containing therapeutically effective concentrations of the compounds, which are formulated for systemic delivery, including parenteral, oral, or intravenous delivery, or for local or topical application for the treatment of nuclear receptor, including the farnesoid X receptor and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including the farnesoid X receptor and/or orphan nuclear receptor activity, is implicated, including, but not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerosis, gallstone disease, acne vulgaris, acneiform skin conditions, diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, or cardiovascular disorders, are administered to an individual exhibiting the symptoms of these diseases or disorders. The amounts are effective to ameliorate or eliminate one or more symptoms of the diseases or disorders.

Articles of manufacture containing packaging material, a compound or composition, or pharmaceutically acceptable derivative thereof, provided herein, which is effective for modulating the activity of nuclear receptors, including the farnesoid X receptor and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including the farnesoid X receptor and/or orphan nuclear receptor mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including the farnesoid X receptor and/or orphan nuclear receptor activity, is implicated, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable derivative thereof, is used for modulating the activity of nuclear receptors, including the farnesoid X receptor and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including the farnesoid X

receptor and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including the farnesoid X receptor and/or orphan nuclear receptor activity, is implicated, are provided.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1: Compound Effects in Normolipidemic mice

Figure 1 shows plasma triglyceride levels in male C57BL/6 mice either treated with Compound A (Figure 1A) or Compound B (Figure 1B) daily by oral gavage at doses of 0.1 mg/kg/day (filled triangles), 1.0 mg/kg/day (Upside down filled triangles) or 10 mg/kg/day (Diamonds) for seven days (n=6/group) compared to vehicle alone (filled squares).

FIG. 2: Compound Effects in Diet-Induced Hyperlipidemic $LDLR^{-/-}$ Mice

Figure 2A shows plasma triglyceride levels in in male LDLR-/- mice fed a "Western" diet (~21% fat, 0.02% cholesterol w/w) ad libitum, for two weeks prior to and during treatment with Compound C daily by oral gavage at a dose of 10 mg/kg/day for 7 days (n=9-10/group) (filled triangles) compared to vehicle-treated controls (filled squares). Figure 2B shows plasma cholesterol levels in the same mice treated with Compound C (filled triangles) compared to vehicle-treated controls (filled squares).

FIG. 3: Longer Term Effects of Compound C in Diet-Induced Hyperlipidemic $LDLR^{-/-}$ Mice

Figure 3A shows plasma triglyceride levels in in male $LDLR^{-/-}$ mice fed a "Western" diet (~21% fat, 0.02% cholesterol w/w) *ad libitum*, for eight weeks prior to and during treatment with Compound B by oral gavage at a dose of 10 mg/kg/day for 6 weeks (n=12-16/group) compared to vehicle-treated controls (filled squares). Figure 3B shows plasma cholesterol levels in the same mice treated with Compound B (filled triangles) compared to the vehicle-treated controls (filled squares).

DETAILED DESCRIPTION OF THE INVENTION

A. Definitions

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art to which this invention belongs. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there are a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

As used herein, a nuclear receptor is a member of a superfamily of regulatory proteins that are receptors for, *e.g.*, steroids, retinoids, vitamin D and thyroid hormones. These proteins bind to cis-acting elements in the promoters of their target genes and modulate gene expression in response to a ligand therefor. Nuclear receptors may be classified based on their DNA binding properties. For example, the glucocorticoid, estrogen, androgen, progestin and mineralocorticoid receptors bind as homodimers to hormone response elements (HREs) organized as inverted repeats. Another example are receptors, including those activated by retinoic acid, thyroid hormone, vitamin D_3, fatty acids/peroxisome proliferators and ecdysone, that bind to HREs as heterodimers with a common partner, the retinoid X receptor (RXR). Among the latter receptors is the farnesoid X receptor.

As used herein, an orphan nuclear receptor is a gene product that embodies the structural features of a nuclear receptor that was identified without any prior knowledge of their association with a putative ligand and/or for which the natural ligand is unknown. Under this definition, orphan nuclear receptors include, without limitation, farnesoid X receptors, liver X receptors (LXR α & β), retinoid X receptosr (RXRα, β & γ), and peroxisome proliferator activator receptors (PPAR α, β, & γ) (see, Giguere, *Endocrine Reviews* (1999), Vol. 20, No. 5: pp. 689-725).

As used herein, farnesoid X receptor refers to all mammalian forms of such receptor including, for example, alternative splice isoforms and naturally occurring isoforms (see, e.g. Huber *et al*, *Gene* (2002), Vol. 290, pp.:35-43). Representative farnesoid X receptor species include, without limitation the rat (GenBank Accession No. NM_021745), mouse (Genbank Accession No. NM_009108), and human (GenBank Accession No. NM_005123) forms of the receptor.

As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, enol ethers, enol esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, solvates, hydrates or prodrugs thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to *N,N'*-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, *N*-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethyl-benzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula C=C(OR) where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl or heterocyclyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula C=C(OC(O)R) where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl or heterocyclyl. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.

As used herein, treatment means any manner in which one or more of the symptoms of a disease or disorder are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating a nuclear receptor mediated diseases or disorders, or

diseases or disorders in which nuclear receptor activity, including the farnesoid X receptor or orphan nuclear receptor activity, is implicated.

As used herein, amelioration of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

As used herein, IC_{50} refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response, such as modulation of nuclear receptor, including the farnesoid X receptor, activity, in an assay that measures such response.

As used herein, EC_{50} refers to a dosage, concentration or amount of a particular test compound that elicits a dose-dependent response at 50% of maximal expression of a particular response that is induced, provoked or potentiated by the particular test compound.

As used herein, a prodrug is a compound that, upon *in vivo* administration, is metabolized by one or more steps or processes or otherwise converted to the biologically, pharmaceutically or therapeutically active form of the compound. To produce a prodrug, the pharmaceutically active compound is modified such that the active compound will be regenerated by metabolic processes. The prodrug may be designed to alter the metabolic stability or the transport characteristics of a drug, to mask side effects or toxicity, to improve the flavor of a drug or to alter other characteristics or properties of a drug. By virtue of knowledge of pharmacodynamic processes and drug metabolism *in vivo*, those of skill in this art, once a pharmaceutically active compound is known, can design prodrugs of the compound (see, *e.g.*, Nogrady (1985) *Medicinal Chemistry A Biochemical Approach*, Oxford University Press, New York, pages 388-392).

When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included.

It is to be understood that the compounds provided herein may contain chiral centers. Such chiral centers may be of either the (R) or (S) configuration, or may be a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. In the case of amino acid residues, such residues may be of either the L- or D-form. The configuration for

naturally occurring amino acid residues is generally L. When not specified the residue is the L form. As used herein, the term "amino acid" refers to α-amino acids which are racemic, or of either the D- or L-configuration. The designation "d" preceding an amino acid designation (*e.g.*, dAla, dSer, dVal, etc.) refers to the D-isomer of the amino acid. The designation "dl" preceding an amino acid designation (*e.g.*, dlPip) refers to a mixture of the L- and D-isomers of the amino acid. It is to be understood that the chiral centers of the compounds provided herein may undergo epimerization *in vivo*. As such, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (S) form.

Optically active (+) and (-), (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as reverse phase HPLC.

As used herein, substantially pure means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC) and mass spectrometry (MS), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter the physical and chemical properties, such as enzymatic and biological activities, of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound.

As used herein, “alkyl”, “alkenyl” and “alkynyl” are straight or branched hydrocarbon chains, and if not specified, contain from 1 to 20 carbons or 2 to 20 carbons, preferably from 1 to 16 carbons or 2 to 16 carbons. Alkenyl carbon chains having 2 to 20 carbons, in certain embodiments, contain 1 to 8 double bonds and alkenyl carbon chains having 2 to 16 carbons, in certain embodiments, contain 1 to 5 double bonds. Alkynyl carbon chains having 2 to 20 carbons, in certain embodiments, contain 1 to 8 triple bonds, and the alkynyl carbon chains having 2 to 16 carbons, in certain embodiments, contain 1 to 5 triple bonds. Exemplary alkyl, alkenyl and alkynyl groups herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, sec-butyl, tert-butyl, isopentyl, neopentyl, tert-pentyl, isohexyl, allyl (propenyl) and propargyl (propynyl). As used herein, lower alkyl, lower alkenyl, and lower alkynyl

refer to carbon chains having from about 1 or about 2 carbons up to about 6 carbons. As used herein, "alk(en)(yn)yl" refers to an alkyl group containing at least one double bond and at least one triple bond.

As used herein, "alkylene" refers to a straight, branched or cyclic divalent aliphatic hydrocarbon group wherein the alkylene is attached to the rest of the molecule through two different bonds in the alkylene. In one embodiment the alkylene has from 1 to about 20 carbon atoms, in another embodiment the alkylene has from 1 to 12 carbons. The term "lower alkylene" refers to alkylene groups having 1 to 6 carbons. In certain embodiments, alkylene groups are lower alkylene, including alkylene of 1 to 3 carbon atoms.

As used herein, "alkylidene" refers to a divalent group, such as $=CR^pR^q$, wherein the alkylidene is attached to an atom of another group through the same carbon in the alkylidene, forming a double bond. Alkylidene groups include, but are not limited to, methylidene ($=CH_2$) and ethylidene ($=CHCH_3$). Alkylidenes may be optionally substituted with halo, cyano, nitro, haloalkyl or pseudohalo substituents. As used herein, "arylalkylidene" refers to an alkylidene group in which either R^p or R^q is an aryl group; "heteroaralkylidene" refers to an alkylidene group in which either R^p or R^q is a heteroaryl group; "cycloalkylidene" refer to an alkylidene group wherein R^p and R^q, together with the carbon to which they are attached, form a cycloalkyl group, or wherein at least one of R^p and R^q is a cycloalkyl ring; and "heterocyclylidene" refer to an alkylidene group wherein R^p and R^q, together with the carbon to which they are attached, form a heterocyclyl group, or wherein at least one of R^p and R^q is a heterocyclyl ring.

As used herein, "amidino" refers to a radical having the formula $-C(=NR^m)N(R^n)R^o$ where R^m, R^n and R^o are each independently hydrogen or alkyl.

As used herein, "aralkyl" refers to a radical of the formula $-R^aR^d$ where R^a is an alkyl radical as defined above, substituted by R^d, an aryl radical, as defined herein, *e.g.*, benzyl. Both the alkyl and aryl radicals may be optionally substituted as described herein.

As used herein, "aryl" refers to aromatic monocyclic or multicyclic ring system containing from 6 to 19 carbon atoms, where the ring system may be partially or fully saturated. Aryl groups include, but are not limited to groups such as unsubstituted or substituted fluorenyl, unsubstituted or substituted phenyl, and unsubstituted or substituted naphthyl.

As used herein, "cycloalkyl" refers to a saturated mono- or multi-cyclic ring system, in certain embodiments of 3 to 10 carbon atoms, in other embodiments of 3 to 6 carbon atoms; cycloalkenyl and cycloalkynyl refer to mono- or multicyclic ring systems that respectively include at least one double bond and at least one triple bond. Cycloalkenyl and cycloalkynyl groups may, in certain embodiments, contain 3 to 10 carbon atoms, with cycloalkenyl groups, in further embodiments, containing 4 to 7 carbon atoms and cycloalkynyl groups, in further embodiments, containing 8 to 10 carbon atoms. The ring systems of the cycloalkyl, cycloalkenyl and cycloalkynyl groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion. "Cycloalk(en)(yn)yl" refers to a cycloalkyl group containing at least one double bond and at least one triple bond.

As used herein, "cycloalkylalkyl" refers to a radical of the formula $-R^aR^b$ where R^a is an alkyl radical as defined above and R^b is a cycloalkyl radical as defined above. The alkyl radical and the cycloalkyl radical may be optionally substituted as defined above.

As used herein, "guanidino" refers to a radical having the formula $-N(R^p)C(=NR^q)NR^rR^s$ wherein R^p, R^q, R^r and R^s are each independently hydrogen or alkyl.

As used herein, "heteroaralkyl" refers to a radical of the formula $-R^aR^e$ where R^a is an alkyl radical as defined above and R^e is a heteroaryl radical as defined herein. The alkyl radical and the heterocyclyl radical may be optionally substituted as defined herein.

As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic heterocyclyl, as defined herein, in certain embodiments, of about 5 to about 15 members where one or more, in one embodiment 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. The heteroaryl group may be optionally fused to a benzene ring. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrimidinyl, tetrazolyl, thienyl, pyridyl, pyrrolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, triazolyl, quinolinyl and isoquinolinyl.

As used herein, a "heteroarylium" group is a heteroaryl group that is positively charged on one or more of the heteroatoms.

As used herein, "heterocyclyl" refers to a stable 3- to 18-membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. For purposes of this invention, the

heterocyclyl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclyl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the ring radical may be aromatic or partially or fully saturated. Examples of such heterocyclyl radicals include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzothiazolyl, benzindolyl, benzothiadiazolyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothiophenyl, benzotriazolyl, benzo[4,6]imidazo[1,2-*a*]pyridinyl; carbazolyl, cinnolinyl, dioxolanyl, dibenzofuranyl, decahydroisoquinolyl, furanyl, furanonyl, isothiazolyl, imidazolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, indolizinyl, isoxazolyl, isoxazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, oxazolyl, oxazolidinyl, oxiranyl, piperidinyl, piperazinyl, 4-piperidonyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrrolidinyl, pyrazolyl, pyrazolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinazolinyl, quinoxalinyl, quinolinyl, quinuclidinyl, isoquinolinyl, thiazolyl, thiazolidinyl, thiadiazolyl, triazolyl, tetrazolyl, tetrahydrofuryl, triazinyl, tetrahydropyranyl, thiophenyl, thiamorpholinyl, thiamorpholinyl sulfoxide, and thiamorpholinyl sulfone.

As used herein, "heterocyclylalkyl" refers to a radical of the formula $-R^aR^c$ where R^a is an alkyl radical as defined above and R^c is a heterocyclyl radical as defined herein. The alkyl radical and the heterocyclyl radical may be optionally substituted as defined herein.

As used herein, "aralkyl" refers to a radical of the formula $-R^aR^d$ where R^a is an alkyl group radical as defined herein and R^d is an aryl radical as defined herein. The alkyl radical and the aryl radical may be optionally substituted as defined herein.

As used herein, "halo", "halogen" or "halide" refers to F, Cl, Br or I.

As used herein, pseudohalides or pseudohalo groups are groups that behave substantially similar to halides. Such compounds can be used in the same manner and treated in the same manner as halides. Pseudohalides include, but are not limited to, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, and azide.

As used herein, "haloalkyl" refers to an alkyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include, but are not limited to, chloromethyl, trifluoromethyl and1-chloro-2-fluoroethyl.

As used herein, "hydrazone" refers to a divalent group such as $=NNR^t$ which is attached to a carbon atom of another group, forming a double bond, wherein R^t is hydrogen or alkyl.

As used herein, "imino" refers to a divalent group such as =NR, which is attached to a carbon atom of another group, forming a double bond, wherein R is hydrogen or alkyl.

"Optionally substituted alkyl", "optionally substituted alkenyl" and "optionally substituted alkynyl" refer to alkyl radicals, alkenyl radicals and alkynyl radicals, as defined herein, respectively, that may be optionally substituted by one or more substituents independently selected from the group consisting of nitro, halo, azido, cyano, cycloalkyl, heteroaryl, heterocyclyl, $-OR^x$, $-N(R^y)(R^z)$, $-SR^x$, $-C(J)R^x$, $-C(J)OR^x$, $-C(J)N(R^y)(R^z)$, $-C(J)SR^x$, $-S(O)_tR^x$ (where t is 1 or 2), $-OC(J)R^x$, $-OC(J)OR^x$, $-OC(J)N(R^y)(R^z)$, $-OC(J)SR^x$, $-N(R^x)C(J)R^x$, $-N(R^x)C(J)OR^x$, $-N(R^x)C(J)N(R^y)(R^z)$, $-N(R^x)C(J)SR^x$, $-Si(R^w)_3$, $-N(R^x)S(O)_2R^w$, $-N(R^x)S(O)_2N(R^y)(R^z)$, $-S(O)_2N(R^y)(R^z)$, $-N(R^x)C(J)R^x$, $-P(O)(R^v)_2$, $-OP(O)(R^v)_2$, $-C(J)N(R^x)S(O)_2R^x$, $-C(J)N(R^x)N(R^x)S(O)_2R^x$, $-C(R^x)=N(OR^x)$, and $-C(R^x)=NN(R^y)(R^z)$, wherein each R^x is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; or R^y and R^z, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl; each R^w is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; each R^v is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, hydroxy,$-OR^x$ or $-N(R^y)(R^z)$; and each J is independently O, NR^x or S.

"Optionally substituted aryl", ""Optionally substituted aralkyl", "optionally substituted cycloalkyl", "optionally substituted cycloalkylalkyl", "optionally substituted heteroaryl", "optionally substituted heteroaralkyl", "optionally substituted heterocyclyl" and "optionally substituted heterocyclylalkyl" refer to aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl radicals, respectively, as defined herein, that are optionally substituted by one or more substituents selected from the group consisting of nitro, halo, azido, cyano, alkyl,

haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, $-R^u-OR^x$, $-R^u-N(R^y)(R^z)$, $-R^u-SR^x$, $-R^u-C(J)R^x$, $-R^u-C(J)OR^x$, $-R^u-C(J)N(R^y)(R^z)$, $-R^u-C(J)SR^x$, $-R^u-S(O)_tR^x$ (where t is 1 or 2), $-R^u-OC(J)R^x$, $-R^u-OC(J)OR^x$, $-R^u-OC(J)N(R^y)(R^z)$, $-R^u-OC(J)SR^x$, $-R^u-N(R^x)C(J)R^x$, $-R^u-N(R^x)C(J)OR^x$, $-R^u-N(R^x)C(J)N(R^y)(R^z)$, $-R^u-N(R^x)C(J)SR^x$, $-R^u-Si(R^w)_3$, $-R^u-N(R^x)S(O)_2R^w$, $-R^u-N(R^x)S(O)_2N(R^y)(R^z)$, $-R^u-S(O)_2N(R^y)(R^z)$, $-R^u-N(R^x)C(J)R^x$, $-R^u-P(O)(R^v)_2$, $-R^u-OP(O)(R^v)_2$, $-R^u-C(J)N(R^x)S(O)_2R^x$, $-R^u-C(J)N(R^x)N(R^x)S(O)_2R^x$, $-R^u-C(R^x)=N(OR^x)$, and $-R^u-C(R^x)=NN(R^y)(R^z)$, wherein each R^u is independently alkylene or a direct bond; each R^v is independently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, hydroxy,$-OR^x$ or $-N(R^y)(R^z)$; each R^w is indpendently alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; each R^x is independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; R^y and R^z are each independently hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, aralkyl, heteroaryl, or heteroaralkyl; or R^y and R^z, together with the nitrogen atom to which they are attached, form a heterocyclyl or heteroaryl; and each J is O, NR^x or S.

Unless stated otherwise specifically in the specification, it is understood that the substitution can occur on any atom of the aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroaralkyl groups.

Optionally substituted cycloalkyl, optionally substituted heterocyclyl and optionally substituted aryl may additionally be substituted with oxo, thioxo, imino, oxime or hydrazone, on a saturated carbon of their respective ring system.

As used herein, "oxime" refers to a divalent group such as =N-OH, which is attached to a carbon atom of another group, forming a double bond.

As used herein, "oxo" refers to an oxygen atom doubly bonded to a carbon.

As used herein, pseudohalides or pseudohalo groups are groups that behave substantially similar to halides. Such compounds can be used in the same manner and treated in the same manner as halides. Pseudohalides include, but are not limited to, cyanide, cyanate, thiocyanate, selenocyanate, trifluoromethoxy, and azide.

As used herein, "thioxo" refers to a sulfur atom doubly bonded to a carbon.

Where the number of any given substituent is not specified (*e.g.*, haloalkyl), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens. As another example, "C_{1-3}alkoxyphenyl" may include one or more of the same or different alkoxy groups containing one, two or three carbons.

As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, or the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) *Biochem. 11*:942-944).

If employed herein, the following terms have their accepted meaning in the chemical literature.

AcOH	acetic acid
CDI	carbodiimide
$CHCl_3$	chloroform
conc	concentrated
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquninone
DIEA	diisopropyl ethylamine
DMAP	4-(dimethylamino) pyridine
DME	1,2-dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
ELSD	Evaporative light scattering detector
EtOAc	ethyl acetate
EtOH	ethanol (100%)
Et_2O	diethyl ether
HBTU	1-H-Benzotriazolium, 1-[bis(dimethylamino)methylene]-hexafluorophosphate(1-),3-oxide O-(Benzotriazol-1-yl)-N,N,N',N' tetramethyluronium hexafluorophosphate
Hex	hexanes
H_2SO_4	sulfuric acid

LDA	Lithium di(*iso*-propyl)amide
MeCN	acetonitrile
MeOH	methanol
$NaBH_3CN$	sodium cyanoborohydride
Pd/C	palladium on activated carbon
TEA	triethylamine
THF	tetrahydrofuran
TFA	trifluoroacetic acid

B. Formulation of pharmaceutical compositions

The pharmaceutical compositions provided herein contain therapeutically effective amounts of one or more of the nuclear receptor activity modulators provided herein that are useful in the prevention, treatment, or amelioration of one or more of the symptoms of diseases or disorders associated with nuclear receptor activity, including the farnesoid X receptor and/or orphan nuclear receptor activity. Such diseases or disorders include, but are not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerotic disease events, gallstone disease, acne vulgaris, acneiform skin conditions, type II diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

Further the pharmaceutical compositions provided herein contain therapeutically effective amounts of one or more of the nuclear receptor activity modulators provided herein that are useful in the prevention, treatment, or amelioration of one or more of the symptoms of diseases or disorders that are not directly associated with a nuclear receptor, but for which a complication of the disease or disorder is treatable with claimed compounds and compositions. By way of example, without limitation, Cystic Fibrosis is not typically associated with a nuclear receptor activity, but can result in cholestasis, which may be treated with the subject compounds and compositions.

The compositions contain one or more compounds provided herein. The compounds are preferably formulated into suitable pharmaceutical preparations such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for parenteral administration, as well as transdermal patch preparation and dry powder inhalers. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art (see, *e.g.*, Ansel *Introduction to Pharmaceutical Dosage Forms, Fourth Edition* **1985**, 126).

In the compositions, effective concentrations of one or more compounds or pharmaceutically acceptable derivatives is (are) mixed with a suitable pharmaceutical carrier or vehicle. The compounds may be derivatized as the corresponding salts, esters, enol ethers or esters, acids, bases, solvates, hydrates or prodrugs prior to formulation, as described above. The concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates one or more of the symptoms of diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated. Such diseases or disorders include, but are not limited to, hypercholesterolemia, hyperlipoproteinemia, hypertriglyceridemia, lipodystrophy, hyperglycemia, diabetes mellitus, dyslipidemia, atherosclerotic disease events, gallstone disease, acne vulgaris, acneiform skin conditions, type II diabetes, Parkinson's disease, cancer, Alzheimer's disease, inflammation, immunological disorders, lipid disorders, obesity, conditions characterized by a perturbed epidermal barrier function, hyperlipidemia, cholestasis, peripheral occlusive disease, ischemic stroke, conditions of disturbed differentiation or excess proliferation of the epidermis or mucous membrane, and cardiovascular disorders.

Typically, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the treated condition is relieved or ameliorated. Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.

In addition, the compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other

active ingredients. Liposomal suspensions, including tissue-targeted liposomes, such as tumor-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as described in U.S. Patent No. 4,522,811. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the patient treated. The therapeutically effective concentration may be determined empirically by testing the compounds in *in vitro* and *in vivo* systems described herein and in International Patent Application Publication Nos. 99/27365 and 00/25134 and then extrapolated therefrom for dosages for humans.

The concentration of active compound in the pharmaceutical composition will depend on absorption, inactivation and excretion rates of the active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to ameliorate one or more of the symptoms of diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated, as described herein.

Typically a therapeutically effective dosage should produce a serum concentration of active ingredient of from about 0.1 ng/ml to about 50-100 μg/ml. The pharmaceutical compositions typically should provide a dosage of from about 0.001 mg to about 2000 mg of compound per kilogram of body weight per day. Pharmaceutical dosage unit forms are prepared to provide from about 1 mg to about 1000 mg and preferably from about 10 to about 500 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form.

The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and

dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

Pharmaceutically acceptable derivatives include acids, bases, enol ethers and esters, salts, esters, hydrates, solvates and prodrug forms. The derivative is selected such that its pharmacokinetic properties are superior to the corresponding neutral compound.

Thus, effective concentrations or amounts of one or more of the compounds described herein or pharmaceutically acceptable derivatives thereof are mixed with a suitable pharmaceutical carrier or vehicle for systemic, topical or local administration to form pharmaceutical compositions. Compounds are included in an amount effective for ameliorating one or more symptoms of, or for treating or preventing diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated, as described herein. The concentration of active compound in the composition will depend on absorption, inactivation, excretion rates of the active compound, the dosage schedule, amount administered, particular formulation as well as other factors known to those of skill in the art.

The compositions are intended to be administered by a suitable route, including orally, parenterally, rectally, topically and locally. For oral administration, capsules and tablets are presently preferred. The compositions are in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration. Preferred modes of administration include parenteral and oral modes of administration. Oral administration is presently most preferred.

Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerine, propylene glycol or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. Parenteral preparations can be enclosed in ampoules, disposable syringes or single or multiple dose vials made of glass, plastic or

other suitable material.

In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using co-solvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN®, or dissolution in aqueous sodium bicarbonate. Derivatives of the compounds, such as prodrugs of the compounds may also be used in formulating effective pharmaceutical compositions.

Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of the compounds or pharmaceutically acceptable derivatives thereof. The pharmaceutically therapeutically active compounds and derivatives thereof are typically formulated and administered in unit-dosage forms or multiple-dosage forms. Unit-dose forms as used herein refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampoules and syringes and individually packaged tablets or capsules. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

The composition can contain along with the active ingredient: a diluent such as lactose, sucrose, dicalcium phosphate, or carboxymethylcellulose; a lubricant, such as magnesium stearate, calcium stearate and talc; and a binder such as starch, natural gums, such as gum acacia gelatin, glucose, molasses, polyvinylpyrrolidone,

celluloses and derivatives thereof, povidone, crospovidones and other such binders known to those of skill in the art. Liquid pharmaceutically administrable compositions can, for example, be prepared by dissolving, dispersing, or otherwise mixing an active compound as defined above and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, glycols, ethanol, and the like, to thereby form a solution or suspension. If desired, the pharmaceutical composition to be administered may also contain minor amounts of nontoxic auxiliary substances such as wetting agents, emulsifying agents, or solubilizing agents, pH buffering agents and the like, for example, acetate, sodium citrate, cyclodextrin derivatives, sorbitan monolaurate, triethanolamine sodium acetate, triethanolamine oleate, and other such agents. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa., 15th Edition, 1975. The composition or formulation to be administered will, in any event, contain a quantity of the active compound in an amount sufficient to alleviate the symptoms of the treated subject.

Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non-toxic carrier may be prepared. For oral administration, a pharmaceutically acceptable non-toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate or sodium saccharin. Such compositions include solutions, suspensions, tablets, capsules, powders and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain 0.001%-100% active ingredient, preferably 0.1-85%, typically 75-95%.

The active compounds or pharmaceutically acceptable derivatives may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings. The compositions may include other active compounds to obtain desired combinations of properties. The compounds provided herein, or pharmaceutically acceptable derivatives thereof as described

herein, may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove, such as diseases or disorders associated with nuclear receptor activity or in which nuclear receptor activity is implicated. It is to be understood that such combination therapy constitutes a further aspect of the compositions and methods of treatment provided herein.

(a) Compositions for oral administration

Oral pharmaceutical dosage forms are either solid, gel or liquid. The solid dosage forms are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated or film-coated. Capsules may be hard or soft gelatin capsules, while granules and powders may be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

In certain embodiments, the formulations are solid dosage forms, preferably capsules or tablets. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder; a diluent; a disintegrating agent; a lubricant; a glidant; a sweetening agent; and a flavoring agent.

Examples of binders include microcrystalline cellulose, gum tragacanth, glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Glidants include, but are not limited to, colloidal silicon dioxide. Disintegrating agents include crosscarmellose sodium, sodium starch glycolate, alginic acid, corn starch, potato starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved certified water soluble FD and C dyes, mixtures thereof; and water insoluble FD and C dyes suspended on alumina hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as saccharin, and any number of spray dried flavors. Flavoring agents include natural flavors extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation, such

as, but not limited to peppermint and methyl salicylate. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Emetic-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, polyethylene glycol 4000 and cellulose acetate phthalate.

If oral administration is desired, the compound could be provided in a composition that protects it from the acidic environment of the stomach. For example, the composition can be formulated in an enteric coating that maintains its integrity in the stomach and releases the active compound in the intestine. The composition may also be formulated in combination with an antacid or other such ingredient.

When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar and other enteric agents. The compounds can also be administered as a component of an elixir, suspension, syrup, wafer, sprinkle, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The active materials can also be mixed with other active materials which do not impair the desired action, or with materials that supplement the desired action, such as antacids, H2 blockers, and diuretics. The active ingredient is a compound or pharmaceutically acceptable derivative thereof as described herein. Higher concentrations, up to about 98% by weight of the active ingredient may be included.

Pharmaceutically acceptable carriers included in tablets are binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, and wetting agents. Enteric-coated tablets, because of the enteric-coating, resist the action of stomach acid and dissolve or disintegrate in the neutral or alkaline intestines. Sugar-coated tablets are compressed tablets to which different layers of pharmaceutically acceptable substances are applied. Film-coated tablets are compressed tablets which have been coated with a polymer or other suitable coating. Multiple compressed tablets are compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable substances previously mentioned. Coloring agents may also be used in the above dosage forms. Flavoring and sweetening agents are used in compressed tablets, sugar-coated, multiple

compressed and chewable tablets. Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in-water or water-in-oil.

Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in emulsions are non-aqueous liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives. Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substances used in effervescent granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic add, sodium benzoate and alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Coloring agents include any of the approved certified water soluble FD and C dyes, and mixtures thereof. Flavoring agents include natural flavors extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

For a solid dosage form, the solution or suspension, in for example propylene carbonate, vegetable oils or triglycerides, is preferably encapsulated in a gelatin capsule. Such solutions, and the preparation and encapsulation thereof, are disclosed in U.S. Patent Nos. 4,328,245; 4,409,239; and 4,410,545. For a liquid dosage form, the solution, *e.g.*, for example, in a polyethylene glycol, may be diluted with a sufficient quantity of a pharmaceutically acceptable liquid carrier, *e.g.*, water, to be easily measured for administration.

Alternatively, liquid or semi-solid oral formulations may be prepared by dissolving or dispersing the active compound or salt in vegetable oils, glycols, triglycerides, propylene glycol esters (*e.g.*, propylene carbonate) and other such carriers, and encapsulating these solutions or suspensions in hard or soft gelatin capsule shells. Other useful formulations include those set forth in U.S. Patent Nos. Re 28,819 and 4,358,603. Briefly, such formulations include, but are not limited to, those containing a compound provided herein, a dialkylated mono- or poly-alkylene glycol, including, but not limited to, 1,2-dimethoxymethane, diglyme, triglyme, tetraglyme, polyethylene glycol-350-dimethyl ether, polyethylene glycol-550-dimethyl ether, polyethylene glycol-750-dimethyl ether wherein 350, 550 and 750 refer to the approximate average molecular weight of the polyethylene glycol, and one or more antioxidants, such as butylated hydroxytoluene (BHT), butylated hydroxyanisole (BHA), propyl gallate, vitamin E, hydroquinone, hydroxycoumarins, ethanolamine, lecithin, cephalin, ascorbic acid, malic acid, sorbitol, phosphoric acid, thiodipropionic acid and its esters, and dithiocarbamates.

Other formulations include, but are not limited to, aqueous alcoholic solutions including a pharmaceutically acceptable acetal. Alcohols used in these formulations are any pharmaceutically acceptable water-miscible solvents having one or more hydroxyl groups, including, but not limited to, propylene glycol and ethanol. Acetals include, but are not limited to, di(lower alkyl) acetals of lower alkyl aldehydes such as acetaldehyde diethyl acetal.

In all embodiments, tablets and capsules formulations may be coated as known by those of skill in the art in order to modify or sustain dissolution of the active ingredient. Thus, for example, they may be coated with a conventional enterically digestible coating, such as phenylsalicylate, waxes and cellulose acetate phthalate.

(b) Injectables, solutions and emulsions

Parenteral administration, generally characterized by injection, either subcutaneously, intramuscularly or intravenously is also contemplated herein. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions, solid forms suitable for solution or suspension in liquid prior to injection, or as emulsions. Suitable excipients are, for example, water, saline, dextrose, glycerol or ethanol. In addition, if desired, the pharmaceutical compositions to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents, stabilizers, solubility enhancers, and other such agents, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate and cyclodextrins.

Implantation of a slow-release or sustained-release system, such that a constant level of dosage is maintained (see, *e.g.*, U.S. Patent No. 3,710,795) is also contemplated herein. Briefly, a compound provided herein is dispersed in a solid inner matrix, *e.g.*, polymethylmethacrylate, polybutylmethacrylate, plasticized or unplasticized polyvinylchloride, plasticized nylon, plasticized polyethyleneterephthalate, natural rubber, polyisoprene, polyisobutylene, polybutadiene, polyethylene, ethylene-vinylacetate copolymers, silicone rubbers, polydimethylsiloxanes, silicone carbonate copolymers, hydrophilic polymers such as hydrogels of esters of acrylic and methacrylic acid, collagen, cross-linked polyvinylalcohol and cross-linked partially hydrolyzed polyvinyl acetate, that is surrounded by an outer polymeric membrane, *e.g.*, polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethyl acrylate copolymers, ethylene/vinylacetate copolymers, silicone rubbers, polydimethyl siloxanes, neoprene rubber, chlorinated polyethylene, polyvinylchloride, vinylchloride copolymers with vinyl acetate, vinylidene chloride, ethylene and propylene, ionomer polyethylene terephthalate, butyl rubber epichlorohydrin rubbers, ethylene/vinyl alcohol copolymer, ethylene/vinyl acetate/vinyl alcohol terpolymer, and ethylene/vinyloxyethanol copolymer, that is insoluble in body fluids. The compound diffuses through the outer polymeric membrane in a release rate controlling step. The percentage of active compound contained in such parenteral compositions is highly dependent on the specific nature thereof, as well as the activity of the compound and the needs of the subject.

Parenteral administration of the compositions includes intravenous, subcutaneous and intramuscular administrations. Preparations for parenteral

administration include sterile solutions ready for injection, sterile dry soluble products, such as lyophilized powders, ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

If administered intravenously, suitable carriers include physiological saline or phosphate buffered saline (PBS), and solutions containing thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof.

Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride. Suspending and dispersing agents include sodium carboxymethylcelluose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (TWEEN® 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the patient or animal as is known in the art.

The unit-dose parenteral preparations are packaged in an ampoule, a

vial or a syringe with a needle. All preparations for parenteral administration must be sterile, as is known and practiced in the art.

Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

Injectables are designed for local and systemic administration. Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 90% w/w or more, preferably more than 1% w/w of the active compound to the treated tissue(s). The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the tissue being treated and may be determined empirically using known testing protocols or by extrapolation from *in vivo* or *in vitro* test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed formulations.

The compound may be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the condition and may be empirically determined.

(c) Lyophilized powders

Of interest herein are also lyophilized powders, which can be reconstituted for administration as solutions, emulsions and other mixtures. They may also be reconstituted and formulated as solids or gels.

The sterile, lyophilized powder is prepared by dissolving a compound provided herein, or a pharmaceutically acceptable derivative thereof, in a suitable solvent. The solvent may contain an excipient which improves the stability or other

pharmacological component of the powder or reconstituted solution, prepared from the powder. Excipients that may be used include, but are not limited to, dextrose, sorbital, fructose, corn syrup, xylitol, glycerin, glucose, sucrose or other suitable agent. The solvent may also contain a buffer, such as citrate, sodium or potassium phosphate or other such buffer known to those of skill in the art at, typically, about neutral pH. Subsequent sterile filtration of the solution followed by lyophilization under standard conditions known to those of skill in the art provides the desired formulation. Generally, the resulting solution will be apportioned into vials for lyophilization. Each vial will contain a single dosage (10-1000 mg, preferably 100-500 mg) or multiple dosages of the compound. The lyophilized powder can be stored under appropriate conditions, such as at about 4 °C to room temperature.

Reconstitution of this lyophilized powder with water for injection provides a formulation for use in parenteral administration. For reconstitution, about 1-50 mg, preferably 5-35 mg, more preferably about 9-30 mg of lyophilized powder, is added per mL of sterile water or other suitable carrier. The precise amount depends upon the selected compound. Such amount can be empirically determined.

(d) Topical administration

Topical mixtures are prepared as described for the local and systemic administration. The resulting mixture may be a solution, suspension, emulsions or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, dermal patches or any other formulations suitable for topical administration.

The compounds or pharmaceutically acceptable derivatives thereof may be formulated as aerosols for topical application, such as by inhalation (see, *e.g.*, U.S. Patent Nos. 4,044,126, 4,414,209, and 4,364,923, which describe aerosols for delivery of a steroid useful for treatment of inflammatory diseases, particularly asthma). These formulations for administration to the respiratory tract can be in the form of an aerosol or solution for a nebulizer, or as a microfine powder for insufflation, alone or in combination with an inert carrier such as lactose. In such a case, the particles of the formulation will typically have diameters of less than 50 microns, preferably less than 10 microns.

The compounds may be formulated for local or topical application, such

as for topical application to the skin and mucous membranes, such as in the eye, in the form of gels, creams, and lotions and for application to the eye or for intracisternal or intraspinal application. Topical administration is contemplated for transdermal delivery and also for administration to the eyes or mucosa, or for inhalation therapies. Nasal solutions of the active compound alone or in combination with other pharmaceutically acceptable excipients can also be administered.

These solutions, particularly those intended for ophthalmic use, may be formulated as 0.01% - 10% isotonic solutions, pH about 5-7, with appropriate salts.

(e) Compositions for other routes of administration

Other routes of administration, such as topical application, transdermal patches, and rectal administration are also contemplated herein.

Transdermal patches, including iotophoretic and electrophoretic devices, are well known to those of skill in the art. For example, such patches are disclosed in U.S. Patent Nos. 6,267,983, 6,261,595, 6,256,533, 6,167,301, 6,024,975, 6,010715, 5,985,317, 5,983,134, 5,948,433, and 5,860,957.

Pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect. Rectal suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients. Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point. Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin, carbowax (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. The typical weight of a rectal suppository is about 2 to 3 gm.

Tablets and capsules for rectal administration are manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

(f) Targeted Formulations

The compounds provided herein, or pharmaceutically acceptable derivatives thereof, may also be formulated to be targeted to a particular tissue, receptor, or other area of the body of the subject to be treated. Many such targeting methods are well known to those of skill in the art. All such targeting methods are contemplated herein for use in the instant compositions. For non-limiting examples of targeting methods, see, *e.g.*, U.S. Patent Nos. 6,316,652, 6,274,552, 6,271,359, 6,253,872, 6,139,865, 6,131,570, 6,120,751, 6,071,495, 6,060,082, 6,048,736, 6,039,975, 6,004,534, 5,985,307, 5,972,366, 5,900,252, 5,840,674, 5,759,542 and 5,709,874.

In one embodiment, liposomal suspensions, including tissue-targeted liposomes, such as tumor-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as described in U.S. Patent No. 4,522,811. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

(g) Articles of manufacture

The compounds or pharmaceutically acceptable derivatives may be packaged as articles of manufacture containing packaging material, a compound or pharmaceutically acceptable derivative thereof provided herein, which is effective for modulating the activity of nuclear receptors, including the farnesoid X receptor and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including the farnesoid X receptor and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including the farnesoid X receptor and/or orphan nuclear receptor activity, is implicated, within the packaging material, and a label that indicates that the compound or composition, or pharmaceutically acceptable derivative thereof, is used for modulating the activity of nuclear receptors, including the farnesoid X

receptor and/or orphan nuclear receptors, or for treatment, prevention or amelioration of one or more symptoms of nuclear receptor, including the farnesoid X receptor and/or orphan nuclear receptor, mediated diseases or disorders, or diseases or disorders in which nuclear receptor activity, including the farnesoid X receptor and/or orphan nuclear receptor activity, is implicated.

The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products are well known to those of skill in the art. See, *e.g.*, U.S. Patent Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. A wide array of formulations of the compounds and compositions provided herein are contemplated as are a variety of treatments for any disease or disorder in which nuclear receptor activity, including the farnesoid X receptor and/or orphan nuclear receptor activity, is implicated as a mediator or contributor to the symptoms or cause.

C. Evaluation of the activity of the compounds

Standard physiological, pharmacological and biochemical procedures are available for testing the compounds to identify those that possess biological activities that modulate the activity or nuclear receptors, including the farnesoid X receptor and/or orphan nuclear receptors. Such assays include, for example, biochemical assays such as binding assays, fluorescence polarization assays, FRET based coactivator recruitment assays (see generally Glickman *et al.*, *J. Biomolecular Screening*, 7 No. 1 3-10 (2002)), as well as cell based assays including the co-transfection assay, the use of LBD-Gal 4 chimeras and protein-protein interaction assays (see, Lehmann. *et al., J. Biol Chem.,* 272(6) 3137-3140 (1997).

High throughput screening systems are commercially available *(see, e.g.,* Zymark Corp., Hopkinton, MA; Air Technical Industries, Mentor, OH; Beckman Instruments Inc., Fullerton, CA; Precision Systems, Inc., Natick, MA) that enable these assays to be run in a high throughput mode. These systems typically automate entire procedures, including all sample and reagent pipetting, liquid dispensing timed incubations, and final readings of the microplate in detector(s) appropriate for the assay. These configurable systems provide high throughput and rapid start up as well

as a high degree of flexibility and customization. The manufacturers of such systems provide detailed protocols for various high throughput systems. Thus, for example, Zymark Corp. provides technical bulletins describing screening systems for detecting the modulation of gene transcription, ligand binding, and the like.

Assays that do not require washing or liquid separation steps are preferred for such high throughput screening systems and include biochemical assays such as fluorescence polarization assays (see for example, Owicki, J., Biomol Screen 2000 Oct;5(5):297) scintillation proximity assays (SPA) (see for example, Carpenter et *al.*, Methods Mol Biol 2002;190:31-49) and fluorescence resonance energy transfer energy transfer (FRET) or time resolved FRET based coactivator recruitment assays (Mukherjee *et al.*, *J Steroid Biochem Mol Biol* 2002 Jul;81(3):217-25; (Zhou *et al.*, *Mol Endocrinol.* 1998 Oct;12(10):1594-604). Generally such assays can be preformed using either the full length receptor, or isolated ligand binding domain (LBD). In the case of the farnesoid X receptor, the LBD comprises amino acids 244 to 472 of the full length sequence.

If a fluorescently labeled ligand is available, fluorescence polarization assays provide a way of detecting binding of compounds to the nuclear receptor of interest by measuring changes in fluorescence polarization that occur as a result of the displacement of a trace amount of the label ligand by the compound. Additionally this approach can also be used to monitor the ligand dependent association of a fluorescently labeled coactivator peptide to the nuclear receptor of interest to detect ligand binding to the nuclear receptor of interest.

The ability of a compound to bind to a receptor, or heterodimer complex with RXR, can also be measured in a homogeneous assay format by assessing the degree to which the compound can compete off a radiolabelled ligand with known affinity for the receptor using a scintillation proximity assay (SPA). In this approach, the radioactivity emitted by a radiolabelled compound generates an optical signal when it is brought into close proximity to a scintillant such as a Ysi-copper containing bead, to which the nuclear receptor is bound. If the radiolabelled compound is displaced from the nuclear receptor the amount of light emitted from the nuclear receptor bound scintillant decreases, and this can be readily detected using standard microplate liquid scintillation plate readers such as, for example, a Wallac MicroBeta reader.

The heterodimerization of the farnesoid X receptor with RXRα can also be measured by fluorescence resonance energy transfer (FRET), or time resolved FRET, to monitor the ability of the compounds provided herein to bind to the farnesoid

X receptor or other nuclear receptors. Both approaches rely upon the fact that energy transfer from a donor molecule to an acceptor molecule only occurs when donor and acceptor are in close proximity. Typically the purified LBD of the nuclear receptor of interest is labeled with biotin then mixed with stoichiometric amounts of europium labeled streptavidin (Wallac Inc.), and the purified LBD of RXRα is labeled with a suitable fluorophore such as CY5™. Equimolar amounts of each modified LBD are mixed together and allowed to equilibrate for at least 1 hour prior to addition to either variable or constant concentrations of the sample for which the affinity is to be determined. After equilibration, the time-resolved fluorescent signal is quantitated using a fluorescent plate reader. The affinity of the compound can then be estimated from a plot of fluorescence versus concentration of compound added.

This approach can also be exploited to measure the ligand dependent interaction of a co-activator peptide with a nuclear receptor in order to characterize the agonist or antagonist activity of the compounds disclosed herein. Typically the assay in this case involves the use a recombinant Glutathione-S-transferase (GST)-nuclear receptor ligand binding domain (LBD) fusion protein and a synthetic biotinylated peptide sequenced derived from the receptor interacting domain of a co-activator peptide such as the steroid receptor coactivator 1 (SRC-1). Typically GST-LBD is labeled with a europium chelate (donor) via a europium-tagged anti-GST antibody, and the coactivator peptide is labeled with allophycocyanin via a streptavidin-biotin linkage.

In the presence of an agonist for the nuclear receptor, the peptide is recruited to the GST-LBD bringing europium and allophycocyanin into close proximity to enable energy transfer from the europium chelate to the allophycocyanin. Upon excitation of the complex with light at 340 nm excitation energy absorbed by the europium chelate is transmitted to the allophycocyanin moiety resulting in emission at 665 nm. If the europium chelate is not brought in to close proximity to the allophycocyanin moiety there is little or no energy transfer and excitation of the europium chelate results in emission at 615 nm. Thus the intensity of light emitted at 665 nm gives an indication of the strength of the protein-protein interaction. The activity of a nuclear receptor antagonist can be measured by determining the ability of a compound to competitively inhibit (*i.e.*, IC_{50}) the activity of an agonist for the nuclear receptor.

In addition a variety of cell based assay methodologies may be successfully used in screening assays to identify and profile the specificity of compounds of the present invention. These approaches include the co-transfection

assay, translocation assays, complementation assays and the use of gene activation technologies to over express endogenous nuclear receptors.

Three basic variants of the co-transfection assay strategy exist, co-transfection assays using full-length nuclear receptor, co transfection assays using chimeric nuclear receptors comprising the ligand binding domain of the nuclear receptor of interest fused to a heterologous DNA binding domain, and assays based around the use of the mammalian two hybrid assay system.

The basic co-transfection assay is based on the co-transfection into the cell of an expression plasmid to express the nuclear receptor of interest in the cell with a reporter plasmid comprising a reporter gene whose expression is under the control of DNA sequence that is capable of interacting with that nuclear receptor. (See for example US Patents Nos. 5,071,773; 5,298,429, 6,416,957, WO 00/76523). Treatment of the transfected cells with an agonist for the nuclear receptor increases the transcriptional activity of that receptor which is reflected by an increase in expression of the reporter gene, which may be measured by a variety of standard procedures.

For those receptors that function as heterodimers with RXR, such as the farnesoid X receptor, the co-transfection assay typically includes the use of expression plasmids for both the nuclear receptor of interest and RXR. Typical co-transfection assays require access to the full-length nuclear receptor and suitable response elements that provide sufficient screening sensitivity and specificity to the nuclear receptor of interest.

Genes encoding the following full-length previously described proteins, which are suitable for use in the co-transfection studies and profiling the compounds described herein, include rat farnesoid X receptor (GenBank Accession No. NM_021745), human farnesoid X receptor (GenBank Accession No. NM_005123), human RXR α (GenBank Accession No. NM_002957), human RXR β (GenBank Accession No. XM_042579), human RXR.γ (GenBank Accession No. XM_053680), human LXR α (GenBank Accession No. NM_005693), human LXR β (GenBank Accession No. NM_007121), human PPARα (GenBank Accession No. NM_005036) and human PPAR δ (GenBank Accession No. NM_006238).

Reporter plasmids may be constructed using standard molecular biological techniques by placing cDNA encoding for the reporter gene downstream from a suitable minimal promoter. For example luciferase reporter plasmids may be constructed by placing cDNA encoding firefly luciferase immediately down stream from

the herpes virus thymidine kinase promoter (located at nucleotides residues-105 to +51 of the thymidine kinase nucleotide sequence) which is linked in turn to the various response elements.

Numerous methods of co-transfecting the expression and reporter plasmids are known to those of skill in the art and may be used for the co-transfection assay to introduce the plasmids into a suitable cell type. Typically such a cell will not endogenously express nuclear receptors that interact with the response elements used in the reporter plasmid.

Numerous reporter gene systems are known in the art and include, for example, alkaline phosphatase Berger, J., *et al.* (1988) Gene 66 1-10; Kain, S.R. (1997) Methods. Mol. Biol. 63 49-60), β-galactosidase (See, U.S. Patent No. 5,070,012, issued Dec, 3, 1991 to Nolan *et al.*, and Bronstein, I., *et al.*, (1989) J. Chemilum. Biolum. 4 99-111), chloramphenicol acetyltransferase (See Gorman *et al.*, Mol Cell Biol. (1982) 2 1044-51), β-glucuronidase, peroxidase, β-lactamase (U.S. Patent Nos. 5,741,657 and 5,955,604), catalytic antibodies, luciferases (U.S. Patents 5,221,623; 5,683,888; 5,674,713; 5,650,289; 5,843,746) and naturally fluorescent proteins (Tsien, R.Y. (1998) Annu. Rev. Biochem. 67 509-44).

The use of chimeras comprising the ligand binding domain (LBD) of the nuclear receptor of interest to a heterologous DNA binding domain (DBD) expands the versatility of cell based assays by directing activation of the nuclear receptor in question to defined DNA binding elements recognized by defined DNA binding domain (see WO95/18380). This assay expands the utility of cell based co-transfection assays in cases where the biological response or screening window using the native DNA binding domain is not satisfactory.

In general the methodology is similar to that used with the basic co-transfection assay, except that a chimeric construct is used in place of the full-length nuclear receptor. As with the full-length nuclear receptor, treatment of the transfected cells with an agonist for the nuclear receptor LBD increases the transcriptional activity of the heterologous DNA binding domain which is reflected by an increase in expression of the reporter gene as described above. Typically for such chimeric constructs, the DNA binding domains from defined nuclear receptors, or from yeast or bacterially derived transcriptional regulators such as members of the GAL 4 and Lex A / Umud super families are used.

A third cell based assay of utility for screening compounds of the present invention is a mammalian two-hybrid assay that measures the ability of the

nuclear hormone receptor to interact with a cofactor in the presence of a ligand. (See for example, US Patent Nos. US 5,667,973, 5,283,173 and 5,468,614). The basic approach is to create three plasmid constructs that enable the interaction of the nuclear receptor with the interacting protein to be coupled to a transcriptional readout within a living cell. The first construct is an expression plasmid for expressing a fusion protein comprising the interacting protein, or a portion of that protein containing the interacting domain, fused to a GAL4 DNA binding domain. The second expression plasmid comprises DNA encoding the nuclear receptor of interest fused to a strong transcription activation domain such as VP16, and the third construct comprises the reporter plasmid comprising a reporter gene with a minimal promoter and GAL4 upstream activating sequences.

Once all three plasmids are introduced into a cell, the GAL4 DNA binding domain encoded in the first construct allows for specific binding of the fusion protein to GAL4 sites upstream of a minimal promoter. However because the GAL4 DNA binding domain typically has no strong transcriptional activation properties in isolation, expression of the reporter gene occurs only at a low level. In the presence of a ligand, the nuclear receptor-VP16 fusion protein can bind to the GAL4-interacting protein fusion protein bringing the strong transcriptional activator VP16 in close proximity to the GAL4 binding sites and minimal promoter region of the reporter gene. This interaction significantly enhances the transcription of the reporter gene, which can be measured for various reporter genes as described above. Transcription of the reporter gene is thus driven by the interaction of the interacting protein and nuclear receptor of interest in a ligand dependent fashion.

Any compound which is a candidate for activation of the farnesoid X receptor may be tested by these methods. Generally, compounds are tested at several different concentrations to optimize the chances that activation of the receptor will be detected and recognized if present. Typically assays are performed in triplicate and vary within experimental error by less than 15%. Each experiment is typically repeated three or more times with similar results.

Activity of the reporter gene can be conveniently normalized to the internal control and the data plotted as fold activation relative to untreated cells. A positive control compound (agonist) may be included along with DMSO as high and low controls for normalization of the assay data. Similarly, antagonist activity can be measured by determining the ability of a compound to competitively inhibit the activity of an agonist.

Additionally the compounds and compositions can be evaluated for their ability to increase or decrease the expression of genes known to be modulated by the farnesoid X receptor and other nuclear receptors in *vivo*, using Northern-blot, RT PCR or oligonucleotide microarray analysis to analyze RNA levels. Western-blot analysis can be used to measure expression of proteins encoded by farnesoid X receptor target genes. Genes that are known to be regulated by the farnesoid X receptor include cholesterol 7 α-hydroxylase (CYP7A1), the rate limiting enzyme in the conversion of cholesterol to bile acids, the small heterodimer partner-1 (SHP-1), the bile salt export pump (BSEP, ABCB11), canalicular bile acid export protein, sodium taurocholate cotransporting polypeptide (NTCP, SLC10A1) and intestinal bile acid binding protein (I-BABP).

Established animal models exist for a number of diseases of direct relevance to the claimed compounds and these can be used to further profile and characterize the claimed compounds. These model systems include diabetic dislipidemia using Zucker (fa/fa) rats or (db/db) mice, spontaneous hyperlipidemia using apolipoprotein E deficient mice ($ApoE^{-/-}$), diet-induced hyperlipidemia, using low density lipoprotein receptor deficient mice ($LDR^{-/-}$) and atherosclerosis using both the Apo $E(^{-/-})$ and $LDL(^{-/-})$ mice fed a western diet, (21% fat, 0.05% cholesterol). Additionally farnesoid X receptor or LXR animal models (e.g., knockout mice) can be used to further evaluate the present compounds and compositions *in vivo* (*see*, for example, Sinal, *et al., Cell*, 102: 731-744 (2000), Peet, *et al., Cell,* 93:693-704 (1998)).

D. Methods of use of the compounds and compositions

Methods of use of the compounds and compositions provided herein are also provided. The methods involve both *in vitro* and *in vivo* uses of the compounds and compositions for altering nuclear receptor activity, including the farnesoid X receptor and/or orphan nuclear receptor activity, and for treatment, prevention, or amelioration of one or more symptoms of diseases or disorder that are modulated by nuclear receptor activity, including the farnesoid X receptor and/or orphan nuclear receptor activity, or in which nuclear receptor activity, including the farnesoid X receptor and/or orphan nuclear receptor activity, is implicated. Such compounds or compositions will typically exhibit farnesoid X receptor agonist, partial agonist, partial antagonist or antagonist activity in one of the in vitro assays described herein.

Methods of altering nuclear receptor activity, including the farnesoid X receptor, and/or orphan nuclear receptor activity, by contacting the receptor with one or more compounds or compositions provided herein, are provided.

Methods of reducing plasma cholesterol levels and of directly or indirectly modulating cholesterol metabolism, catabolism, synthesis, absorption, re-absorption, secretion or excretion are provided through administering the claimed compounds and compositions provided herein. Methods of reducing dietary cholesterol absorption (see, *e.g.*, International Patent Application Publication No. 00/40965) using the compounds and compositions are provided herein. Also provided, are methods of increasing the expression of ATP-Binding Cassette (ABCA1), thereby increasing reverse cholesterol transport in mammalian cells using the claimed compounds and compositions (see, *e.g.*, International Patent Application Publication No. WO 00/78972).

Methods of reducing plasma triglyceride levels and of directly or indirectly modulating triglyceride metabolism, catabolism, synthesis, absorption, re-absorption, secretion or excretion are provided through administering the claimed compounds and compositions provided herein.

Methods of reducing bile acid levels and of directly or indirectly modulating bile acid metabolism, catabolism, synthesis, absorption, re-absorption, secretion, excretion, or bile acid pool size or composition are provided through administering the claimed compounds and compositions provided herein.

Methods of treatment, prevention, or amelioration of one or more symptoms of a disease or disorder affecting cholesterol, triglyceride, or bile acid levels, or any combination thereof, are provided using the compounds and compositions provided herein.

Methods are provided for the treatment, prevention, or amelioration of one or more symptoms of, as well as treating the complications of, hyperlipidemia, hypercholesterolemia, dyslipidemia and lipodystrophy.

The term "hyperlipidemia" refers to the presence of an abnormally elevated level of lipids in the blood. Hyperlipidemia can appear in at least three forms: (1) hypercholesterolemia, i.e., an elevated LDL cholesterol level (120 mg/dL and above); (2) hypertriglyceridemia, i.e., an elevated triglyceride level; (150 mg/dL and above) and (3) combined hyperlipidemia, i.e., a combination of hypercholesterolemia and hypertriglyceridemia.

The term "dyslipidemia" refers to abnormal levels of lipoproteins in blood plasma including both depressed and/or elevated levels of lipoproteins (e.g., elevated levels of Low Density Lipoprotein, (LDL), Very Low Density Lipoprotein (VLDL) and depressed levels of High Density Lipoprotein (HDL) (less than 40 mg/dL)).

Methods are also provided for the treatment, prevention, or amelioration of one or more symptoms of atherosclerosis, atherosclerotic disease, atherosclerotic disease events and atherosclerotic cardiovascular diseases.

Atherosclerosis is the process in which deposits of fatty substances, cholesterol, cellular waste products, calcium and other substances build up in the inner lining of an artery. This buildup is called plaque. It initially affects large and medium-sized arteries. Some hardening of arteries often occurs when people grow older.

Plaques can grow large enough to significantly reduce the blood's flow through an artery. However significant damage to the body can also occur when the artery walls become fragile and rupture. Atherosclerotic plaques that rupture can cause blood clots to form that can block blood flow or break off and travel to another part of the body. If either happens and the blood clot blocks a blood vessel that feeds the heart, it can cause a heart attack. If the blood clot blocks a blood vessel that feeds the brain, it can cause a stroke. And if blood supply to the arms or legs is reduced, it can cause difficulty walking and eventually gangrene.

Accordingly atherosclerosis encompasses a range of vascular diseases and conditions that arise as a result of the primary disease modality. Atherosclerotic cardiovascular diseases can be recognized and understood by physicians practicing in the relevant fields of medicine and include the following: Restenosis following revascularization procedures, coronary heart disease (also known as coronary artery heart disease or ischemic heart disease), cerebrovascular disease including ischemic stroke, multi-infarct dementia, and peripheral vessel disease, including erectile dysfunction.

A compound or composition of the present invention may be administered to prevent or reduce the risk of occurrence, or recurrence where the potential exists, of coronary heart disease event, a cerebrovascular event, and /or intermittent claudication.

Coronary heart disease events are intended to include coronary heart disease death, myocardial infarction and coronary revascularization procedures. Cerebrovascular events are intended to include ischemic or hemorrhagic stroke (also

known as cerebrovascular accidents) and transient ischemic attacks. Intermittent claudication is a clinical manifestation of peripheral vessel disease.

The term "atherosclerotic disease event" as used herein is intended to encompass coronary heart disease events, cerebrovascular events, and intermittent claudication. It is intended that person who have previously experienced one or more non-fatal atherosclerotic disease events are those for whom the potential for recurrence of such an event exists.

Additionally, the instant invention also provides a method for preventing or reducing the risk of a first or subsequent occurrence of an atherosclerotic disease event comprising the administration of a prophylactically effective amount of a compound or composition of the present invention to a patient at risk for such an event. The patient may already have atherosclerotic disease at the time of administration, or may be at risk for developing it.

Risk factors for developing atherosclerotic disease events include increasing age (65 and over), male gender, a family history of atherosclerotic disease events, high blood cholesterol (especially LDL or "bad" cholesterol over 100 mg/dL), cigarette smoking and exposure to tobacco smoke, high blood pressure, Diabetes mellitus, obesity and physical inactivity.

In another aspect, the method of this invention also serves to remove cholesterol from tissue deposits such as atherosclerotic plaques or xanthomas in a patient with atherosclerotic disease manifest by clinical signs such as angina, claudication, bruits, one that has suffered a myocardial infarction or transient ischemic attack, or one diagnosed by angiography, sonography or MRI.

Methods of treatment, prevention, or amelioration of one or more of the symptoms of diabetes mellitus, as well as treating the complications of diabetes mellitus, (see, *e.g.*, International Patent Application Publication No. WO 01/82917) are also provided using the compounds and compositions provided herein.

Diabetes mellitus, commonly called diabetes, refers to a disease or condition that is generally characterized by metabolic defects in production and utilization of glucose which result in the failure to maintain appropriate blood sugar levels in the body (see, e.g., LeRoith, D. et al., (eds.), DIABETES MELLITUS (Lippincott-Raven Publishers, Philadelphia, Pa. U.S.A. 1996)).

In the case of diabetes of the type 2 form, the disease is characterized by insulin resistance, in which insulin loses its ability to exert its biological effects across a broad range of concentrations. This resistance to insulin responsiveness

results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver (see, e.g., Reaven, G. M., J. Basic & Clin. Phys. & Pharm. (1998) 9: 387-406 and Flier, J. Ann Rev. Med. (1983) 34:145-60). The resulting condition is elevated blood glucose, which is called "hyperglycemia." Uncontrolled hyperglycemia is associated with increased and premature mortality due to an increased risk for microvascular and macrovascular diseases, including retinopathy (the impairment or loss of vision due to blood vessel damage in the eyes); neuropathy (nerve damage and foot problems due to blood vessel damage to the nervous system); and nephropathy (kidney disease due to blood vessel damage in the kidneys), hypertension, cerebrovascular disease and coronary heart disease. Therefore, control of glucose homeostasis is an important approach for the treatment of diabetes.

Methods of treatment, prevention, or amelioration of one or more of the symptoms of insulin insensitivity or resistance as well as treating the complications of insulin insensitivity or resistance (see, *e.g.*, International Patent Application Publication No. WO 01/82917) are also provided using the compounds and compositions provided herein.

Methods of treatment, prevention, or amelioration of one or more of the symptoms of hyperglycemia as well as treating the complications of hyperglycemia (see, *e.g.*, International Patent Application Publication No. WO 01/82917) are also provided using the compounds and compositions provided herein.

Insulin resistance has been hypothesized to unify the clustering of hypertension, glucose intolerance, hyperinsulinemia, increased levels of triglyceride and decreased HDL cholesterol, and central and overall obesity. The association of insulin resistance with glucose intolerance, an increase in plasma triglyceride and a decrease in high-density lipoprotein cholesterol concentrations, hypertension, hyperuricemia, smaller denser low-density lipoprotein particles, and higher circulating levels of plasminogen activator inhibitor-1, has been referred to as "Syndrome X" (see, e.g., Reaven, G. M., Physiol. Rev. (1995) 75: 473-486). Accordingly, methods of treatment, prevention, or amelioration of any disorders related to diabetes, hyperglycemia or insulin resistance including the cluster of disease states, conditions or disorders that make up "Syndrome X" are provided.

Additionally the instant invention also provides a method for preventing or reducing the risk of hyperglycemia, insulin resistance or diabetes development in a

patient, comprising the administration of a prophylactically effective amount of a compound or composition of the present invention to a patient at risk for such an event. The patient may already be obese, (BMI of 30.0 or greater), overweight (BMI of 25.0 to 30.0) or possess other risk factors for developing diabetes including age, family history and physical inactivity.

Further provided herein are methods for the treatment, prevention, or amelioration of one or more symptoms of cholestasis, as well as for the treatment of the complications of cholestasis by administering a compound or composition provided herein.

Cholestasis is typically caused by factors within the liver (intrahepatic) or outside the liver (extrahepatic) and leads to the accumulation of bile salts, bile pigment bilirubin, and lipids in the blood stream instead of being eliminated normally.

Intrahepatic cholestasis is characterized by widespread blockage of small ducts or by disorders, such as hepatitis, that impair the body's ability to eliminate bile. Intrahepatic cholestasis may also be caused by alcoholic liver disease, primary biliary cirrhosis, cancer that has spread (metastasized) from another part of the body, primary sclerosing cholangitis, gallstones, biliary colic and acute cholecystitis. It can also occur as a complication of surgery, serious injury, cystic fibrosis, infection, or intravenous feeding or be drug induced. Cholestasis may also occur as a complication of pregnancy and often develops during the second and third trimesters.

Extrahepatic cholestasis is most often caused by choledocholithiasis (Bile Duct Stones), benign biliary strictures (non-cancerous narrowing of the common duct), cholangiocarcinoma (ductal carcinoma), and pancreatic carcinoma. Extrahepatic cholestasis can occur as a side effect of many medications.

Accordingly, compounds or compositions provided herein may be used for the treatment, prevention, or amelioration of one or more symptoms of intrahepatic or extrahepatic cholestasis, including without limitation, biliary artesia, obstetric cholestasis, neonatal cholestasis, drug induced cholestasis, cholestasis arising from Hepatitis C infection, chronic cholestatic liver disease such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).

Further provided by this invention are methods for treating obesity, as well as treating the complications of obesity, by administering a compound or composition of the present invention. The terms "obese" and "obesity" refers to, according to the World Health Organization, a Body Mass Index (BMI) greater than 27.8 kg/m^2 for men and 27.3 kg/m^2 for women (BMI equals weight (kg)/height (m^2).

Obesity is linked to a variety of medical conditions including diabetes and an atherosclerotic disease event. (See, e.g., Barrett-Conner, E., Epidemol. Rev. (1989) 11: 172-181; and Knowler, et al., Am. J Clin. Nutr. (1991) 53:1543-1551). Accordingly the claimed compounds or compositions that may be used for treating obesity or its complications, and can be identified, formulated, and administered as previously described above.

E. Combination Therapy

Also contemplated herein is combination therapy using one or more compounds or compositions provided herein, or a pharmaceutically acceptable derivative thereof, in combination with one or more of the following: antihyperlipidemic agents, plasma HDL-raising agents, antihypercholesterolemic agents, cholesterol biosynthesis inhibitors (such as HMG CoA reductase inhibitors, such as lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin and rivastatin), acyl-coenzyme A: cholesterol acytransferase (ACAT) inhibitors, probucol, raloxifene, nicotinic acid, niacinamide, cholesterol absorption inhibitors, bile acid sequestrants (such as anion exchange resins, or quaternary amines (*e.g.*, cholestyramine or colestipol)), low density lipoprotein receptor inducers, clofibrate, fenofibrate, benzofibrate, cipofibrate, gemfibrizol, vitamin B_6, vitamin B_{12}, anti-oxidant vitamins, β-blockers, anti-diabetes agents, angiotensin II antagonists, angiotensin converting enzyme inhibitors, platelet aggregation inhibitors, fibrinogen receptor antagonists, LXR α or β agonists, antagonists or partial agonists, aspirin or fibric acid derivatives. The compound or composition provided herein, or pharmaceutically acceptable derivative thereof, is administered simultaneously with, prior to, or after administration of one or more of the above agents. Pharmaceutical compositions containing a compound provided herein and one or more of the above agents are also provided.

Combination therapy includes administration of a single pharmaceutical dosage formulation which contains a compound of the present invention and one or more additional active agents, as well as administration of a compound of the present invention and each active agent in its own separate pharmaceutical dosage formulation. For example, a farnesoid X receptor agonist, partial agonist, partial antagonist, or antagonist of the present invention and an HMG-CoA reductase inhibitor can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosage

formulations. Where separate dosage formulations are used, the compounds described herein and one or more additional active agents can be administered at essentially the same time, *i.e.,* concurrently, or at separately staggered times, *i.e.,* sequentially; combination therapy is understood to include all these regimens.

An example of combination therapy that modulates, or prevents the onset of the symptoms, or associated complications of atherosclerosis, is administered with one or more of the following active agents: an antihyperlipidemic agent; a plasma HDL-raising agent; an antihypercholesterolemic agent, such as a cholesterol biosynthesis inhibitor, e.g., an hydroxymethylglutaryl (HMG) CoA reductase inhibitor (also referred to as statins, such as lovastatin, simvastatin, pravastatin, fluvastatin, and atorvastatin), an HMG-CoA synthase inhibitor, a squalene epoxidase inhibitor, or a squalene synthetase inhibitor (also known as squalene synthase inhibitor); an acyl-coenzyme A cholesterol acyltransferase (ACAT) inhibitor, such as melinamide; probucol; nicotinic acid and the salts thereof and niacinamide; a cholesterol absorption inhibitor, such as β-sitosterol; a bile acid sequestrant anion exchange resin, such as cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran; an LDL (low density lipoprotein) receptor inducer; fibrates, such as clofibrate, bezafibrate, fenofibrate, and gemfibrizol; vitamin B_6 (also known as pyridoxine) and the pharmaceutically acceptable salts thereof, such as the HCl salt; vitamin B_{12} (also known as cyanocobalamin); vitamin B_3 (also known as nicotinic acid and niacinamide, supra); anti-oxidant vitamins, such as vitamin C and E and beta carotene; a beta-blocker; LXR α or β agonists, antagonists, or partial agonists, an angiotensin II antagonist; an angiotensin converting enzyme inhibitor; and a platelet aggregation inhibitor, such as fibrinogen receptor antagonists (i.e., glycoprotein IIb/IIIa fibrinogen receptor antagonists) and aspirin.

A compound or composition of the present invention is preferably administered with a cholesterol biosynthesis inhibitor, particularly an HMG-CoA reductase inhibitor. The term HMG-CoA reductase inhibitor is intended to include all pharmaceutically acceptable salt, ester, free acid and lactone forms of compounds which have HMG-CoA reductase inhibitory activity and, therefore, the use of such salts, esters, free acids and lactone forms is included within the scope of this invention. Other HMG-CoA reductase inhibitors can be readily identified using assays well-known in the art. For instance, suitable assays are described or disclosed in U.S. Patent No. 4,231,938 and WO 84/02131. Examples of suitable HMG-CoA reductase inhibitors include, but are not limited to, lovastatin (MEVACOR®; *see,* U.S. Patent No.

4,231,938); simvastatin (ZOCOR®; *see,* U.S. Patent No. 4,444,784); pravastatin sodium (PRAVACHOL®; *see,* U.S. Patent No. 4,346,227); fluvastatin sodium (LESCOL®; *see,* U.S. Patent No. 5,354,772); atorvastatin calcium (LIPITOR®; *see,* U.S. Patent No. 5,273,995) and rivastatin (also known as cerivastatin; *see,* U.S. Patent No. 5,177,080). The structural formulas of these and additional HMG-CoA reductase inhibitors that can be used in the methods of the present invention are described at page 87 of M. Yalpani, "Cholesterol Lowering Drugs," *Chemistry & Industry,* pp. 85-89 (5 February 1996). In one embodiment, the HMG-CoA reductase inhibitor is selected from lovastatin and simvastatin.

Dosage information for HMG-CoA reductase inhibitors is well known in the art, since several HMG-CoA reductase inhibitors are marketed in the U.S. In particular, the daily dosage amounts of the HMG-CoA reductase inhibitor may be the same or similar to those amounts which are employed for anti-hypercholesterolemic treatment and which are described in the *Physicians' Desk Reference* (PDR). For example, see the 50th Ed. of the PDR, 1996 (Medical Economics Co); in particular, see at page 216 the heading "Hypolipidemics," sub-heading "HMG-CoA Reductase Inhibitors," and the reference pages cited therein. Preferably, the oral dosage amount of HMG-CoA reductase inhibitor is from about 1 to 200 mg/day and, more preferably, from about 5 to 160 mg/day. However, dosage amounts will vary depending on the potency of the specific HMG-CoA reductase inhibitor used as well as other factors as noted above. An HMG-CoA reductase inhibitor which has sufficiently greater potency may be given in sub-milligram daily dosages.

As examples, the daily dosage amount for simvastatin may be selected from 5 mg, 10 mg, 20 mg, 40 mg, 80 mg and 160 mg for lovastatin, 10 mg, 20 mg, 40 mg and 80 mg; for fluvastatin sodium, 20 mg, 40 mg and 80 mg; and for pravastatin sodium, 10 mg, 20 mg, and 40 mg. The daily dosage amount for atorvastatin calcium may be in the range of from 1 mg to 160 mg and, more particularly, from 5 mg to 80 mg. Oral administration may be in a single or divided doses of two, three, or four times daily, although a single daily dose of the HMG-CoA reductase inhibitor is preferred.

Diabetic patients are likely to suffer from premature development of atherosclerotic disease events and increased rate of cardiovascular and peripheral vascular diseases. Hyperlipidemia and dyslipidemia are important precipitating factors for these diseases. See, e.g., Wilson, J. et al., (ed.), Disorders of Lipid Metabolism, Chapter 23, Textbook of Endocrinology, 9th Edition, (W. B. Sanders Company, Philadelphia, Pa. U.S.A. 1998). Dyslipidemia is characterized by abnormal levels of

lipoproteins in blood plasma (e.g. elevated levels of LDL, VLDL and depressed levels of HDL), and has been shown to be one of the main contributors to the increased incidence of coronary events and deaths among diabetic subjects (see, e.g., Joslin, E. Ann. Chim. Med. (1927) 5: 1061-1079). Epidemiological studies since then have confirmed the association and have shown a several-fold increase in coronary deaths among diabetic subjects when compared with non-diabetic subjects (see, e.g., Garcia, M. J. et al., Diabetes (1974) 23: 105-11 (1974); and Laakso, M. and Lehto, S., Diabetes Reviews (1997) 5(4): 294-315).

The methods of the present invention can be used effectively in combination with one or more additional active anti-diabetes agents depending on the desired target therapy (see, e.g., Turner, N. et al. Prog. Drug Res. (1998) 51: 33-94; Haffner, S. Diabetes Care (1998) 21: 160-178; and DeFronzo, R. et al. (eds.), Diabetes Reviews (1997) Vol. 5 No. 4).

A number of studies have investigated the benefits of combination therapies with oral agents (see, e.g., Mahler, R., J. Clin. Endocrinol. Metab. (1999) 84: 1165-71; United Kingdom Prospective Diabetes Study Group: UKPDS 28, Diabetes Care (1998) 21: 87-92; Bardin, C. W.,(ed.), CURRENT THERAPY IN ENDOCRINOLOGY AND METABOLISM, 6th Edition (Mosby-Year Book, Inc., St. Louis, Mo. 1997); Chiasson, J. et al., Ann. Intern. Med. (1994) 121: 928-935; Coniff, R. et al., Clin. Ther. (1997) 19: 16-26; Coniff, R. et al., Am. J. Med. (1995) 98: 443-451; and Iwamoto, Y. et al, Diabet. Med. (1996) 13 365-370; Kwiterovich, P. Am. J. Cardiol (1998) 82(12A): 3U-17U). These studies indicate that the modulation of hyperlipidemia associated with diabetes can further improve the treatment outcome of diabetics.

Accordingly, another combination therapy claimed herein is suitable for treating diabetes and its related symptoms, complications, and disorders, and includes the co-administration of the compounds or compositions provided herein with for example, sulfonylureas (such as chlorpropamide, tolbutamide, acetohexamide, tolazamide, glyburide, gliclazide, glynase, glimepiride, and glipizide), biguanides (such as metformin), thiazolidinediones (such as ciglitazone, pioglitazone, troglitazone, and rosiglitazone); and related insulin sensitizers, such as selective and non-selective activators of PPARα, PPARβ, and PPARγ; LXR α or β agonists, antagonists and partial agonists, dehydroepiandrosterone (also referred to as DHEA or its conjugated sulphate ester, DHEA-SO_4); antiglucocorticoids; TNFα-inhibitors; α-glucosidase inhibitors (such as acarbose, miglitol, and voglibose), pramlintide (a synthetic analog of the human hormone amylin), other insulin secretogogues (such as repaglinide, gliquidone, and

nateglinide), insulin, as well as the active agents discussed above for treating atherosclerosis.

Another example of combination therapy claimed herein is the co-administration of the claimed compounds or compositions provided herein with compounds or compositions for treating obesity or obesity-related disorders, wherein the claimed compounds can be effectively used in combination with, for example, phenylpropanolamine, phentermine, diethylpropion, mazindol; fenfluramine, dexfenfluramine, phentiramine, β_3 adrenoceptor agonist agents; sibutramine, gastrointestinal lipase inhibitors (such as orlistat), LXR α or β agonists, antagonists and partial agonists, and leptins. Other agents used in treating obesity or obesity-related disorders include neuropeptide Y, enterostatin, cholecytokinin, bombesin, amylin, histamine H_3 receptors, dopamine D_2 receptors, melanocyte stimulating hormone, corticotrophin releasing factor, galanin and gamma amino butyric acid (GABA).

Another example of a claimed combination therapy is the co-administration of the claimed compound or composition provided herein with compounds or compositions for treating cholestasis and its related symptoms, complications, and disorders. Such co-administered compounds include for example, Actigall (Ursodeoxycholic acid - UDCA), corticosteroids, anti-infective agents (Rifampin, Rifadin, Rimactane), anti-viral agents, Vitamin D, Vitamin A, phenobarbital, cholestyramine, UV light, antihistamines, oral opiate receptor antagonists and biphosphates, for the treatment, prevention, or amelioration of one or more symptoms of intrahepatic or extrahepatic cholestasis. Dosage information for these agents is well known in the art.

F. Preferred Embodiments

In one preferred embodiment, the compound is a compound of formula (I) in the Summary of the Invention, where:

a) R^4 and R^5 are each independently selected from hydrogen or halo; and R^6 and R^7 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$, and

$-R^{21}-SC(J)R^{10}$; or R^6 and R^7, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene;

b) R^4 and R^5 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; or R^4 and R^5, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, an optionally substituted cycloalkenyl ring, an optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene; and R^6 and R^7 are each independently selected from hydrogen or halo; or

c) R^4 and R^6 are each independently selected from hydrogen or halo; and R^5 and R^7 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$;

d) R^4 is hydrogen or halo; R^5 is selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; and R^6 and R^7 are each independently selected from a group consisting of hydrogen, halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted

cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; or R^6 and R^7, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene;

e) R^4 and R^5 are each independently selected from a group consisting of hydrogen, halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; or R^4 and R^5, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene; R^6 is hydrogen or halo; and R^7 is selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$;

f) R^4 and R^5 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; or R^4 and R^5, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally

substituted heterocyclyl, an optionally substituted cycloalkenyl ring, an optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene; and R^6 and R^7 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$, and $-R^{21}-SC(J)R^{10}$; or R^6 and R^7, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene; and R^{1-3}, R^{8-26} and R^{32-34} are as defined in the Summary of the Invention.

In another preferred embodiment, R^4, R^5, R^6 and R^7 cannot all be hydrogen.

In another preferred embodiment, the compound is a compound of formula (I) wherein R^4 and R^5 are hydrogen, and R^6 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ or $-R^{21}-SC(J)R^{10}$;

R^7 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ or $-R^{21}-SC(J)R^{10}$; or

R^6 and R^7, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted

cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene.

In another preferred embodiment, R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ or $-R^{21}-SC(J)R^{10}$;

and R^4 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ or $-R^{21}-SC(J)R^{10}$; or R^4 and R^5 together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, an optionally substituted cycloalkenyl ring, an optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene; and R^6 and R^7 are hydrogen.

In another preferred embodiment, the compound is a compound having the formula (I) wherein R^4, R^5, R^6 and R^7 are selected from g) and h) below:

g) R^4 and R^5 are hydrogen, and R^6 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ or $-R^{21}-SC(J)R^{10}$;

R^7 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ or $-R^{21}-SC(J)R^{10}$; or

R^6 and R^7, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally

substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene.

h) R^5 is optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ or $-R^{21}-SC(J)R^{10}$;

R^4 is hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ or $-R^{21}-SC(J)R^{10}$; or R^4 and R^5 together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, an optionally substituted cycloalkenyl ring, an optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene; and R^6 and R^7 are hydrogen;

R^{8a}, R^{8b}, R^{8c} and R^{8d} are each independently selected from the group consisting of hydrogen, halo, pseudohalo, cyano, azido, amidino, guanidino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-R^{21}-OR^{22}$, $-R^{21}-SR^{22}$, $-R^{21}-N(R^{23})(R^{24})$, $-R^{21}-C(J)R^{22}$, $-R^{21}-C(J)OR^{22}$, $-R^{21}-C(J)SR^{22}$, $-R^{21}-C(J)N(R^{23})(R^{24})$, $-R^{21}-N(R^{25})S(O)_2R^{26}$ and $-R^{21}-S(O)_2N(R^{23})(R^{24})$;

R^{21} is a alkylene or a direct bond;

each R^{22} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted

heteroaralkyl, -R^{21}-OR^{32}, -R^{21}-SR^{32}, -R^{21}-$N(R^{33})(R^{34})$, -R^{21}-$C(J)R^{32}$, -R^{21}-$C(J)OR^{32}$, -R^{21}-$C(J)SR^{32}$, and-R^{21}-$C(J)N(R^{33})(R^{34})$; and

R^{23} and R^{24} are independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, -R^{21}-OR^{32}, -R^{21}-SR^{32}, -R^{21}-$N(R^{33})(R^{34})$, -R^{21}-$C(J)R^{32}$, -R^{21}-$C(J)OR^{32}$, -R^{21}-$C(J)SR^{32}$ and -R^{21}-$C(J)N(R^{33})(R^{34})$;

or R^{23} and R^{24}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl.

G. Preparation of the Compounds of the Invention

Starting materials in the synthesis examples provided herein are either available from commercial sources or via literature procedures (*e.g.*, March *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, (1992) 4th Ed.; Wiley Interscience, New York). All commercially available compounds were used without further purification unless otherwise indicated. $CDCl_3$ (99.8% D, Cambridge Isotope Laboratories) was used in all experiments as indicated. Proton (^1H) nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. Significant peaks are tabulated and typically include: number of protons, and multiplicity (s, singlet; d, double; t, triplet; q, quartet; m, multiplet; br s, broad singlet). Chemical shifts are reported as parts per million (δ) relative to tetramethylsilane. Low resolution mass spectra (MS) were obtained as electrospray ionization (ESI) mass spectra, which were recorded on a Perkin-Elmer SCIEX HPLC/MS instrument using reverse-phase conditions (acetonitrile/water, 0.05% trifluoroacetic acid). Flash chromatography was performed using Merck Silica Gel 60 (230-400 mesh) following standard protocol (Still *et al.* (1978) *J. Org. Chem. 43*:2923).

It is understood that in the following description, combinations of substituents and/or variables of the depicted formulae are permissible only if such contributions result in stable compounds under standard conditions.

It will also be appreciated by those skilled in the art that in the process described below the functional groups of intermediate compounds may need to be

protected by suitable protecting groups. Such functional groups include hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (*e.g.*, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for amino, amidino and guanidino include *t*-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for mercapto include -C(O)-R (where R is alkyl, aryl or aralkyl), *p*-methoxybenzyl, trityl and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or aralkyl esters.

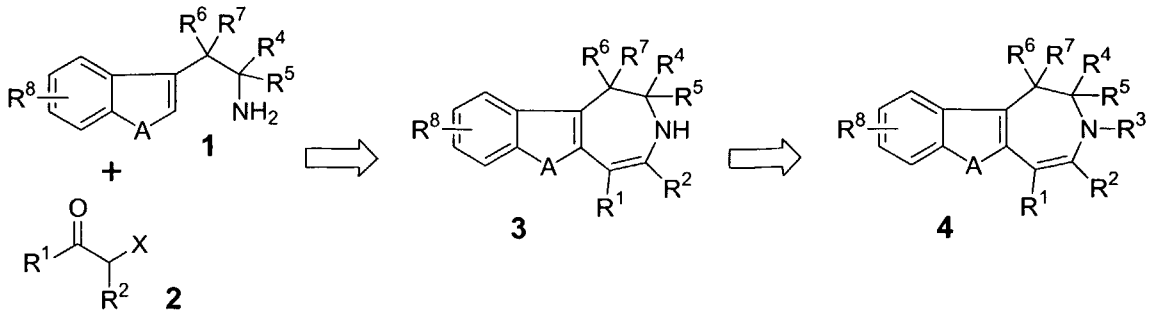
Protecting groups may be added or removed in accordance with standard techniques, which are well-known to those skilled in the art and as described herein. The use of protecting groups is described in detail in Green, T.W. and P.G.M. Wutz, *Protective Groups in Organic Synthesis* (1991), 2nd Ed., Wiley-Interscience.

In the following Schemes, unless otherwise noted, the various substituents $R^{1\text{-}26}$, and $R^{32\text{-}34}$ are as defined above in the Summary of the Invention, X is halo and Y is O, N or S, and A is S, O or NH. R^8 groups in the following schemes also correspond to the R^8 groups in the Summary of the Invention which are more specifically designated as R^{8a}, R^{8b}, R^{8c} and R^{8d}. One of ordinary skill in the art could easily ascertain which choices for each substituent are possible for the reaction conditions of each Scheme. Moreover, the substituents are selected from components as indicated in the specification heretofore, and may be attached to starting materials, intermediates, and/or final products according to schemes known to those of ordinary skill in the art.

Also it will be apparent that many of the products could exist as one or more isomers, that is E/Z isomers, enantiomers and/or diastereomers.

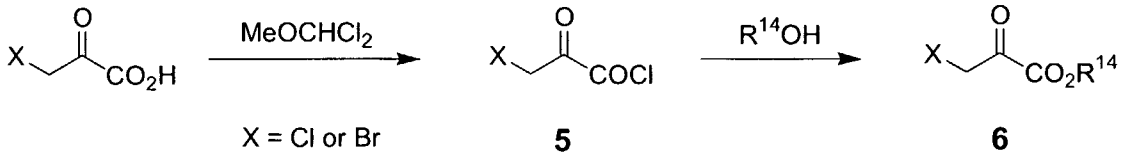
Scheme 1 below depicts the synthesis of compounds of formula (I). In general, heteroar-3-yl-2-ethylamines (**1**) are condensed with haloketones (**2**) (or haloaldehydes) and undergo subsequent rearrangement to give azepines (**3**), which then can react with electrophiles to afford products (**4**) of formula I. In particular, heteroar-3-yl-2-ethylamines **1** (R^4-R^8 as above) consist of optionally substituted tryptamines (A = NH), benzofuran-3-yl (A = O) and benzo[b]thiophene-3-yl-2-ethylamines (A = S). By example, a haloketone **2** can be chloro- or bromopyruvate (R^1 = CO_2R and R^2 = H) and the electrophiles can be acyl or sulfonyl chlorides, chloroformates, isocyanates or isothiocyanates (R^3 = COR, SO_2R, CO_2R, CONRR' and CSNRR', respectively).

SCHEME 1



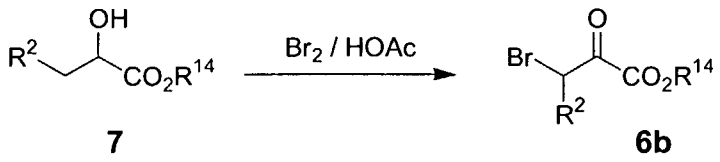
Many haloketones **2** (e.g. R^1 and R^2 = alkyl or aryl) are commercially available and can be prepared readily *via* common literature procedures. In addition, as depicted in Scheme 2 below, various 3-halopyruvates (**6**, R^2 = H) can be prepared by esterification of the corresponding alcohols (R^1OH) with 3-halopyruvic chloride (**5**) (Teague, *et al*, *Bioorg. & Med. Chem. Lett.* **1995**, *5*, 2341-2346).

SCHEME 2



As depicted in Scheme 3 below, higher 3-halopyruvates **6b** (e.g. R^2 = alkyl) can be synthesized *via* oxidative bromination of α-hydroxyesters (**7**) (*Heterocycles* **1991**, *32*, 693). While the non-hydrogen R^2 substituent can be incorporated into the final azepine products of formula I (e.g. **4**), the following Schemes will feature examples that have been simplified by omission of R^2.

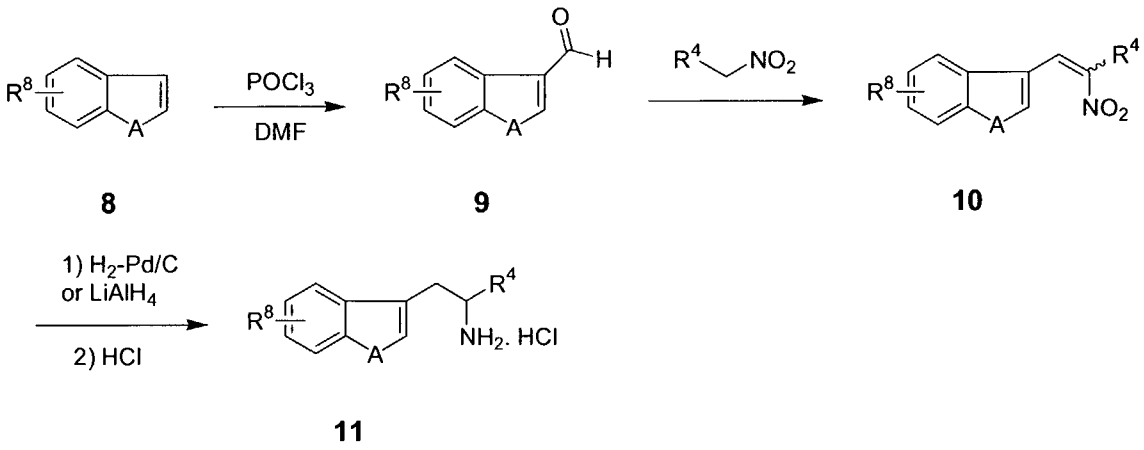
SCHEME 3



Some substituted tryptamines (**11**, A = NH) are commercially available, though many can be prepared from indoles (**8**, A = NH) as depicted in Scheme 4 below. For example, indoles **8** can be formylated to give aldehydes (**9**, A = NH) (Mor

et al. J. Med. Chem. **1998**, *41*, 3831-3844). These 3-formylindoles **9** can undergo a Henry reaction (Rosini *Comp. Org. Syn.* **1991**, *2*, 321-340) with 1-nitroalkanes to afford nitroalkenes (**10**, A = NH), which can be reduced (i.e., catalytic hydrogenation or lithium aluminum hydride) and then treated with HCl to yield tryptamine hydrochlorides **11**. Likewise, other substituted heteroar-3-yl-2-ethylamines **11** (A = O or S) can be synthesized from their corresponding heterocycle **8**, i.e. benzofurans and benzothiophenes. A variety of indoles also can be prepared *via* Fischer indole synthesis (Smith & March, *March's Advanced Organic Chemistry*, 5th Ed., John Wiley and Sons:NY, **2001,** pp1453-24).

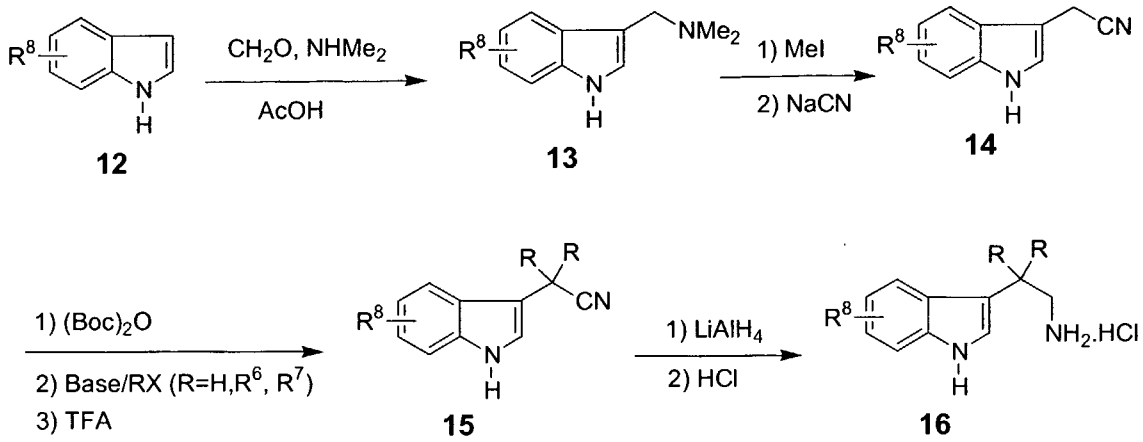
SCHEME 4



As depicted in Scheme 5 below, other substituted tryptamines (**16**) also can be prepared. Protection of 3-indolylacetonitriles (**14**), for example, with Boc (*tert*-butoxycarbonyl) followed by mono- or dialkylation, and then deprotection can yield substituted 3-indolylacetonitriles (**15**). Reduction of **15**, e.g. with lithium aluminum hydride, followed by treatment with HCl affords tryptamine hydrochlorides **16**. Thus, for example, monoalkyl species **15** (e.g. R_2 = H, R^6) can be prepared by addition of 1 equiv of alkyl halide. *Gem*-dialkyl species **15** (R = R^6 = R^7) can be prepared from 2 equiv of alkyl halide and hetero-dialkyl species **15** (R_2 = R^6,R^7) can be prepared upon sequential addition of 1 equiv each of two alkyl halides. Intermediates **14** can be prepared readily from gramines (**13**), which are either commercially available or synthesized from indoles (**12**) (Brown and Carrison, *J. Chem. Chem. Soc.* **1955,** *77*, 3839-3842). In general, gramines (**13**) can be treated with methyl iodide to form a quaternary ammonium salt, which can be displaced with cyanide to give 3-indolylacetonitriles **14**. Benzofuran-3-yl and benzo[b]thiophene-3-yl ethylamines **7**

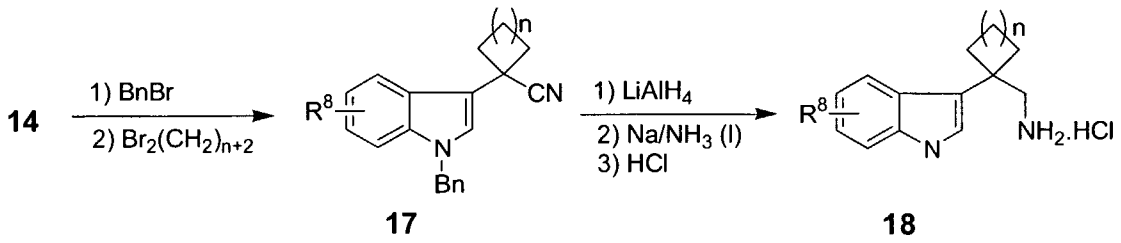
(A = O and S) can be prepared using similar methods, in which protection and deprotection steps are not required.

SCHEME 5



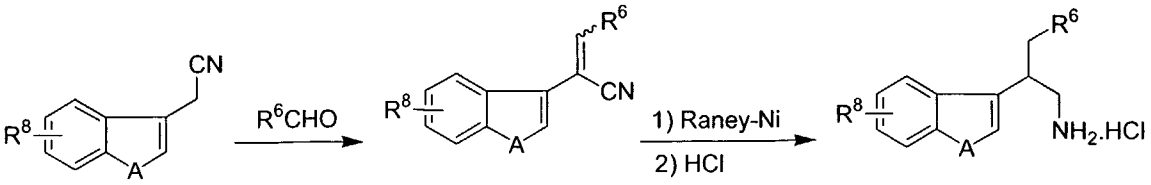
Preparation of spirocyclic analogs (**18**) of tryptamine also can be achieved as depicted in Scheme 6 below. For example, intermediate **14** can be protected with benzyl bromide followed by alkylation with an alkyl dihalide, e.g. 1,4-dibromobutane, to afford the corresponding intermediate (**17**, n = 2). Subsequently **17** can be reduced, deprotected (e.g. with sodium metal in liquid ammonia) and treated with HCl to yield the spiro-substituted tryptamine hydrochloride **18**.

SCHEME 6



As depicted in Scheme 7 below, substituted tryptamines (**21**, A = NH) can also be prepared by Knoevenagel condensation of 3-indolylacetonitrile (**19**, A = NH) with an aldehyde to afford acrylonitriles (**20**, A = NH). Subsequent reduction, e.g. Raney nickel, and treatment with HCl can yield tryptamine hydrochlorides **21**. Analogous benzofuran-3-yl and benzo[b]thiophene-3-yl ethylamines **21** (A = O and S) also can be prepared using similar methods.

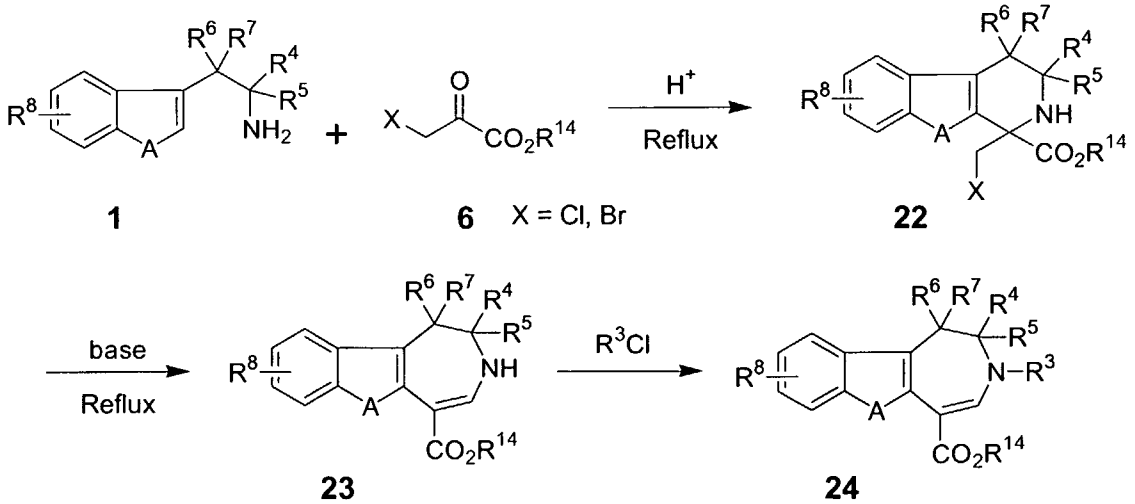
SCHEME 7



19 20 21

As depicted in Scheme 8 below, the azepine ring found in compounds of formula I (e.g. **23**) can be achieved by a Pictet-Spengler reaction and a subsequent rearrangement. Thus, for example, tryptamines **1** (A = NH) can react with a ketone such as 3-halopyruvates **6** to afford β-carboline intermediates (**22**), which are then heated under basic conditions, i.e. with TEA or in pyridine, to give azepines (**23**) (Kuehne *et al.* (1985) *J. Org. Chem. 50*:919-924). Subsequent treatment of **23** with electrophiles, i.e. acyl or sulfonyl chlorides, isocyanates and chloroformates, in the presence of a base, e.g. TEA, affords final products **24**. These intermediates **23** and products **24** can be further derivatized to yield additional compounds of formula I, as described in subsequent Schemes. In addition, azepino[4,5-*b*]benzofurans (**24**, A = O) and azepino[4,5-*b*]benzothiophenes (**24**, A = S) can be prepared in a similar manner from the respective heteroar-3-yl-2-ethylamines **1** (A = O and S).

SCHEME 8

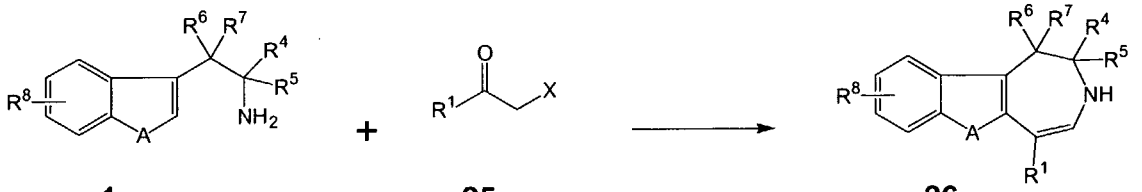


1 6 X = Cl, Br 22

23 24

Likewise other haloketones **25** (e.g. R^1 = alkyl or aryl) can undergo a similar reaction sequence to afford the corresponding azepines (**26**), as depicted in Scheme 9 below.

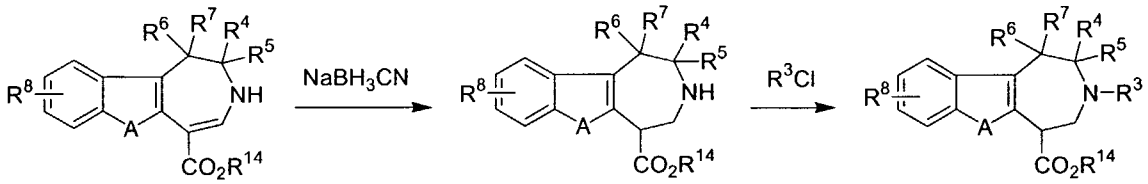
SCHEME 9



1 **25** **26**

As depicted in Scheme 10 below, hexahydroazepino compounds (**25**) can be synthesized by reduction of azepines **23**. For example, tetrahydroazepino[4,5-*b*]indoles **23** can be reduced with $NaBH_3CN$ to give hexahydroazepino[4,5-*b*]indoles **25** (Kuehne *et al.* (1985) *J. Org. Chem. 50*:919-924), which can be treated with an electrophile, e.g. acyl chloride, to afford the corresponding azepine product (**26**).

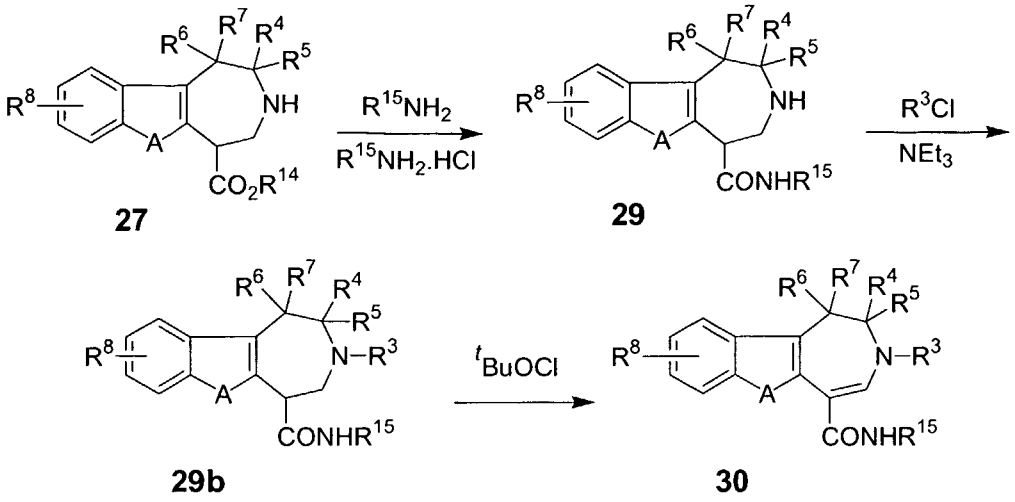
SCHEME 10



23 **27** **28**

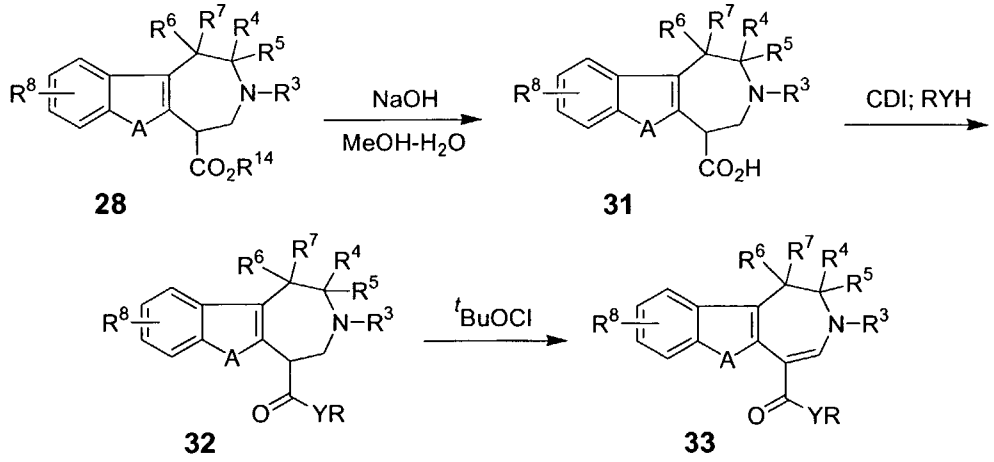
As depicted in Scheme 11 below, 5-esters **27** can be converted to 5-amides (**30**) *via* a multi-step reaction sequence. Azepine **27** can be treated with various amines to give the corresponding amides (**29**), which can then be reacted with an electrophile, e.g. an acyl chloride to afford the corresponding amide (**29b**). Oxidation of **29b** with *tert*-butyl hypochlorite (Kuehne *et al.* (1985) *J. Org. Chem. 50*:919-924) then can yield the azepine product (**30**).

SCHEME 11



A more general approach for modification of the 5-ester group is depicted in Scheme 12 below. Azepine **28** can be saponified to give the respective acid (**31**). A nucleophile RYH (i.e. alcohols, phenols, amines, thiols) can be coupled with **31**, e.g. using carbonyldiimidazole (CDI), followed by oxidation with *tert*-butyl hypochlorite to yield azepine (**33**).

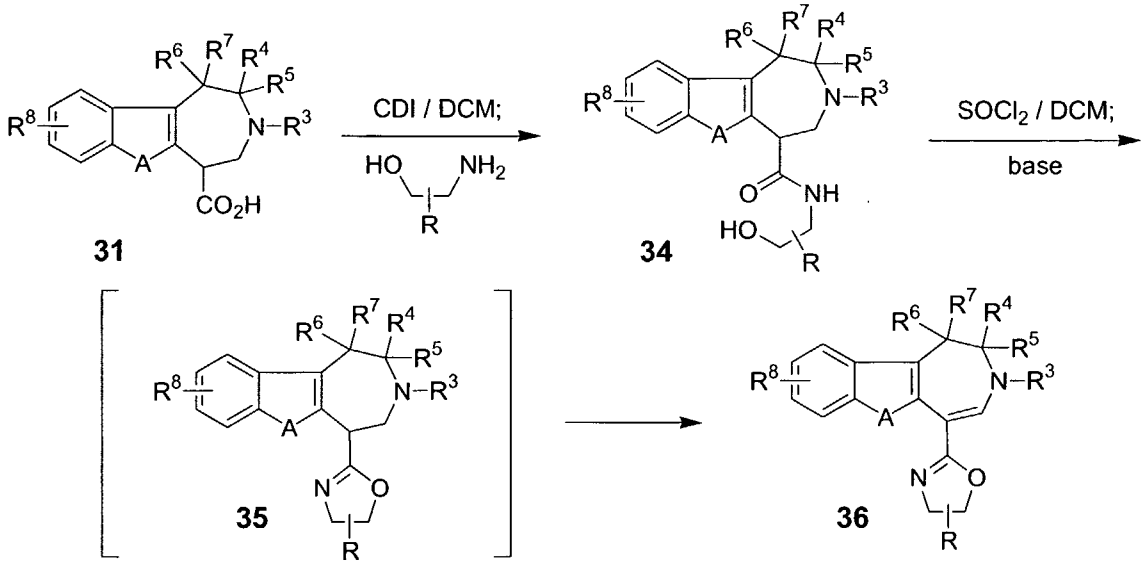
SCHEME 12



Heterocyclyl groups can be introduced at 5-position from acid **31**. For example, as depicted in Scheme 13 below, oxazolines are prepared by formation of amides (**34**) from respective aminoalcohols and acid **31**. The resulting amides **34** then can be cyclized, e.g. *via* treatment with thionyl chloride followed by strong base, to

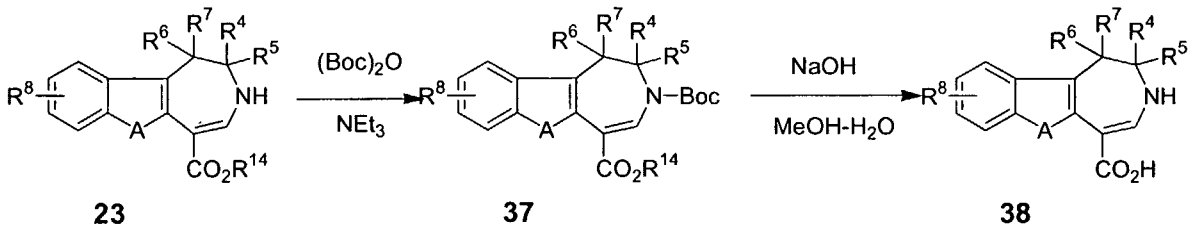
afford the corresponding heterocycle (**36**). Halogenation and subsequent dehydrohalogenation of intermediate (**35**) (not isolated) can occur under the reaction conditions. Similar reactions can be envisaged for other heterocycles, i.e. imidazolines and thiazolines. Also further oxidation would afford the corresponding heteroaromatic product, e.g. oxazole.

SCHEME 13



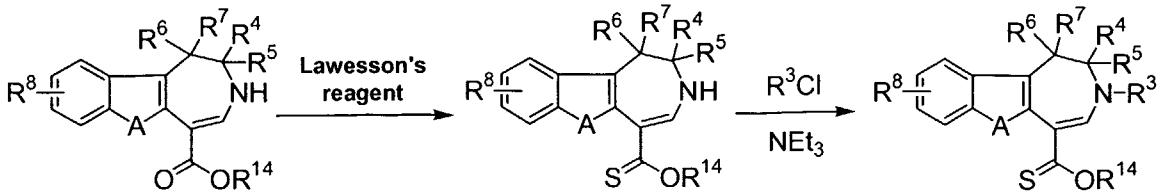
The 5-ester group of **23** can be hydrolyzed to give 5-carboxylic acid (**38**). However, direct hydrolysis affords **38** in low yield. Accordingly, as depicted in Scheme 14 below, azepine **23** was transformed into the 3-Boc-protected compound (**37**), which can be hydrolyzed under the standard basic conditions with Boc elimination to afford acid **38**.

SCHEME 14



As depicted in Scheme 15 below, azepine **23** can be treated with Lawesson's reagent (Curphey, *et al*, *J. Org. Chem.* **2002**, *67*, 6461-6473) to afford *O*-alkyl thioester (**39**), which can be, for example, acylated to yield the azepine product (**40**).

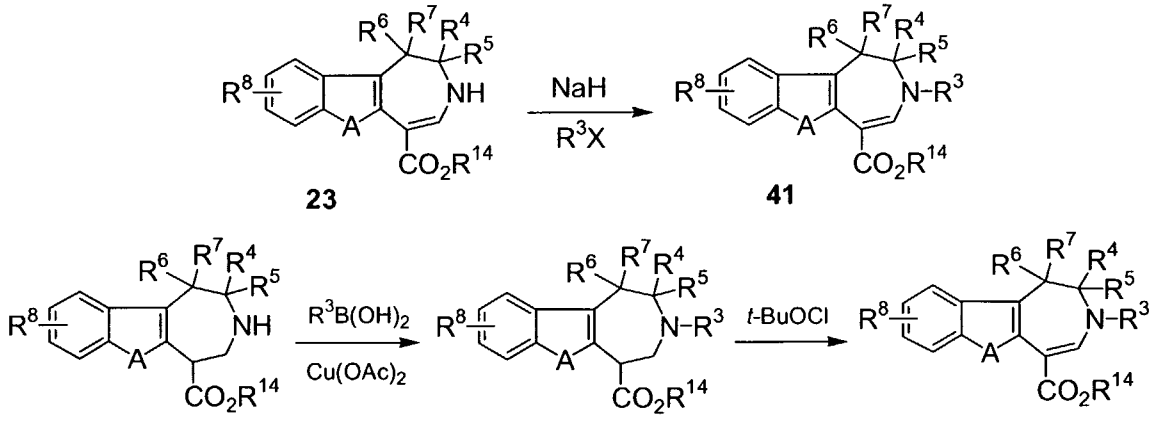
SCHEME 15



22 39 40

Scheme 16 below depicts the incorporation of 3-alkyl/aryl groups. For example, azepine **23** can be treated with a base, e.g. NaH, and then an alkyl halide (R^3X) to yield a 3-alkyl azepine (**41**). An aryl or heteroaryl group (R^3) can be introduced *via* coupling of **27** with boronic acids (Lam, *et al*, *Tetrahedron Lett.* **2001**, *42*, 3415-3418), followed by oxidation of intermediate (**42**) to give the corresponding azepine product (**43**).

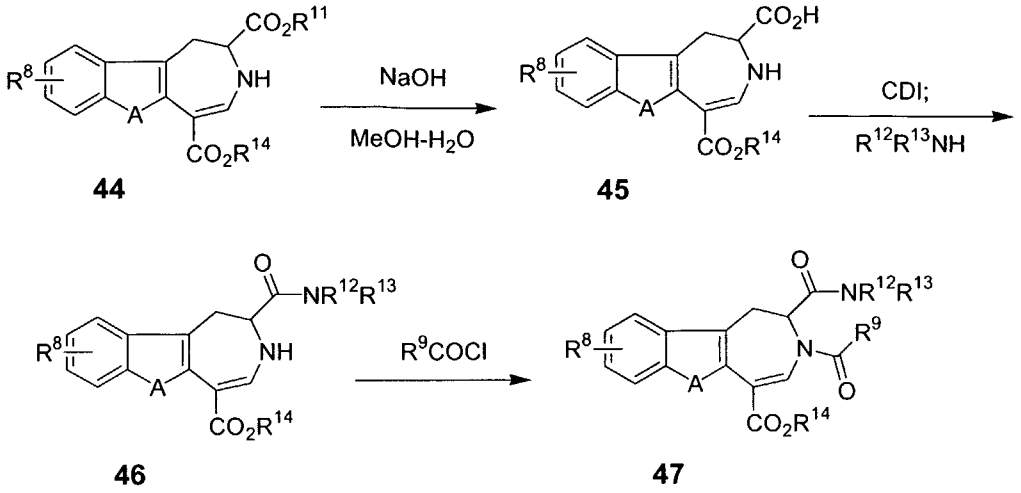
SCHEME 16



23 41 27 42 43

Derivatization of 2-substituted azepines (**44**) is depicted in Scheme 17 below. Diester (**44**) can be partially hydrolyzed to give acid (**45**), which can be transformed into amides (**46**), e.g. using CDI. Intermediates **46** can be further substituted upon addition of an electrophile, e.g. acyl chloride, to give the corresponding diamides (**47**).

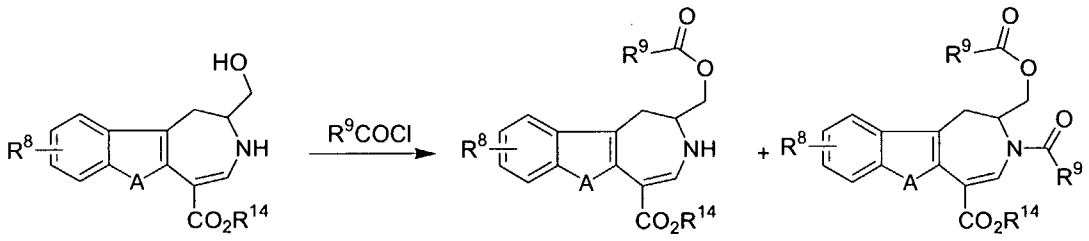
SCHEME 17



44 45 46 47

As depicted in Scheme 18 below, alcohol (**48**) can be derivatized by addition of an electrophile (i.e. acyl chloride, chloroformate or isocyanate). For example, **48** can be esterified in the presence of base to yield diester (**49**), though a mixture containing diester-amide (**50**) may result.

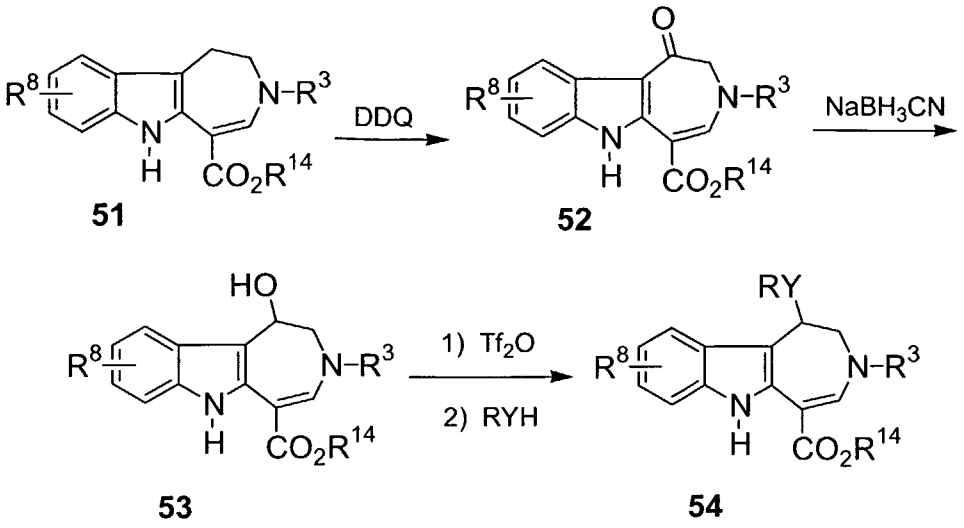
SCHEME 18



48 49 50

As depicted in Scheme 19 below, 1-oxoazepines (**52**) can be employed as key intermediates for introduction of other functional groups. For example, azepine (**51**) can be oxidized, e.g. with DDQ, to yield1-oxoazepine **52**, which can be reduced to give the corresponding alcohol (**53**). Treatment of **53** with trifluoromethanesulfonic anhydride followed by addition of nucleophiles RYH (alcohols, thiols, amines, hydroxylamines and hydrazines) can yield the corresponding azepine products (**54**).

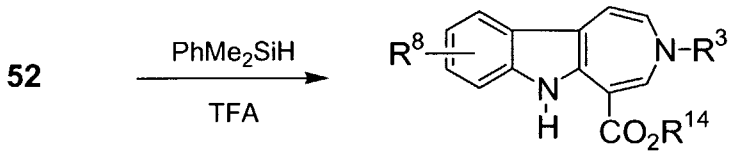
SCHEME 19



51 52 53 54

As depicted in Scheme 20 below, 1-oxoazepine **52** can be converteded, e.g. with dimethylphenylsilane in TFA, to the corresponding azepine (**55**).

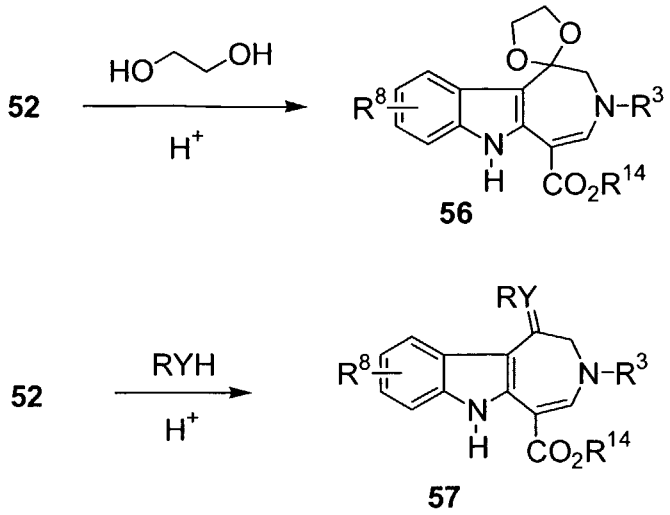
SCHEME 20



55

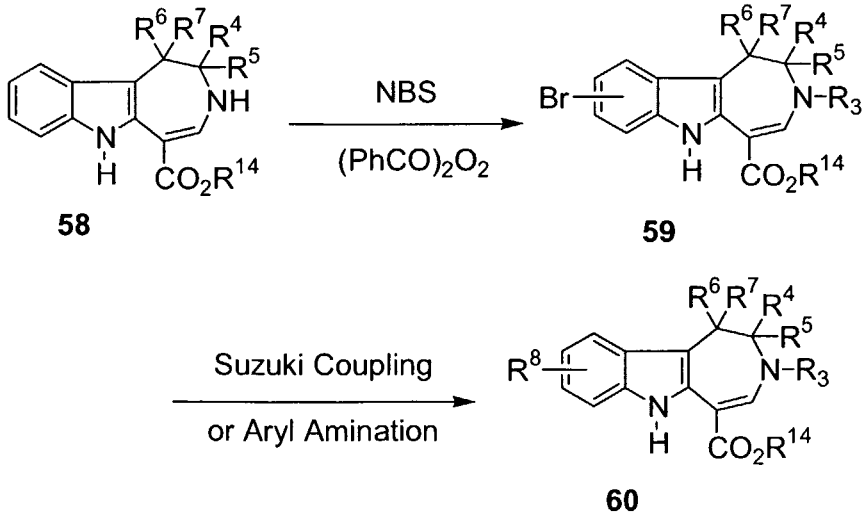
Likewise, as depicted in Scheme 21 below, 1-oxoazepine **52** can be treated with ethylene glycol under acid-catalysis to form cyclic acetal (**56**). Also **52** can be treated with amines, hydroxylamines and hydrazines to give imines (**57**, YR = NR^{15}), oximes (**57**, YR = NOR^{14}) and hydrazones (**57**, YR = $NNR^{15}R^{16}$), respectively. Furthermore **52** can undergo a Wittig or Horner-Wadsworth-Emmons reaction (Maercker (1965) *Org. React. 14*:270-490; Wadsworth, Jr. (1977) *Org. React. 25*:73-253) to yield exocyclic alkylidenes (**57**, e.g. YR = CRR').

SCHEME 21



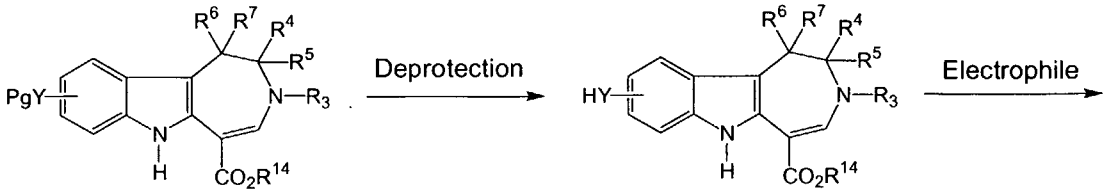
As depicted in Scheme 22 below, substituents on the indole ring can be introduced, i.e. *via* Suzuki cross-coupling and aryl amination reactions from the corresponding aryl bromides (**59**). Bromo-substituted indoles **59** can be prepared *via* direct bromination of indoles (**58**) with NBS or from commercially available tryptamine. These intermediates **59** can be used in Suzuki cross-coupling reactions (Miyaura, *et al*, *Chem. Rev.* **1995**,956, 2457-2483) with boronic acids to afford, for example, aryl-substituted products (**60**, R^8 = aryl) and in aryl amination reactions (Wolfe, *et at, J. Org. Chem.* **2000**, *65*, 1144-1157) to afford amino-substituted products (**60**, $R^8 = NR^{28}R^{29}$).

SCHEME 22

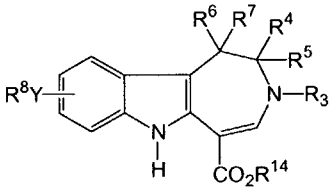


As depicted in Scheme 23 below, other transformations of functional groups can be achieved, for example, on the indole ring of azepine (**61**). Protective groups, such as alkyl and aryl groups, on oxygen, sulfur or nitrogen containing substituents of azepine **61** can be removed under suitable conditions to yield azepine (**62**). Treatment of **62** with electrophiles, such as carbamoyl chlorides, can yield the corresponding azepines (**63**), for which the substituent R^8 is $C(O)NR^{32}R^{33}$ in this representative example.

SCHEME 23



61 Y = NR or O **62**
Pg = Protecting group



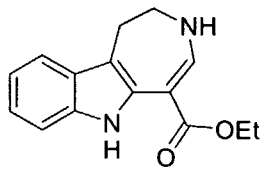
63

The following examples are provided for illustrative purposes only and are not intended to limit the scope of the invention.

EXAMPLES

EXAMPLE 1

PREPARATION OF ETHYL 1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. A mixture of tryptamine hydrochloride (1.96 g, 10 mmol), ethyl 3-bromopyruvate (1.67 mL, 1.2 equiv) and decolorizing charcoal (0.5 g) in absolute

ethanol was heated to reflux under nitrogen overnight. TEA was added and the reaction mixture was heated to reflux for another 7.5 hours. After cooling, charcoal was removed by filtration and washed with ethanol. The filtrate was concentrated under vacuum and diluted with water (20 mL). It was then extracted by EtOAc (3×30 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of solvent and recrystallization from DCM-Hexane gave the title compound (1.17g). ^{1}H-NMR ($CDCl_3$): δ 10.49 (1 H, br s), 7.79 (1H, d), 7.43 (1H, d), 7.43 (1 H, d), 7.06 (2H, m), 5.27 (1H, br s), 4.29 (2H, q) 3.58 (2H, m), 3.17 (2H, m), 1.36 (3H, t); MS (ES): 257 (MH^+).

B. In a similar manner, but replacing tryptamine hydrochloride with the appropriately substituted tryptamine, the following compounds were prepared:

ethyl 9-methoxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.36 (1H, br s), 7.80 (1H, d), 7.21 (1H, d), 6.87 (1H, d), 6.75 (1H, dd), 5.28 (1H, br s), 4.27 (2H, q), 3.86 (3H, s), 3.62 (2H, m), 3.14 (2H, t), 1.34 (3H, t); MS (ES): 287 (MH^+);

ethyl 8-methoxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate;

ethyl 9-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.50 (1H, br s), 7.82 (1 H, d), 7.20 (1H, dd), 7.03 (1H, dd), 6.81 (1H, m), 5.30 (1H, br s), 4.27 (2H, q), 3.61 (2H, m), 3.11 (2H, t), 1.34 (3 H, t); MS (ES): 275 (MH^+);

ethyl 9-chloro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.56 (1H, br s), 7.82 (1H, d), 7.35 (1 H, d), 7.21 (1H, d), 7.14 (1H, dd), 5.34 (1H, br s), 4.26 (2H, q), 3.58 (2H, m), 3.10 (2H, m), 1.34 (1 H, t); MS (ES): 290 (MH^+);

ethyl 8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.51 (1H, br s), 7.79 (1H, d), 7.28 (1H, dd), 6.99 (1H, dd), 6.80 (1H, m), 4.27 (2H, q), 3.59 (2H, m), 3.14 (2H, m), 1.34 (1H, t); MS (ES): 274 (MH^+);

ethyl 7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.43 (1H, br s), 7.82 (1H, d), 7.27 (1 H, m), 6.98 (1H, m), 6.89 (1H, d), 5.29 (1H, br s), 4.27 (2H, q), 3.61 (2H, m), 3.17 (2H, t), 2.51 (3H, s), 1.36 (3H, t); MS (ES): 271 (MH^+);

9-hydroxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 273 (MH^+);

9-bromo-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester ^{1}H-NMR ($CDCl_3$): δ 10.37 (1H, s), 7.62 (1H, d), 7.31 (1H, d), 6.96 (2H, m), 5.13(1H, s), 4.17 (2H, dd), 3.38 (2H, m), 2.90 (2H, m), 1.13 (3H, t); MS (ESI): 335, 337 (MH^+);

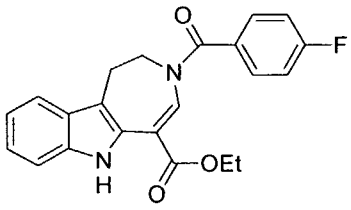
7-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 275 (MH^+);

7-benzyloxy1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; and

10-benzyloxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester and 4-benzyloxytryptamine hydrochloride.

EXAMPLE 2

PREPARATION OF ETHYL 3-(4-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. To a solution of ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (Example 1, 52 mg, 0.2 mmol) in DCM was added 4-fluorobenzoyl chloride (36 µL, 0.2 mmol) and TEA (56 µL, 0.4 mmol) and the mixture was shaken overnight at 20°C. Trisamine resin (50 mg) was added and the suspension was shaken for 2 hours at 20°C. The resin was removed by filtration through a Florisil® cartridge. Evaporation of solvent gave a crude product, which was purified by trituration with methanol to give the title compound (28 mg); ^{1}H-NMR ($CDCl_3$): δ 10.31 (1H, br s), 7.79 (1H, s), 7.41 (2H, m), 7.36 (1H, d), 6.90-7.04 (5H, m), 3.99-4.06 (4H, m), 3.06 (2H, t), 1.02 (3H, t); MS (ES): 379 (MH^+).

B. In a manner similar to that described in Step A, but using the appropriately substituted ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate in Example 1B, the following compounds were prepared:

3-(4-fluorobenzoyl)-9-hydroxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester. ^{1}H-NMR ($CDCl_3$): δ 10.57 (1H, s), 8.26 (1H, m), 7.83 (1H,

d), 7.32-7.16 (5H, m), 6.88 (1H, d), 5.35 (1H, s), 4.28 (2H, q), 3.62 (2H, m), 3.14 (2H, m), 1.35 (3H, t). MS (ES): 395 (MH+);

7-fluoro-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 397 (MH^+);

7-benzyloxy-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 485 (MH^+); and

10-benzyloxy-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 485 (MH^+).

C. In a manner similar to Step A, but replacing ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with 10-benzyloxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester and 4-fluorobenzoyl chloride with 3,4-difluorobenzoyl chloride, the following compound was prepared:

10-benzyloxy-3-(3,4-difluorobenzoyl)-1,2,3,6-tetrahydroazepino [4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 503 (MH^+).

D. In a manner similar to Step A, but replacing ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with 5,6,7,12- tetrahydrobenzo [2,3]azepino[4,5-*b*]indole, the following compound was prepared:

(6,7-Dihydro-12H-benzo[2,3]azepino[4,5-b]indol-5-yl)-(4-fluoro-phenyl)-methanone 5,6,7,12-Tetrahydro-benzo[2,3]azepino[4,5-b]indole. ^{1}H-NMR ($CDCl_3$): δ 8.31 (1H, s), 7.70 (H, d), 7.61 (1H, d), 7.44 (1H, d), 7.25-7.32 (2H, m), 7.18 (1H, m), 7.10 (2H, m), 6.99 (1H, m), 6.99 (1H, m), 6.76 (3H, dd), 5.28 (1H, m), 3.63 (1H, m), 3.20 (2H, m). MS (ES): 437 (MH+).

E. In a similar manner to that described in Step A, but replacing 4-fluorobenzoyl chloride with the appropriately substituted acyl chloride, chloroformate or isocyanate, the following compounds were prepared:

ethyl 3-(4-anisoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.46 (1H, br s), 8.04 (1H, s), 7.45 (1H, d), 7.30 (2H, m), 7.13 (1H, m), 6.98-7.06 (4H, m), 4.12-4.18 (4H, m), 3.78 (3H), s) 3.20 (2H, m), 1.15 (3H, t); MS (ES): 779 (MH^+);

ethyl 3-(4-chlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.34 (1H, br s), 7.81 (1H, s), 7.34-7.37 (3H, m), 7.27-7.29 (2H, m), 7.20 (1H, d), 7.05 (1H, m), 6.94 (1H, m), 4.09 (2H, q), 4.08 (2H, t), 3.09 (2H, t), 1.02 (3 H, t); MS (ES): 395 (MH^+);

ethyl 3-(2,4-dichlorobenzoyl)-1,2,3,6-tetrahydroazepino-[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.55 (1H, br s), 7.60 (2H, m), 7.42-7.48 (3H, m), 7.23 (1H, m), 7.01-7.08 (1H, m), 6.94 (1H, m), 4.30 (4H, m), 3.34 (2H, m), 1.35 (3H, m) MS (ES): 429 (MH^+);

ethyl 3-benzoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.46 (1 H, br s), 8.01 (1H, s), 7.50 (2H, m), 7.46 (2H, m), 7.42 (2H, m), 7.34 (1H, m), 7.14 (1H, m), 7.05 (1H, m), 4.19-4.33 (4H, m), 3.22 (2H, t), 1.13 (3 H, t); MS (ES): 361 (MH^+);

ethyl 3-(2,4-difluorobenzoyl)-1,2,3,6-tetrahydroazepino-[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.49 (1H, br s), 7.79 (1H, s), 7.50 (2H, m), 7.37 (1H, d), 7.19 (1H, m), 7.10 (1H, m), 7.02 (1H, m), 6.93 (1H, m), 4.25 (2H, q), 4.16 (2H, m), 3.24 (2H, t), 1.25 (3H, t); MS (ES): 397 (MH^+);

ethyl 3-nicotinoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.46 (1H, br s), 8.80 (2H, m), 7.97 (1H, br s), 7.91 (1H, m), 7.51 (1H, d), 7.42 (2H, m), 7.22 (1H, m), 7.12 (1H, m), 4.25 (4H, m), 3.29 (2H, m), 1.22 (3H, t); MS (ES): 362 (MH^+);

ethyl 3-(2-naphthoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.48 (1H, br s), 8.14 (1H, s), 7.66 (4H, m), 7.54 (1H, d), 7.48 (2H, m), 7.39 (2H, m), 7.20 (1H, m), 7.11 (1H, m), 4.23 (4H, m), 3.30 (2H, m), 1.21 (3H, t); MS (ES): 411 (MH^+);

ethyl 3-(3-toluoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.53 (1H, br s), 8.11 (1H, s), 7.52 (1H, d), 7.37 (5H, m), 7.20 (1H, m), 7.11 (1H, m), 4.22 (4H, m), 3.26 (2H, m), 2.41 (3H,S), 1.21 (3H, t); MS (ES): 375 (MH^+);

ethyl 3-[2,5-bis(trifluoromethyl)]benzoyl)-1,2,3,6-tetrahydroazepino-[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): rotomers (3:7) δ 10.58 (0.3H, br s), 10.41 (0.7H, s), 8.67 (0.3H, br s) 7.93 (2H, m), 7.55 (1H, d), 7.50 (0.7H, s), 7.34 (1.3H, m), 7.22 (1.7H, m), 7.12 (1H, m), 4.0-4.40 (3.4H, m), 3.85 (0.3H, m), 3.69 (0.3H, m), 3.29 (1.4H, m), 2.99-3.18 (0.6H, m), 1.43 (0.9H, m), 1.06 (2.1H, t); MS (ES): 497 (MH^+);

ethyl 3-(4-methoxyphenoxycarbonyl)-1,2,3,6-tetrahydroazepino-[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.51 (1H, br s), 8.37 (1H, s), 7.45 (1H, m), 7.20 (5H, m), 6.86 (2H, m), 4.31 (2H, m), 4.08 (2H, m), 3.76 (3H, br s), 3.20 (2H, m), 1.32 (3H, m); MS (ES): 407 (MH^+);

ethyl 3-(2,4-dichlorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino-[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.51 (1H, br s), 8.15 (1H, d), 8.10 (1 H, s), 7.46 (1H, d), 7.12-7.35 (4H, m) 7.04 (1H, m), 4.33 (2H, q), 4.04 (2H, t), 3.18 (2H, t), 1.34 (3H, t); MS (ES): 444 (MH^+);

ethyl 3-(4-ethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 393 (MH^+);

3-(thiophene-2-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 367 (MH^+);

3-cyclohexanecarbonyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 367 (MH^+);

3-[3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carbonyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 494 (MH^+);

3-(benzo[*b*]thiophene-2-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 417 (MH^+);

3-phenylacetyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 375 (MH^+);

3-(3-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 391 (MH^+);

1,6-dihydro-2*H*-azepino[4,5-*b*]indole-3,5-dicarboxylic acid 5-ethyl ester 3-phenyl ester; MS (ES): 377 (MH^+);

1,6-dihydro-2*H*-azepino[4,5-*b*]indole-3,5-dicarboxylic acid 3-(4-chlorophenyl) ester 5-ethyl ester MS (ES): 411 (MH^+);.

1,6-dihydro-2*H*-azepino[4,5-*b*]indole-3,5-dicarboxylic acid 5-ethyl ester 3-p-tolyl ester; MS (ES): 391 (MH^+);

3-phenylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester MS (ES): 376 (MH^+);

3-(4-chlorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 410 (MH^+);

3-(4-methoxyphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 406 (MH^+);

3-*p*-tolylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 390 (MH^+);

3-acetyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 299 (MH^+);

3-(2,3-difluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 397 (MH^+);

3-(2,5-difluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 397 (MH^+);

3-(2,6-difluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 397 (MH^+);

3-(3,4-difluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 397 (MH^+);

3-(3,5-difluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 397 (MH^+);

3-(2,3,4-trifluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+);

3-(2,3,6-trifluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+);

3-(2,4,5-trifluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+);

3-(2,3,4,5-tetrafluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 433 (MH^+);

3-pentafluorobenzoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 451 (MH^+);

3-(3,5-bis-trifluoromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 497 (MH^+);

3-(2-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 379 (MH^+);

3-(3-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 379 (MH^+);

3-(2-trifluoromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 429 (MH^+);

3-(3-trifluoromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 429 (MH^+);

3-(4-trifluoromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 429 (MH^+);

3-(pyridine-4-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 362 (MH^+);

3-(4-cyanobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 386 (MH^+);

3-(4-nitrobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 406 (MH^+);

3-(4-methyl-3-nitrobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 420 (MH^+);

3-(3,4-dimethoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 421 (MH^+);

3-(2-methylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 375 (MH^+);

3-(4-methylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 375 (MH^+);

3-(2-chlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 395 (MH^+);

3-(4-methoxycarbonylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 419 (MH^+);

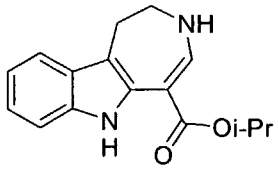
3-(biphenyl-4-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 437 (MH^+);

3-(3-chlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 395 (MH^+); and

3-(4-fluorosulfonyl-benzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 443 (MH^+).

EXAMPLE 3

PREPARATION OF *ISO*-PROPYL 1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. 3-Bromopyruvic acid•hydrate (3.34 g, 20 mmol) was placed in a flask and 1,1-dichloromethyl methyl ether (3.7 mL, 20 mmol) was added at 20°C. The mixture was heated to 50°C with stirring and a clear solution was obtained in 10 minutes. Heating was continued for 2 h. Solvent was removed under high vacuum to

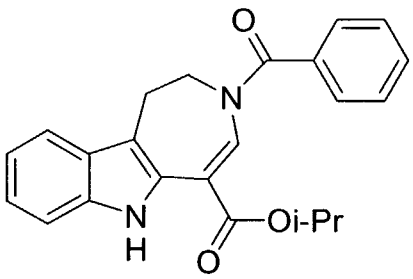
give 3-bromopyruvic chloride (6 g, 90% pure by ^{1}H NMR) and the compound was used without further purification.

B. To *iso*-propanol was added 3-bromopyruvic chloride (5 g) at -5°C dropwise and the solution was stirred overnight at 20°C. Evaporation of solvent gave *iso*-propyl 3-bromopyruvate (3.5 g), which was used in the next step without further purification.

C. The title compound was prepared in a manner similar to that described in Example 1A by using *iso*-propyl 3-bromopyruvate in *iso*-propanol; ^{1}H-NMR (DMSO): δ 10.61 (1H, br s), 7.81 (1H, s), 7.67 (1H, m), 7.28 (2H, m), 6.83 (1H, m), 4.96 (1H, br s), 3.39 (2H, m), 3.27 (1H, m), 2.93 (2H, m), 1.20 (6H, d); MS (ES): 271 (MH^+).

EXAMPLE 4

PREPARATION OF *ISO*-PROPYL 3-BENZOYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. The title compound was prepared in a manner similar to that described in Example 2A by using *iso*-propyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (Example 3) and benzoyl chloride; ^{1}H-NMR ($CDCl_3$): δ 10.48 (1H, br s), 7.98 (1H, s), 7.47 (2H, m), 7.41 (2H, m), 7.40 (2H, m), 7.30 (1H, m), 7.15 (1H, m), 6.99 (1H, m), 5.04 (1H, m), 4.15 (2H, t), 3.2 (2H, d), 1.10 (6H, d); MS (ES): 375 (MH^+).

B. In a similar manner, but replacing benzoyl chloride with the appropriately substituted acyl chloride, chloroformate, isocyanate or sulfonyl chloride, the following compounds were made:

iso-propyl 3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.43 (1H, br s), 7.86 (1H, s), 7.50 (2H, m), 7.41 (1H, d)), 7.26 (1H, d), 6.98-7.15 (4H, m), 5.02 (1H, m), 4.10 (2H, t), 3.2 (2H, d), 1.09 (6H, m); MS (ES): 393 (MH^+);

iso-propyl 3-(4-anisoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.45 (1H, br s), 8.27 (1H, s), 7.47 (1H, d), 7.22 (1H, d), 7.03 (1H, m), 6.90 (4H, m), 6.77 (2H, m), 5.07 (1H, m), 3.99 (2H, m), 3.11 (2H, d), 1.21 (6H, d); MS (ES): 421 (MH^+);

iso-propyl 3-piperonyloyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.52 (1H, br s), 8.04 (1H, s), 7.48 (1H, d), 7.33 (1H, d), 7.15 (1H, m), 7.08 (3H, m), 6.82 (1H, 8.5), 6.02 (2H, s), 5.17 (1H, m), 4.17 (2H, d), 3.11 (2H, d), 1.20 (6H, d); MS (ES): 419 (MH^+);

iso-propyl 3-phenoxylcarbonyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.47 (1H, br s), 8.29 (1H, s), 7.38 (1H, d), 7.23-7.31 (3H, m), 7.16 (1H, d), 7.06 (3H, m), 6.97 (1H, m), 5.10 (1H, m), 4.02 (2H, m), 3.13 (2H, d), 1.24 (6H, d); MS (ES): 391 (MH^+);

iso-propyl 3-(2,4-dichlorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.41 (1H, br s), 8.06 (1H, d), 7.92 (1H, s), 7.31 (1H, d), 7.07-7.21 (4H, m), 6.90 (1H, m), 6.97 (1H, m), 5.07 (1H, m), 3.89 (2H, t), 3.04 (2H, t), 1.18 (6H, d); MS (ES): 458 (MH^+);

iso-propyl 3-(4-*tert*-butylbenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.52 (1H, br s), 8.43 (1H, d), 7.79 (2H, d), 7.56 (2H, d), 7.40 (1H, d), 7.33 (1H, d), 7.15 (1H, m), 7.05 (1H, m), 5.23 (1H, m), 3.84 (2 H, t), 3.00 (2H, t), 1.41 (6H, d), 1.33 (9H, s); MS (ES): 467 (MH^+);

3-(4-chlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 409 (MH^+);

3-phenylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 390 (MH^+);

3-(4-chlorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 424 (MH^+);

3-*p*-tolylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 404 (MH^+);

3-phenylacetyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 389 (MH^+);

3-(4-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 405 (MH^+);

1,6-dihydro-2*H*-azepino[4,5-*b*]indole-3,5-dicarboxylic acid 3-(4-chlorophenyl) ester 5-isopropyl ester; MS (ES): 425 (MH^+);

1,6-dihydro-2*H*-azepino[4,5-*b*]indole-3,5-dicarboxylic acid 5-isopropyl ester 3-p-tolyl ester MS (ES): 405 (MH^+);

3-(4-methoxyphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 420 (MH^+);

3-nonanoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 411 (MH^+);

3-(2-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 405 (MH^+);

3-(3-phenylpropionyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 403 (MH^+);

3-(toluene-4-sulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 425 (MH^+);

3-(4-chlorobenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 445 (MH^+);

3-(4-methoxybenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 441 (MH^+);

3-(3,4-dimethoxybenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 471 (MH^+);

3-(4-trifluoromethoxybenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 495 (MH^+);

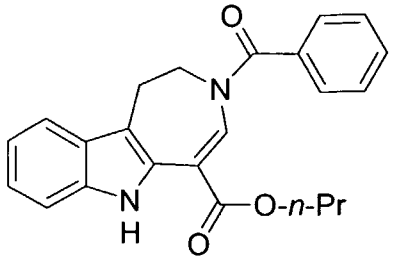
3-(2,4-dichlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 443 (MH^+);

3-(3-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 405 (MH^+); and

3-(benzo[1,3]dioxole-5-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; MS (ES): 419 (MH^+).

EXAMPLE 5

PREPARATION OF *N*-PROPYL 3-BENZOYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. In a similar manner as described in Example 1A, but using *n*-propyl 3-bromopyruvate and *n*-propanol, the following compound was prepared:

n-propyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.41 (1H, br s), 7.74 (1H, d), 7.35 (1H, s), 7.56 (1H, d), 7.26 (1H, d), 7.09 (1H, m), 5.23 (1H, br s), 4.11 (2H, d), 3.54 (2H, br s), 3.12 (2H, br s), 1.68 (2H, m), 0.95 (3H, t); MS (ES): 271 (MH^+).

B. The title compound was prepared in a manner similar to that described in Example 2A by using n-propyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (compound of step A) and benzoyl chloride; ^{1}H-NMR ($CDCl_3$): δ 10.55 (1H, br s), 8.07 (1H, s), 7.52-7.58 (4H, m), 7.47 (2H, m), 7.33 (1H, d), 7.21 (1H, m), 7.12 (1H, m), 4.23 (2H, t), 4.13 (2H, m), 3.28 (2H, m), 1.56 (2H, m), 1.40 (3H, t); MS (ES): 375 (MH^+).

C. In a similar manner, but replacing benzoyl chloride with the appropriately substituted acyl chloride, chloroformate, isocyanate or sulfonyl chloride, the following compounds were prepared:

n-propyl 3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.54 (1H, br s), 8.00 (1H, s), 7.62 (2H, m), 7.53 (1H, d), 7.38 (1H, d), 7.10-7.24 (4H, m), 4.23 (2H, t), 4.15 (2H, t), 3.28 (2H, t), 1.51 (2H, m), 0.81 (3H, t); MS (ES): 393 (MH^+);

n-propyl 3-(3-anisoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.54 (1H, br s), 8.09 (1H, s), 7.54 (1H, d), 7.36 (2H, m), 7.20 (1H, m), 7.05-7.13 (4H, m), 4.22 (2H, t), 4.12 (2H, t), 3.84 (3H, s), 3.27 (2H, t), 1.67 (2H, m), 0.80 (3H, t); MS (ES): 405 (MH^+);

n-propyl 3-piperonyloyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.55 (1H, br s), 8.09 (1H, s), 7.52 (1H, d), 7.38 (1 H,

d), 7.23 (1H, m), 7.09-7.14 (3H, m), 6.86 (1H, d), 6.05 (2H, s), 4.22 (2H, t), 4.17 (2H, t3.26 (2H, t), 1.62 (2H, m), 0.85 (3H, t); MS (ES): 419 (MH^+);

3-(4-chlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid propyl ester; MS (ES): 409 (MH^+);

n-propyl 3-phenylacetyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ester; (MS (ES): 389 (MH^+);

3-(2,4-dichlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid propyl ester; MS (ES): 443 (MH^+);

3-(2-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid propyl ester; MS (ES): 405 (MH^+);

3-(4-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid propyl ester; MS (ES): 405 (MH^+);

1,6-dihydro-2*H*-azepino[4,5-*b*]indole-3,5-dicarboxylic acid 3-phenyl ester 5-propyl ester; MS (ES): 491 (MH^+);

3-(2,4-dichlorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid propyl ester; MS (ES): 448 (MH^+);

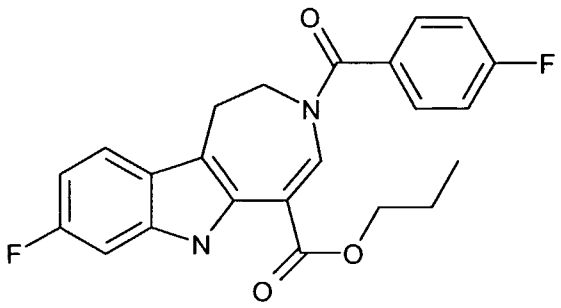
3-(4-methoxybenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid propyl ester; MS (ES): 448 (MH^+);

3-(4-chlorobenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid propyl ester; MS (ES): 448 (MH^+); and

n-propyl 3-(3,4-difluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ES): 411 (MH^+).

EXAMPLE 6

PREPARATION OF N-PROPYL3(4-FLUOROBENZOYL)-8-FLUORO-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE)



A. In a manner similar to that described in Example 1A, by using 6-fluoro-tryptamine-HCl and *n*-propyl 3-bromopyruvate, the following compound was prepared:

8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid *n*-propyl ester MS (ESI): 289 (MH^+).

B. In a manner similar to that described in Example 2A, but replacing ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with 8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid *n*-propyl ester (the compound in Step A) and using the appropriate acyl chloride, the following compounds were prepared:

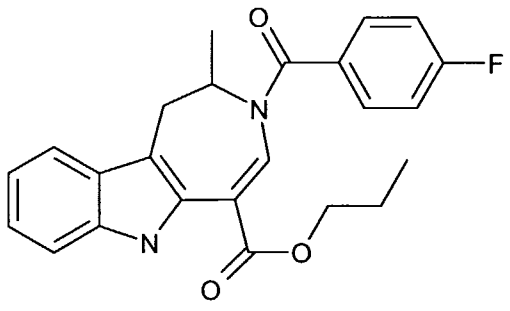
n-propyl 3-(4-fluorobenzoyl)-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ES): 411 (MH^+);

n-propyl 3-(4-methoxybenzoyl)-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 423 (MH^+); and

n-propyl 3-(4-chlorobenzoyl)-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS(ESI): 427(MH^+).

EXAMPLE 7

PREPARATION OF N-PROPYL 3(4-FLUOROBENZOYL)-2-METHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. 2-Methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid *n*-propyl ester was prepared in the manner described in Example 1A using α-methyl tryptamine and *n*-propyl 3-bromopyruvate; MS (ESI): 285 (MH^+).

B. The title compound was prepared in a manner similar to that described in Example 2A by using 2-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid *n*-propyl ester (compound in Paragraph A) and 4-fluorobenzoyl chloride; MS (ES): 407 (MH^+). The racemic sample was submitted to chiral separation

using a 10 mm x 250 mm Chiralcel OD column and a 10 % iPrOH/hexane isocratic mobile phase to give two isomers.

C. In a similar manner as described above, but replacing 4-fluorobenzoyl chloride with the appropriately substituted benzoyl chloride, the following compounds were prepared:

n-propyl 3-(3,4-difluorobenzoyl)-2-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ES): 425 (MH^+);

n-propyl 3-(4-chlorobenzoyl)-2-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ES): 423 (MH^+);

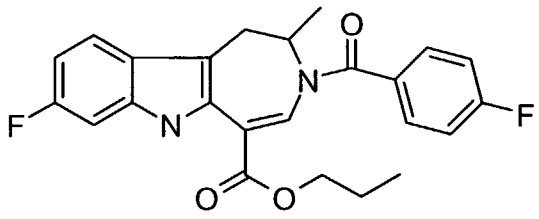
n-propyl 3-(4-methoxybenzoyl)-2-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 419 (MH^+);

n-propyl 2-methyl-3-(2-toluoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 403 (MH^+); and

n-propyl 3-[2,5-bis(trifluoromethyl)benzoyl]-2-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 525 (MH^+).

EXAMPLE 8

PREPARATION OF *N*-PROPYL 3(4-FLUOROBENZOYL)-2-METHYL-8-FLUORO-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. 6-Fluoro-3-(2-nitropropenyl)-1H-indole was prepared by combining 6-fluoroindole-3-carboxaldehyde (485 mg, 2.97 mmol), nitroethane (6.0 mL), and ammonium acetate (250 mg, 3.27 mmol). The reaction solution was allowed to reflux 2 hours. The reaction solution was diluted with EtOAc (100 mL), washed with H_2O (50 mL x 2), partitioned, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide 560 mg (86 % yield) of 6-fluoro-3-(2-nitropropenyl)-1*H*-indole; ^1H NMR ($CDCl_3$) δ 11.03 (1H, br s), 8.41 (1H, s), 7.63 (1H, dd), 7.50 (1H, s), 7.06 (1H, dd), 6.92 (1H, t), 2.44 (3H, s); TLC (SiO_2 plate, 100 % DCM) R_f = 0.7.

B. α-Methyl-6-fluorotryptamine was prepared by the dropwise addition of an anhydrous THF solution of 6-fluoro-3-(2-nitropropenyl)-1H-indole (560

mg, 2.54 mmol) to a stirred mixture of $LiAlH_4$ (480 mg, 12.7 mmol) in THF (40 mL) at 0°C. The reaction slurry was allowed to stir under N_2 from 0°C to ambient room temperature over 3.5 hours. The reaction solution was again cooled to 0°C prior to the dropwise addition of H_2O to quench excess $LiAlH_4$. The reaction suspension was filtered through a pad of Celite to remove Al salts. The filtrate was concentrated under reduced pressure, diluted with EtOAc (200 mL), washed with NaCl (50 mL x 2), dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide 450 mg of α-methyl-6-fluorotryptamine as a viscous oil; ^1H NMR ($CDCl_3$) δ 8.30 (1H, br s), 7.52 (1H, m), 6.98-7.04 (2H, m), 6.87 (1H, t), 3.29 (1H, m), 2.87 (1H, dd), 2.64 (1H, q), 1.25 (3H, d); MS (ESI): 193 (MH^+); TLC (SiO_2 plate, 100 % DCM) R_f = 0.1.

C. 2-Methyl-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid *n*-propyl ester was prepared in a manner similar to that described in Example 1A by using α-methyl–6-fluorotryptamine and *n*-propyl 3-bromopyruvate; MS (ESI): 303 (MH^+).

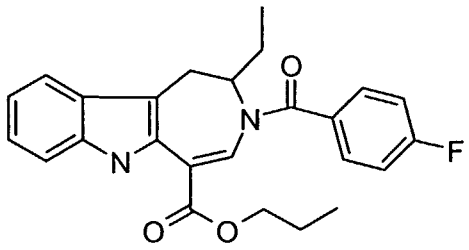
D. The title compound was prepared in a manner similar to that described in Example 2A by using 2-methyl-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid n-propyl ester and 4-fluorobenzoyl chloride; ^1H NMR ($CDCl_3$) δ 10.47 (1H, s), 7.96 (1H, s), 7.61-7.65 (2H, m), 7.41 (1H, m), 7.17 (2H, t), 7.05 (1H, dd), 6.90 (1H, t), 5.63 (1H, m), 4.17 (2H, m), 4.05 (2H, m), 3.38 (1H, dd), 3.07 (1H, dd), 1.55 (2H, m), 1.07 (3H, d), 0.77 (3H, t); MS (ES): 425 (MH^+).

E. In a similar manner as described in Steps A through D, but replacing 4-fluorobenzoyl chloride with 3,4-difluorobenzoyl chloride in Step D, the following compound was prepared:

n-propyl 3(3,4-difluorobenzoyl)-2-methyl-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 427 (MH^+).

EXAMPLE 9

PREPARATION OF *N*-PROPYL-3(4-FLUOROBENZOYL)-2-ETHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. α-Ethyl tryptamine was prepared in a manner similar to that described in Steps A and B of Example 8 by replacing nitroethane with 1-nitropropane at Step A; MS (ESI): 207 (MH^+).

B. 2-Ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid *n*-propyl ester was prepared in a manner similar to that described in Example 1A but replacing tryptamine hydrochloride with α-ethyl tryptamine and ethyl 3-bromopyruvate with *n*-propyl 3-bromopyruvate; MS (ESI): 303 (MH^+).

C. The title compound was prepared in a manner similar to that described in Example 2A but replacing ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with 2-ethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid *n*-propyl ester; MS(ESI): 421(MH^+). The racemic sample was submitted to chiral chromatography using a Chiralcel OD 10 mm x 250 mm column and a 10 % iPrOH / hexane mobile phase to give two isomers.

D. In a similar manner as described above in Step C, but replacing 4-fluorobenzoyl chloride with the appropriately substituted benzoyl chloride, the following compounds were prepared:

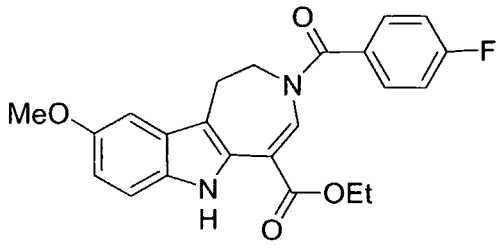
n-propyl 3(3,4-difluorobenzoyl)-2-ethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 439 (MH^+);

n-propyl 3(4-chlorobenzoyl)-2-ethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 437 (MH^+); and

n-propyl 3(4-methoxybenzoyl)-2-ethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 433 (MH^+).

EXAMPLE 10

PREPARATION OF ETHYL 3-(4-FLUOROBENZOYL)-9-METHOXY-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. The title compound was prepared in a manner similar to that described in Example 2A by using ethyl 9-methoxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate and 4-fluorobenzoyl chloride; ^{1}H-NMR ($CDCl_3$): δ 10.42 (1H, br s), 7.98 (1H, s), 7.62 (2H, m), 7.28 (1H, m), 7.16 (2H, m), 6.93 (1H, d), 6.88 (1H, dd), 4.24 (4H, m), 3.88 (3H, s), 3.23 (2H, m), 1.23 (3H, t); MS (ES): 409 (MH^+).

B. In a similar manner, but replacing 4-fluorobenzoyl chloride with the appropriately substituted acyl chloride, chloroformate or isocyanate, the following compounds were prepared:

ethyl 9-methoxy-3-piperonyloyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.43 (1H, br s), 8.06 (1H, s), 7.27 (2H, m), 7.12 (2H, m), 6.93 (1H, d), 6.86 (2H, m), 6.01 (2H, s), 4.25 (2H, q), 4.21 (2H, t), 3.88 (3H, s), 3.21 (2H, m), 1.26 (3H, t); MS (ES): 435 (MH^+);

3-(2,4-dichlorobenzoyl)-9-methoxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester;

ethyl 3-benzoyl-9-methoxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ES): 390 (M^+);

3-(4-chlorobenzoyl)-9-methoxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 390 (MH^+);

3-acetyl-9-methoxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 329 (MH^+);

9-methoxy-3-(2-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 421 (MH^+);

9-methoxy-3-(3-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 421 (MH^+);

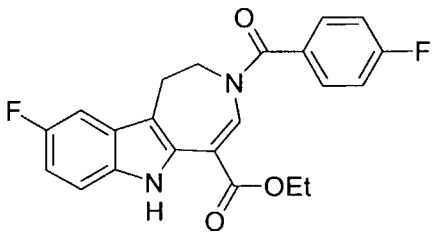
9-methoxy-3-(4-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 421 (MH^+);

9-methoxy-1,6-dihydro-2H-azepino[4,5-*b*]indole-3,5-dicarboxylic acid 5-ethyl ester 3-phenyl ester; MS (ES): 407 (MH^+); and

3-(2,4-dichlorophenylcarbamoyl)-9-methoxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 474 (MH^+).

EXAMPLE 11

PREPARATION OF ETHYL 9-FLUORO-3-(4-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. The title compound was prepared in a manner similar to that described in Example 2 by using ethyl 9-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate and 4-fluorobenzoyl chloride; ^{1}H-NMR ($CDCl_3$): δ 10.57 (1H, br s), 8.04 (1H, s), 7.62 (2H, dd), 7.29 (1H, m), 7.16 (3H, m), 6.95 (1H, m), 4.24 (4H, m), 3.20 (2H, m), 1.22 (3H, t); MS (ES): 397 (MH^+).

B. In a similar manner, but replacing 4-fluorobenzoyl chloride with the appropriately substituted acyl chloride, chloroformate or isocyanate, the following compounds were prepared:

ethyl 9-fluoro-3-(4-toluoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.57 (1H, br s), 8.14 (1H, s), 7.49 (2H, d), 7.27 (3H, m), 7.15 (1H, dd), 6.93 (1H, m), 4.23 (4H, m), 3.19 (2H, m), 2.43 (3H, s), 1.22 (3H); MS (ES): 393 (MH^+);

3-benzoyl-9-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 379 (MH^+);

9-fluoro-3-(3-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 397 (MH^+);

3-(2,3-difluorobenzoyl)-9-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+);

3-(2,4-difluorobenzoyl)-9-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+);

3-(2,5-difluorobenzoyl)-9-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+);

3-(3,4-difluorobenzoyl)-9-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+);

3-(3,5-difluorobenzoyl)-9-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+);

3-(4-Chlorobenzoyl)-9-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester;MS (ES): 413 (MH^+);

3-(2,4-dichlorobenzoyl)-9-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 447 (MH^+);

9-fluoro-3-(3-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 409 (MH^+);

9-fluoro-3-(4-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 409 (MH^+);

3-(benzo[1,3]dioxole-5-carbonyl)-9-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 423 (MH^+);

9-fluoro-3-(pyridine-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 380 (MH^+);

9-fluoro-3-(pyridine-4-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 380 (MH^+);

9-fluoro-3-(4-fluorosulfonyl-benzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 461 (MH^+);

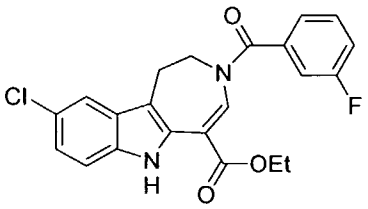
9-fluoro-3-(4-nitrobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 424 (MH^+);

9-fluoro-1,6-dihydro-2*H*-azepino[4,5-*b*]indole-3,5-dicarboxylic acid 5-ethyl ester; 3-phenyl ester; MS (ES): 395 (MH^+); and

3-(2,4-dichlorophenylcarbamoyl)-9-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 463 (MH^+).

EXAMPLE 12

PREPARATION OF ETHYL 9-CHLORO-3-(3-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. The title compound was prepared in a manner similar to that described in Example 2A by using ethyl 9-chloro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate and 3-fluorobenzoyl chloride; ^{1}H-NMR ($CDCl_3$): δ 10.61 (1H, br s), 8.07 (1H, s), 7.46 (2H, m), 7.28 (4H, m), 7.14 (1H, dd), 4.25 (2H, q), 4.19 (2H, t), 3.21 (2H, t), 1.22 (3H, t); MS (ES): 413 (MH^+).

B. In a similar manner, but replacing 3-fluorobenzoyl chloride with the appropriately substituted acyl chloride, chloroformate or isocyanate, the following compounds were prepared:

ethyl 9-chloro-3-(4-chlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.52 (1H, br s), 8.04 (1H, s), 7.55 (2H, m), 7.46 (3H, m), 7.29 (1H, d), 7.14 (1H, dd), 4.26 (2H, q), 4.19 (2H, t), 3.21 (2H, t), 1.23 (3H, t); MS (ES): 429 (MH^+);

ethyl 9-chloro-3-(2-anisoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.56 (1H, br s), 8.05 (1H, br s), 7.48 (2H, m), 7. (1H, dd), 7.26 (1H, d), 7.10 (2H, m), 6.98 (1H, d), 4.21 (2H, br s), 3.90 (2H, br s), 3.24 (2H, br s), 1.21 (3H, br s); MS (ES): 425 (MH^+);

ethyl 9-chloro-3-(2,5-difluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ES): 431 (MH^+);

3-benzoyl-9-chloro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 395 (MH^+);

9-chloro-3-(2,3-difluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 431 (MH^+);

9-chloro-3-(2,4-difluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 431 (MH^+);

9-chloro-3-(2,6-difluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 431 (MH^+);

9-chloro-3-(3,4-difluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 431 (MH^+);

9-chloro-3-(3,5-difluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 431 (MH^+);

9-chloro-3-(2,4-dichlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 463 (MH^+);

9-chloro-3-(3-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 425 (MH^+);

9-chloro-3-(4-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 425 (MH^+);

9-chloro-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 413 (MH^+);

3-(benzo[1,3]dioxole-5-carbonyl)-9-chloro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 439 (MH^+);

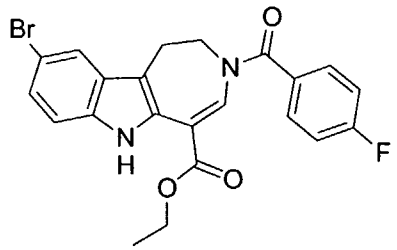
9-chloro-1,6-dihydro-2H-azepino[4,5-*b*]indole-3,5-dicarboxylic acid 5-ethyl ester; 3-phenyl ester; MS (ES): 410 (MH^+);

9-chloro-3-(2,4-dichlorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 478 (MH^+); and

9-chloro-3-(2-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 413 (MH^+).

EXAMPLE 13

PREPARATION OF 9-BROMO-3-(4-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. The title compound was prepared in a manner similar to that described in Example 2A by using 9-bromo-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester and 4-fluorobenzoyl chloride; ^{1}H-NMR ($CDCl_3$): δ 10.56 (1H, s), 7.98 (1H, s), 7.56 (3H, m), 7.19 (1H, m), 7.09 (2H, m), 4.17 (4H, m), 3.13 (2H, m), 1.13 (3H, t). MS (ESI): 457, 459 (MH^+).

B. In a similar manner, but replacing 4-fluorobenzoyl chloride with the appropriate benzoyl chloride, the following compounds were prepared:

9-bromo-3-(3-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 457, 459 (MH^+);

9-bromo-3-(2-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 457, 459 (MH^+);

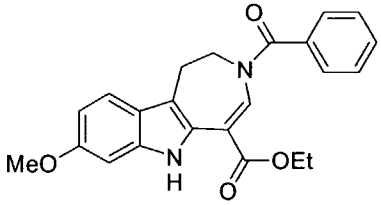
3-benzoyl-9-bromo-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 439, 441 (MH^+);

9-bromo-3-(4-chlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 473, 475 (MH^+); and

9-bromo-3-(3-chlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester;MS (ESI): 473, 475 (MH^+).

EXAMPLE 14

PREPARATION OF ETHYL 3-BENZOYL-8-METHOXY-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. The title compound was prepared in a manner similar to that described in Example 2A by using ethyl 8-methoxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate and benzoyl chloride; ^{1}H-NMR ($CDCl_3$): δ 10.41 (1H, br s), 7.98 (1H, s), 7.56 (2H, m), 7.52 (1H, m), 7.46 (2H, m), 7.39 (1H, d), 6.86 (1H, d), 6.79 (1H, dd), 4.22 (2H, q), 4.19 (2H, t), 3.86 (3H, s), 3.23 (2H, t), 1.20 (3H, t); MS (ES): 391 (MH^+).

B. In a similar manner as described above, but replacing benzoyl chloride with the appropriately substituted acyl chloride, chloroformate and isocyante, the following compounds were prepared:

ethyl 3-benzoyl-8-methoxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.40 (1H, br s), 7.90 (1H, s), 7.61 (2H, m), 7.40 (1H, d), 7.15 (2H, m), 6.86 (1H, d), 6.79 (1H, dd), 4.25 (2H, q), 4.19 (2H, t), 3.86 (3 H, s), 3.23 (2H, t), 1.23 (3H, t); MS (ES): 408 (M^+);

ethyl 8-methoxy-3-(2,3,4-trifluorobenzoyl)-1,2,3,6-tetrahydroazepino-[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.35 (1H, br s), 7.38 (1H, d), 7.26 (2 H, m), 7.12 (1H, m), 7.15 (1H, m), 6.85 (1H, d), 6.79 (1H, dd), 4.25 (2H, m), 4.19 (2H, t), 3.86 (3H, s), 3.23 (2H, t), 1.23 (3H, t); MS (ES): 444 (M^+);

3-(2,4-difluorobenzoyl)-8-methoxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 427 (MH^+);

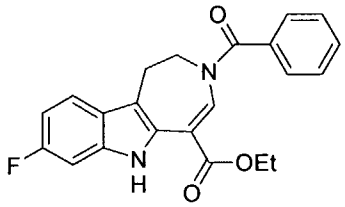
3-(benzo[1,3]dioxole-5-carbonyl)-8-methoxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 435 (MH^+);

3-(2,4-dichlorophenylcarbamoyl)-8-methoxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 474 (MH^+); and

8-methoxy-1,6-dihydro-2*H*-azepino[4,5-*b*]indole-3,5-dicarboxylic acid 5-ethyl ester; 3-phenyl ester; MS (ES): 407 (MH^+).

EXAMPLE 15

PREPARATION OF ETHYL 8-FLUORO-3-BENZOYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. The title compound was prepared in a manner similar to that described in Example 2A by using ethyl 8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate and benzoyl chloride; ^{1}H-NMR ($CDCl_3$): δ 10.57 (1H, br s), 8.05 (1H, s), 7.55 (3H, m), 7.45 (3H, m), 7.05 (1H, dd), 6.87 (1H, m), 4.22 (4H, m), 3.24 (2H, t), 1.2 (3H, t); MS (ES): 379 (MH^+).

B. In a similar manner, but replacing benzoyl chloride with the appropriately substituted acyl chloride, chloroformate or isocyanate, the following compounds were prepared:

ethyl 8-fluoro-3-(3-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.56 (1H, br s), 7.99 (1H, s), 7.44 (2H, m), 7.32 (2H, m), 7.24 (1H, m), 7.04 (1H, dd), 6.88 (1H, m), 4.25 (2H, q), 4.19 (2H, t), 3.24 (2H, m), 1.23 (3H, t); MS (ES): 397 (MH^+);

ethyl 8-fluoro-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.46 (1H, br s), 7.97 (1H, s), 7.62 (2H, m), 7.43 (1H, m), 7.17 (2H, m), 7.05 (1H, dd), 6.88 (1H, m), 4.25 (2H, q), 4.21 (2H, t), 3.24 (2H, t), 1.25 (3H, t); MS (ES): 396 (M^+);

ethyl 3-(3,4-difluorobenzoyl)-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.55 (1H, br s), 7.93 (1H, s), 7.46 (2H, m), 7.35 (1H, m), 7.25 (1H, m), 7.05 (1H, dd), 6.88 (1H, m), 4.28 (2H, q), 4.19 (2H), 3.24 (2 H, t), 1.25 (3H, t); MS (ES): 415 (MH^+);

ethyl 3-(4-anisoyl)-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.58 (1H, br s), 8.07 (1H, s), 7.59 (2H, m), 7.41 (1H, m), 7.05 (1H, dd), 6.96 (2H, m), 6.87 (1H, m), 4.26 (2H, q), 4.21 (2H, t), 3.88 (3H, s), 3.23 (2H, t), 1.24 (3H, t); MS (ES): 409 (MH^+);

ethyl 8-fluoro-3-piperonyloyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.57 (1H, br s), 8.06 (1H, s), 7.4 (1H, dd), 7.10 (2H, m), 7.04 (1H, dd), 6.87 (2H, m), 6.06 (2H, s), 4.27 (2H, q), 4.19 (2H, t), 3.22 (2H, t), 1.26 (3H, t); MS (ES): 422 (M^+);

ethyl 3-(2,4-dichlorophenylcarbamoyl)-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.60 (1H, br s), 8.21 (1H, d), 8.13 (1 H, s), 7.42 (2H, m), 7.27 (1H, m), 7.05 (1H, d), 6.87 (1H, m), 4.39 (2H, q), 4.1 (2H, m), 3.22 (2H, m), 1.41 (3H, t); MS (ES): 462 (MH^+);

3-acetyl-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 317 (MH^+);

8-fluoro-3-(2-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 397 (MH^+);

3-(2,3-difluorobenzoyl)-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+);

3-(2,5-difluorobenzoyl)-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+);

3-(2,6-difluorobenzoyl)-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+);

3-(3,5-difluorobenzoyl)-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+);

3-(4-chlorobenzoyl)-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 413 (MH^+);

3-(2,4-dichlorobenzoyl)-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 447 (MH^+);

8-fluoro-3-(2-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 409 (MH^+);

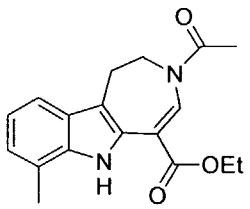
8-fluoro-3-(3-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 409 (MH^+);

3-(2,4-difluorobenzoyl)-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+); and

8-fluoro-1,6-dihydro-2*H*-azepino[4,5-*b*]indole-3,5-dicarboxylic acid 5-ethyl ester; 3-phenyl ester; MS (ES): 395 (MH^+).

EXAMPLE 16

PREPARATION OF ETHYL 3-ACETYL-7-METHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. The title compound was prepared in a manner similar to that described in Example 2A using ethyl 7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate and acetyl chloride; ^{1}H-NMR ($CDCl_3$): δ 10.50 (1H, br s), 8.12 (1H, br s), 7.36 (1H, d), 7.01 (2H, m), 4.39 (2H, q), 4.01 (2H, m), 3.16 (2H, m), 2.53 (3H, s), 2.39 (3H, s), 1.43 (3H, t); MS (ES): 313 (MH^+).

B. In a similar manner, but replacing acetyl chloride with the appropriately substituted acyl chloride, chloroformate and isocyanate, the following compounds were prepared:

ethyl 3-(4-fluorobenzoyl)-7-methyl-3-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.49 (1H, br s), 8.01 (1H, s), 7.61 (2H, m), 7.38 (1H, d), 7.16 (2H, m), 7.02 (2H, m), 4.27 (2H, q), 4.21 (2H, t), 3.27 (2H, t), 2.53 (3H, s), 126 (3H, t); MS (ES): 392 (MH^+);

3-benzoyl-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 375 (MH^+);

3-(2-fluorobenzoyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 393 (MH^+);

3-(3-fluorobenzoyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 393 (MH^+);

3-(2,3-difluorobenzoyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 411 (MH^+);

3-(2,4-difluorobenzoyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 411 (MH^+);

3-(2,5-difluorobenzoyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 411 (MH^+);

3-(2,6-difluorobenzoyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 411 (MH^+);

3-(3,4-difluorobenzoyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 411 (MH^+);

3-(3,5-difluorobenzoyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 411 (MH^+);

3-(4-chlorobenzoyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 409 (MH^+);

3-(2,4-dichlorobenzoyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 443 (MH^+);

3-(2-methoxybenzoyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 405 (MH^+);

3-(3-methoxybenzoyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 405 (MH^+);

3-(4-methoxybenzoyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 405 (MH^+);

3-(benzo[1,3]dioxole-5-carbonyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 419 (MH^+);

7-methyl-3-(4-nitrobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 420 (MH^+);

7-methyl-3-(4-methyl-3-nitrobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 434 (MH^+);

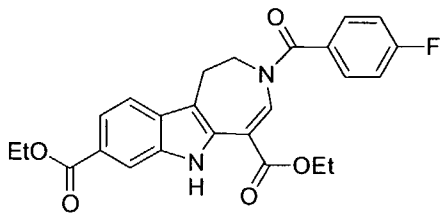
3-(4-methoxycarbonyl-benzoyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 433 (MH^+);

7-methyl-1,6-dihydro-2*H*-azepino[4,5-*b*]indole-3,5-dicarboxylic acid 5-ethyl ester; 3-phenyl ester; MS (ES): 391 (MH^+); and

3-(2,4-dichlorophenylcarbamoyl)-7-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 458 (MH^+).

EXAMPLE 17

PREPARATION OF DIETHYL 3-(4-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5,8-DICARBOXYLATE



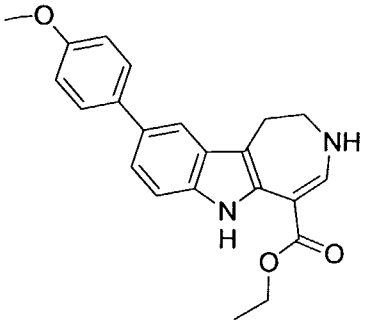
A. A suspension of methyl 3-formyl-6-indolecarboxylate (10 g, 49.2 mmol) and ammonium acetate (2 g) in nitromethane (50 mL) was heated to reflux for 1 hour. After cooling, solid was collected by filtration and washed with methanol and dried under high vacuum to afford methyl 3-(2'-nitrovinyl)-6-carboxylate (11.2 g). All of the material was then submitted for hydrogenation in ethanol (100 mL) in the presence of 5% Pd/C (2 g) at 40 psi hydrogen for 2 hours. Catalyst was then removed by filtration and washed with ethanol. Evaporation of solvent under high vacuum gave methyl tryptamine-6-carboxylate (7.76 g), which was used in the next step without further purification.

B. Diethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5,8-dicarboxylate was the transesterification product of the method similar to that described in Example 1A but in which tryptamine hydrochloride was replaced with methyl tryptamine-6-carboxylate.

C. The title compound was prepared in a manner similar to that described in Example 2A by using diethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5,8-dicarboxylate and 4-fluorobenzoyl chloride; ^{1}H-NMR ($CDCl_3$): δ 10.78 (1H, br s), 8.13 (2H, m), 7.81 (1H, m), 7.63 (2H, m), 7.53 (1H, d), 7.17 (2H, m), 4.39 (2H, q), 4.26 (4H, m), 3.28 (2H, t), 1.42 (3H, t), 1.23 (3H, t); MS (ES): 451 (MH^+).

EXAMPLE 18

PREPARATION OF 9-(4-METHOXYPHENYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. To a stirred solution of 9-bromo-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester (0.20 g, 0.60 mmol), (o-tolyl)$_3$P (0.19g, 0.6 mmol) and 4-methoxyphenylboronic acid (0.23 g, 1.5 mmol) in DME/EtOH (1:1, 12 mL) was added 2.1 mL of 1M Na_2CO_3 solution and $Pd(OAc)_2$ (27 mg) at ambient temperature. The reaction mixture was heated at 80°C under N_2 for 1 hour and monitored by LC-MS. The solution was diluted with DCM (20 mL), and washed with brine. The aqueous phase was extracted with DCM (20 mL) twice. The combined organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatograph on silica gel, eluting with EtOAc-hexane (0-30%) to yield the title compound (0.136 g) as a light yellow solid; ^{1}H-NMR ($CDCl_3$): δ 10.41 (1H, s), 7.73 (1H, d), 7.50 (3H, m), 7.29 (1H, d), 7.21 (1H, d), 6.90 (2H, m), 5.23(1H, s), 4.20 (2H, dd), 3.76 (3H, s), 3.55 (2H, m), 3.12 (2H, m), 1.26 (3H, t); MS (ESI): 363 (MH^+).

B. In a manner similar to that described in Example 2A, but replacing ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with 9-(4-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester, the following compound was prepared:

3-(4-fluorobenzoyl)-9-(4-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; ^{1}H-NMR ($CDCl_3$): δ 10.46 (1H, s), 8.06 (2H, m), 7.55 (4H, m), 7.08 (4H, m), 6.92 (2H, m), 4.18 (4H, m), 3.79 (3H, s), 3.23 (2H, m), 1.18 (3H, t); MS (ESI): 485 (MH^+).

C. In a similar manner as described in Step B, but replacing 4-Fluorobenzoyl chloride with the appropriately substituted benzoyl chloride, the following compounds were prepared:

3-(3-fluorobenzoyl)-9-(4-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 485 (MH^+);

3-(2-fluorobenzoyl)-9-(4-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 485 (MH^+);

3-benzoyl-9-(4-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 467 (MH^+);

3-(4-methoxybenzoyl)-9-(4-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 497 (MH^+);

3-(4-chlorobenzoyl)-9-(4-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 501 (MH^+);

3-(3-chlorobenzoyl)-9-(4-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 501 (MH^+); and

3-acetyl-9-(4-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 405 (MH^+).

D. In a manner similar to Step A, but replacing 4-methoxyphenylboronic acid with 3-methoxyphenylboronic acid, the following compound was prepared:

9-(3-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 363 (MH^+).

E. In a manner similar to that described in Example 2A, but replacing ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with 9-(3-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester, the following compound was prepared:

3-(4-fluorobenzoyl)-9-(3-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; ^{1}H-NMR ($CDCl_3$): δ 10.52 (1H, s), 7.97 (1H, s), 7.65 (1H, s), 7.57 (2H, m), 7.38 (2H, m), 7.11 (3H, m), 6.80 (1H, m), 4.18 (4H, m), 3.82 (3H, s), 3.24 (2H, m), 1.18 (3H, t); MS (ESI): 485 (MH^+).

F. In a manner similar to that described in Step E, but replacing 4-fluorobenzoyl chloride with the appropriately substituted benzoyl chloride, the following compounds were prepared:

3-(3-fluorobenzoyl)-9-(3-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 485 (MH^+);

3-(2-fluorobenzoyl)-9-(3-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 485 (MH^+); and

3-acetyl-9-(3-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 405 (MH^+).

G. In a manner similar to Step A, but replacing 4-methoxyphenylboronic acid with 2-methoxyphenylboronic acid, the following compound was prepared:

9-(2-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 363 (MH^+).

H. In a manner similar to that described in Example 2A, but replacing ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with 9-(2-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester, the following compound was prepared:

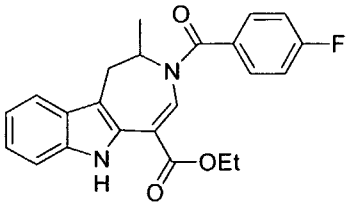
3-(4-fluorobenzoyl)-9-(2-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; ^{1}H-NMR ($CDCl_3$): δ 10.49 (1H, s), 7.97 (1H, s), 7.59 (3H, m), 7.36 (3H, m), 7.27 (1H, m), 7.12 (2H, m), 6.98 (2H, m), 4.20 (4H, m), 3.78 (3H, s), 3.34 (2H, m), 1.20 (3H, t); MS (ESI): 485 (MH^+).

I. In a manner similar to that described in Step H, but replacing 4-fluorobenzoyl chloride with acetyl chloride, the following compound was prepared:

3-acetyl-9-(2-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 405 (MH^+).

EXAMPLE 19

PREPARATION OF ETHYL 3-(4-FLUOROBENZOYL)-2-METHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. Ethyl 2-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate was prepared in a manner similar to that described in Example 1A by replacing tryptamine hydrochloride with 2-methyltryptamine hydrochloride.

B. The title compound was prepared in a manner similar to that described in Example 2A by using ethyl 2-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate and 4-fluorobenzoyl chloride; ^{1}H-NMR

($CDCl_3$): δ 10.44 (1H, br s), 8.01 (1H, s), 7.63 (2H, m), 7.52 (1H, d), 7.39 (1H, d), 7.24 (4H, m), 5.61 (1H, br s), 4.22 (2H, m), 3.43 (1H, dd), 3.10 (1H, dd), 1.19 (3H, t), 1.06 (3H, d); MS (ES): 393 (MH^+).

C. In a similar manner as described above, but replacing 4-fluorobenzoyl chloride with the appropriately substituted acyl chloride, the following compounds were prepared:

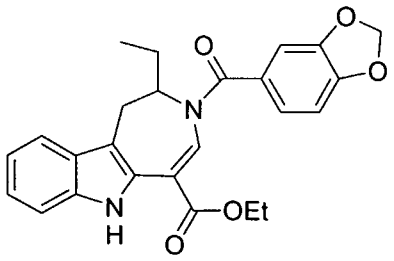
ethyl 3-benzoyl-2-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.44 (1H, br s), 8.09 (1H, s), 7.59 (2H, m), 7.51 (4H, m), 7.31 (1H, d), 7.19 (1H, m), 7.10 (1H, m), 5.61 (1H, m), 4.18-4.27 (2H, m), 3.43 (1H, dd), 3.10 (1H, d), 1.15 (3H, t), 1.06 (3H, d); MS (ES): 375 (MH^+);

ethyl 3-(chlorobenzoyl)-2-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.43 (1H, br s), 7.99 (1H, s), 7.54 (3H, m), 7.47 (2H, m), 7.38 (1H, d), 7.20 (1H, m), 7.11 (1H, m), 5.59 (1H, m), 4.15-4.30 (2H, m), 3.43 (1H, dd), 3.10 (1H, dd), 1.20 (3H, t), 1.06 (3H, d); MS (ES): 409 (MH^+); and

ethyl 2-methyl-3-piperonyloyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.45 (1H, br s), 8.10 (1H, s), 7.51 (1H, d), 7.38 (1H, d), 7.15 (4H, m), 7.20 (1H, d), 6.07 (1H, d), 6.06 (1H, d), 5.58 (1H, m), 4.17-4.33 (2H, m), 3.40 (1H, dd), 3.08 (1H, dd), 1.20 (3H, t), 1.05 (3H, d); MS (ES): 419 (MH^+).

EXAMPLE 20

PREPARATION OF ETHYL 2-ETHYL-3-PIPERONYLOYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. A solution of 3-(2'-ethyl-2'-nitrovinyl)indole (2.5 g, 11.5 mmol, prepared according to the literature procedure: Young (1958) *J. Chem. Soc.*:3493-3496) in ethanol was hydrogenated at 40 psi hydrogen in the presence of 10% Pd/C (0.5 g) for 16 h. Catalyst was removed by filtration and washed with ethanol. Solvent was removed and the crude was dissolved in ethanol (5 mL). The solution was acidified with aqueous HCl (1 N, 30 mL). The solution was extracted with toluene

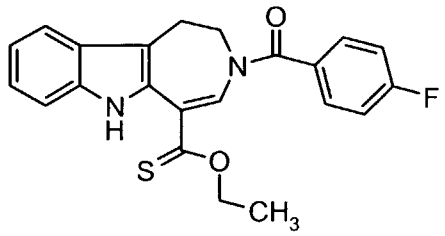
(3×50 mL). The aqueous layer was concentrated under high vacuum to give 2-ethyltryptamine hydrochloride (0.74 g), which was used without further purification.

B. Ethyl 2-ethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate was prepared in a manner similar to that described in Example 1A by using 2-ethyltryptamine hydrochloride.

C. The title compound was prepared in a manner similar to that described in Example 2A by using ethyl 2-ethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate and piperonyloyl chloride. ^{1}H-NMR ($CDCl_3$): δ 10.38 (1H, br s), 8.15 (1H, s), 7.52 (1H, d), 7.37 (1H, d), 7.10 (4H, m), 6.88 (1H, d), 6.07 (1H, d), 6.06 (1H, d), 5.34 (1H, m), 4.16-4.33 (2H, m), 3.53 (1H, dd), 3.00 (1H, dd), 1.29-1.45 (2H, m), 1.24 (3H, t), 0.81 (3H, t); MS (ES): 433 (MH^+).

EXAMPLE 21

PREPARATION OF 3-(4-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOTHIOIC ACID O-ETHYL ESTER

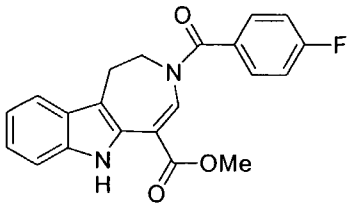


A. To a solution of ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (0.51g, 2 mmol) in toluene (20 mL) was added Lawesson's reagent (1.45 g, 3.6 mmol). The resulting suspension was heated to reflux under nitrogen for 24 hours. Solvent was evaporated to give the crude product, which was purified by column chromatography on silica gel eluting with MeOH-DCM (1:19) to give 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carbothioic acid O-ethyl ester (27 mg); MS (ES): 273 (MH+).

B. In a manner similar to that described in Step 2A, but replacing ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with benzyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carbothioic acid O-ethyl ester, the title compound was prepared; NMR ($CDCl_3$): δ 9.76 (1H, s), 7.95 (1H, s), 7.64 (2H, m), 7.54 (1H, d), 7.37 (1H, d), 7.11-7.24 (4H, m), 4.65 (2H, m), 4.23 (2H, t), 3.27 (2H, t), 1.40 (3H, t). MS (ES): 395 (MH+).

EXAMPLE 22

PREPARATION OF METHYL 3-(4-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. Methyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate was prepared in a manner similar to that described in Example 1A, but replacing ethyl-3-bromopyruvate with methyl 3-bromopyruvate; MS (ES): 243 (MH+).

B. The title compound was prepared in a manner similar to that described in Example 2A by using methyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (Kuehne *et al.*(1985) *J. Org. Chem. 50*:919-924) and 4-fluorobenzoyl chloride; ^{1}H-NMR ($CDCl_3$): δ 10.51 (1H, br s), 7.99 (1H, s), 7.62 (2H, m), 7.53 (1H, d), 7.23 (1H, d), 7.10-7.24 (4H, m), 4.22 (2H, t), 3.80 (3H, s), 3.27 (2H, m); MS (ES): 365 (MH^+).

C. In a similar manner as Step B, but by replacing 4-fluorobenzoyl chloride with the appropriate acyl chloride, chloroformate or isocyanate, the following compounds were prepared:

3-benzoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid methyl ester; MS (ES): 347 (MH^+);

3-acetyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid methyl ester; MS (ES): 381 (MH^+);

3-(4-chlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid methyl ester; MS (ES): 285 (MH^+);

3-(2,4-dichlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid methyl ester; MS (ES): 415 (MH^+);

3-(4-*tert*-butyl-benzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid methyl ester; MS (ES): 403 (MH^+);

3-(toluene-4-sulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid methyl ester; MS (ES): 397 (MH^+);

3-(4-*tert*-butyl-benzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid methyl ester; MS (ES): 439 (MH^+);

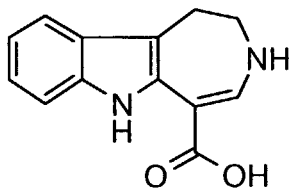
3-(2-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid methyl ester; MS (ES): 377 (MH^+);

3-(3-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid methyl ester; MS (ES): 377 (MH^+); and

3-(4-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid methyl ester; MS (ES): 377 (MH^+).

EXAMPLE 23

PREPARATION OF 1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID



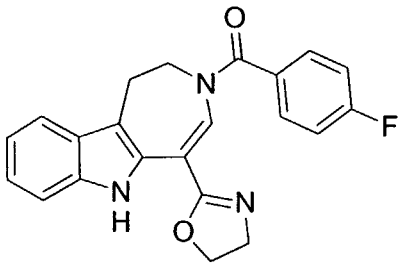
A. A mixture of 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid methyl ester (1.21 g, 5 mmol), di-*tert*-butyl dicarbonate (1.69 g, 1.5 eq.) and diisopropylethylamine (1.3 mL, 1.5 eq.) in benzene was heated to reflux with a Dean-Stark trap for 48 hours. After cooling, the solvent was removed and the crude product was redissolved in DCM and passed through a plug of silica gel, and eluted with DCM. Evaporation of the solvent gave a glue-like product (1,6-dihydro-2*H*-azepino[4,5-*b*]indole-3,5-dicarboxylic acid 3-tert-butyl ester 5-methyl ester); ^{1}H-NMR ($CDCl_3$): δ 10.52 (1H, br s), 8.40 (1H, s), 7.47 (2H, d), 7.34 (1H, m), 7.15 (1H,dd), 7.07 (1H,dd), 3.97 (2H, t), 3.87 (3H, s), 3.14 (2H, t), 1.57 (9H, s), 1.52 (3H, t).

B. To a solution of 1,6-dihydro-2*H*-azepino[4,5-*b*]indole-3,5-dicarboxylic acid 3-tert-butyl ester 5-methyl ester (0.293 g, 0.62 mmol) in MeOH (4 mL) was added 4 N NaOH (2 mL) and the mixture was heated for 5 hours under nitrogen. After cooling, the reaction mixture was diluted with water and extracted with EtOAc. The aqueous layer was acidified with AcOH. Precipitate was collected by filtration and washed with water and ether and dried under high vacuum to give the title compound (70 mg); ^{1}H-NMR (DMSO-d6): δ 11.40 (1H, s), 10.73 (1H, br s), 7.83 (1H, m), 7.73 (2H,

d), 7.38 (1H, m), 7.25 (1H, m), 6.88 (2H, m), 3.45 (2H, t), 3.87 (3H, s), 3.2.98 (2H, t), MS (ES): 229 (MH+).

EXAMPLE 24

PREPARATION OF 3-(4-FLUOROBENZOYL)-5-(4,5-DIHYDROOXAZOL-2-YL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE



A. To a stirred solution of 3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid (176 mg, 0.50 mmol) in DCM (5 mL, anhyd) was added CDI (81 mg, 0.50 mmol). After 1 hour ethanolamine (60 μL, 1.0 mmol) was added to the reaction mixture and stirring was continued. After 2 hours the solution was diluted with $CHCl_3$ (100 mL), washed with H_2O (100 mL) and brine, then dried (Na_2SO_4) and concentrated to give the corresponding 2-hydroxyethylamide intermediate (0.20 g, quant) as a white solid, which was used without purification in the next step; MS(ESI): 396 (MH^+).

B. To a stirred suspension of this intermediate (175 mg, 0.44 mmol) in $CHCl_3$ (4 mL, anhydrous) was added dropwise thionyl chloride (73 μL, 1.0 mmol) at ambient temperature. After 1 hour, the reaction mixture was diluted with $CHCl_3$ (4 mL) and charged with 2N NaOH (4 mL) and tetrabutylammonium iodide (5 mg). After 16 hours, the organic layer was isolated, concentrated under reduced pressure and purified by chromatography on silica gel, eluting with EtOAc-DCM (0:100 to 25:75) to afford the title compound (8 mg) as a yellow solid; ^{1}H-NMR ($CDCl_3$): δ 11.74 (1H, s), 7.66 (1H, br s), 7.60 (2H, m), 7.54 (1H, d), 7.42 (1H, d), 7.20 (1H, app t), 7.14 (2H, app t), 7.11 (1H, app t), 4.19-4.28 (4H, m), 4.12 (2H, m), 3.29 (2H, dd); MS (ESI): 376 (MH^+).

C. In a similar manner, but replacing ethanolamine with 2-amino-2-methylpropanol, 1-amino-2-propanol, or 1-amino-2-butanol, the following compounds were prepared:

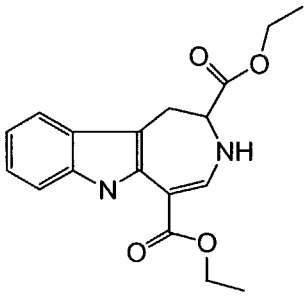
5-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole; ^{1}H-NMR ($CDCl_3$): δ 11.77 (1H, s), 7.64 (1H, br s), 7.61 (2H, m), 7.54 (1H, d), 7.44 (1H, d), 7.21 (1H, app t), 7.08-7.17 (3H, m), 4.21 (2H, app t), 3.92 (2H, s), 3.28 (2H, dd), 1.41 (6H, s); MS (ESI): 404 (MH^+);

3-(4-fluorobenzoyl)-5-(5-methyl-4,5-dihydrooxazol-2-yl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole; MS (ESI): 390 (MH^+); and

5-(5-ethyl-4,5-dihydrooxazol-2-yl)-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole; MS (ESI): 404 (MH^+).

EXAMPLE 25

PREPARATION OF DIETHYL -1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-2,5-DICARBOXYLATE



In a manner similar to that described in Example 1A, but replacing tryptamine hydrochloride with the appropriate tryptophan-methyl ester-HCl, the following compounds were prepared:

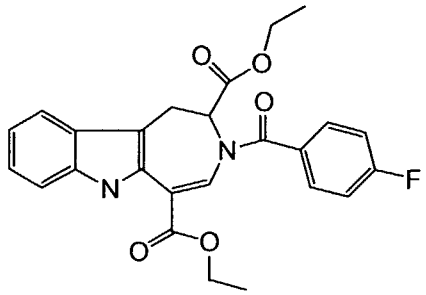
diethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2,5-dicarboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.44 (1H, br s), 7.86 (1H, d), 7.48 (1H, m), 7.33 (1H, d), 7.09 (2H, m), 6.10 (1H, d), 4.29 (4H, m), 4.10 (1H, m), 3.84 (1H, d), 2.97 (1H, dd), 1.33 (6H, m); MS (ES): 329 (MH^+);

diethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2-(R),5-dicarboxylate MS(ESI): 329(MH^+); and

diethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2-(S),5-dicarboxylate, MS(ESI): 329(MH^+).

EXAMPLE 26

PREPARATION OF DIETHYL 3-(4-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-2,5-DICARBOXYLATE



A. The title compound was prepared in a manner similar to that described in Example 2A , but replacing ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with the compounds of Example 25:

diethyl 3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-b]indole-2,5-dicarboxylate; 1H-NMR (CDCl3): δ 10.21 (1H, br s), 8.24 (1H, s), 7.72 (2H, m), 7.55 (1H, d), 7.33 (1H, m), 7.19 (3H, m), 7.10 (1H, m), 6.23 (1H, m), 4.19 (2H, m), 4.09 (1H, dd), 3.82 (2H, q), 3.07 (1 H, dd), 1.17 (3H, t), 0.73 (3H, t); MS (ES): 451 (MH^+);

diethyl 3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-b]indole-2(R),5-dicarboxylate; MS (ESI): 451(MH^+); and

diethyl 3-(4-fluorobenzoyl) -1,2,3,6-tetrahydroazepino[4,5-b]indole—2(S),5-dicarboxylate; MS (ESI): 451(MH^+).

B. In a similar manner, but replacing 4-fluorobenzoyl chloride with the appropriately substituted acyl chloride, the following compounds were prepared:

diethyl 3-benzoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2,5-dicarboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.22 (1H, br s), 8.30 (1H, s), 7.66 (2H, m), 7.44 (4H, m), 7.32 (1H, d), 7.17 (1H, m), 6.25 (1H, m), 4.16 (2H, m), 4.09 (1H, dd), 3.82 (2H, q), 3.07 (1 H, dd), 1.12 (3H, t), 0.73 (3H, t); MS (ES): 433 (MH^+);

diethyl 3-piperonyloyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2,5-dicarboxylate; ^{1}H-NMR ($CDCl_3$): δ 10.44 (1H, br s), 8.33 (1H, s), 7.52 (1H, d), 7.34 (1H, d), 7.25 (1H, m), 7.14-7.19 (2H, m), 7.11 (1H, m), 6.90 (1H, d), 6.19 (1H, m), 6.08 (2H, m), 4.24 (2H, m), 4.08 (1H, dd), 3.82 (2H, q), 3.06 (1H, dd), 1.22 (3H, t), 0.73 (3H, t); MS (ES): 477 (MH^+);

3-(2,4-dichlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2,5-dicarboxylic acid diethyl ester; MS (ES): 501 (MH^+);

3-(4-nitrobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2,5-dicarboxylic acid diethyl ester MS (ES): 478 (MH^+);

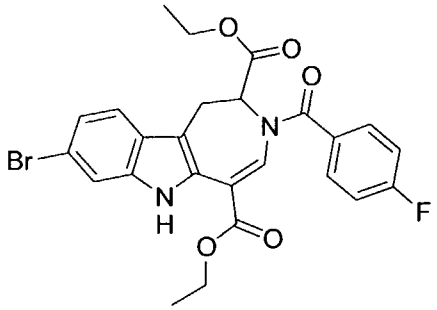
3-(3-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2,5-dicarboxylic acid diethyl ester; MS (ES): 463 (MH^+);

3-(4-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2,5-dicarboxylic acid diethyl ester; MS (ES): 463 (MH^+); and

3-(4-chlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2,5-dicarboxylic acid diethyl ester; MS (ES): 467 (MH^+).

EXAMPLE 27

PREPARATION OF 8-BROMO-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-2,5-DICARBOXYLIC ACID DIETHYL ESTER AND VARIATIONS



A. 8-Bromo-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2,5-dicarboxylic acid diethyl ester was prepared in a manner described in Example 1A, using 6-bromo-DL-tryptophan and ethyl bromopyruvate; ^{1}H-NMR ($CDCl_3$): δ 10.41 (1H, s), 7.80 (1H, d), 7.38 (1H, d), 7.24 (1H, d), 7.18 (1H, dd), 6.06 (1H, s), 4.21 (4H, dd), 4.03 (1H, m), 3.68 (1H, d), 2.88 (H, dd), 1.24 (6H, m); MS (ESI): 407, 409 (MH^+).

B. The title compound was prepared in a manner similar to that described in Example 2A by using 8-Bromo-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2,5-dicarboxylic acid diethyl ester (the compound in Step A) and 4-fluorobenzoyl chloride; ^{1}H-NMR ($CDCl_3$): δ 10.20 (1H, s), 8.20 (1H, s), 7.63 (2H, m), 7.41 (1H, d), 7.32 (1H, d), 7.13 (3H, m), 6.14 (1H, m), 4.12 (2H, m), 3.97 (1H, dd), 3.76 (1H, m), 2.98 (H, dd), 1.11 (3H, t), 0.68 (3H, t); MS (ESI): 529, 531 (MH^+).

C. In a similar manner as Step B, but replacing 4-fluorobenzoyl chloride with the appropriate acyl chloride, the following compounds were prepared:

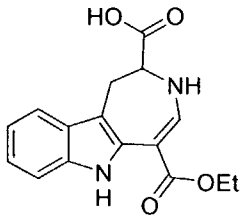
8-bromo-3-(3-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2,5-dicarboxylic acid diethyl ester; MS (ESI): 529, 531 (MH^+);

8-bromo-3-(2-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2,5-dicarboxylic acid diethyl ester; MS (ESI): 529, 531 (MH^+); and

3-acetyl-8-bromo-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2,5-dicarboxylic acid diethyl ester; MS (ESI): 449, 451 (MH^+).

EXAMPLE 28

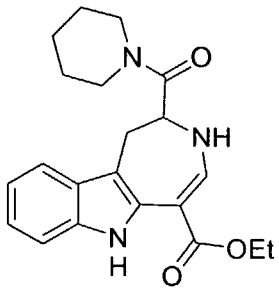
PREPARATION OF 1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-2,5-DICARBOXYLIC ACID 5-ETHYL ESTER



To a suspension of diethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2,5-dicarboxylate (0.48 g, 1.46 mmol) in MeOH (6 mL) was added 4 N aqueous LiOH (1 mL) and the suspension was stirred for 2 hours at 20°C. Solvent was removed and the crude was dissolved in water (50 mL). The aqueous solution was then extracted with EtOAc (3×30 mL) and acidified with HOAc. Precipitate appeared and were collected by filtration and washed with water and EtOAc, then dried under high vacuum to give the title compound (300 mg); ^{1}H-NMR (MeOH-d_4): δ 8.06 (1H, s), 7.54 (1H, dd), 7.44 (1H, dd), 7.12 (2H, m), 4.43 (3H, m), 3.61 (1H, d), 3.41 (1H, m), 1.49 (3H,t); MS (ES): 301 (MH^+).

EXAMPLE 29

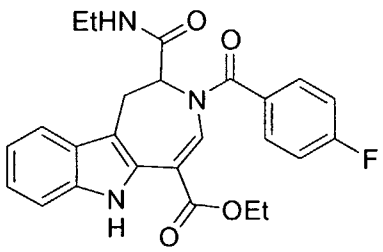
PREPARATION OF ETHYL 2-(PIPERIDINE-1-CARBONYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



To a suspension of 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-2,5-dicarboxylic acid 5-ethyl ester (45 mg, 0.15 mmol) in DCM (3 mL) was added CDI (27 mg, 1.1 equiv.). After stirring for 1 hour at 20°C, piperidine (23 µL, 1.5 equiv.) was added. The mixture was stirred overnight at 20°C and a clear solution was obtained. Evaporation of solvent gave a crude product, which was purified by trituration with MeOH to afford the title compound (22 mg); ^{1}H-NMR ($CDCl_3$): δ 10.44 (1H, br s), 7.95 (1H, d), 7.38 (2H, d), 7.05-7.13 (2H, m), 6.69 (1H, d), 4.29 (2H, q), 3.98 (1H, dd), 3.65-3.73 (2H, m), 3.46 (1H, m), 3.31 (1H, m), 2.71 (1H, dd), 1.58-1.76 (6H, m), 1.36 (3H, t); MS (ES): 368 (MH^+).

EXAMPLE 30

PREPARATION OF ETHYL 2-ETHYLCARBAMOYL-3-(4-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO-[4,5-*B*]INDOLE-5-CARBOXYLATE

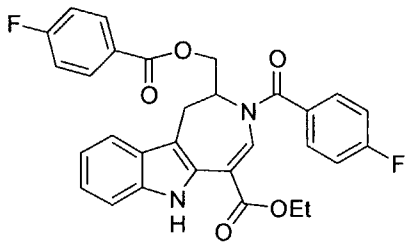


A. Ethyl 2-Ethylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate was prepared in a similar manner to that described in Example 29 by using ethylamine and purified on chromatography on silica gel eluting by EtOAc-Hexane (1:1).

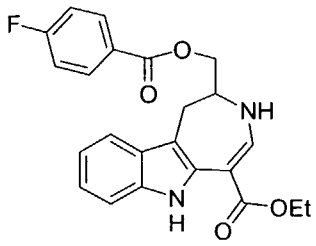
B. The title compound was prepared in a manner similar to that described in Example 2A by using ethyl 2-ethylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate and 4-fluorobenzoyl chloride; ^{1}H-NMR ($CDCl_3$): δ 10.21 (1H, br s), 8.27 (1H, s), 7.71-7.79 (3H, m), 7.53 (1H, m), 7.36 (1H, d), 7.20 (1H, m), 7.11 (2H, m), 6.11 (1H, d), 5.32 (1H, t), 4.21 (2H, m), 3.87 (1H, dd), 3.20 (1H, dd), 2.86-3.06 (2H, m), 1.18(3H, t), 0.57 (3H, t); MS (ES): 450 (MH^+).

EXAMPLE 31

PREPARATION OF ETHYL 3-(4-FLUOROBENZOYL)-2-(4-FLUOROBENZOYLOXY)METHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-DICARBOXYLATE AND ETHYL 2-(4-FLUOROBENZOYLOXY)METHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-DICARBOXYLATE



31a



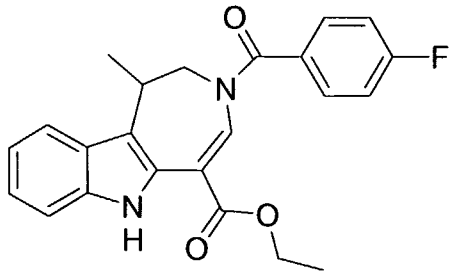
31b

A. Ethyl 2-hydroxymethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate was prepared in a manner similar to that described in Example 1A by using 2-hydroxymethyltryptamine oxalate.

B. The title compounds were prepared in a manner similar to that described in Example 2A by using ethyl 2-hydroxymethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate and 4-fluorobenzoyl chloride; 31a: ^{1}H-NMR ($CDCl_3$): δ 10.46 (1H, br s), 8.15 (1H, s), 7.97 (2H, m), 7.58 (2H, m), 7.53 (1H, d), 7.39 (1H, d), 7.06-7.24 (6H, m), 5.96 (1H, m), 4.12-31 (4H, m), 3.73 (1H, dd), 3.17 (1H, dd), 1.20 (3H, t); MS (ES): 531 (MH^+); 31b: ^{1}H-NMR ($CDCl_3$): δ 10.42 (1H, br s), 8.14 (1H, s), 8.05 (2H, m), 7.81 (1H, d), 7.42 (1H, d), 7.34 (1H, m), 7.04-7.22 (3H, m), 5.62 (1H, m), 4.45 (1H, dd), 4.25-4.35 (3H, m), 4.08 (1H, m), 3.25 (2H, m), 1.35 (3H, t); MS (ES): 409 (MH^+).

EXAMPLE 32

PREPARATION OF ETHYL 3-(4-FLUOROBENZOYL)-1-METHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-B]INDOLE-5-CARBOXYLATE



A. To a stirred solution of 3-indolylacetonitrile (3.9 g, 25 mmol) in DCM (100 mL, anhyd) was added BOC anhydride (6.5 g, 30 mmol), DMAP (3.6 g, 30 mmol) and TEA (4.2 mL, 30 mmol). After 2 hours, the reaction mixture was diluted with DCM (100 mL), washed with 1N HCl (2 x 50 mL) and brine, then dried (Na_2SO_4), concentrated and chromatographed (silica gel, 6% EtOAc/Hex) to yield (1-*tert*-butoxycarbonylindol-3-yl)acetonitrile (5.4 g, 84%) as a pale yellow solid; ^{1}H-NMR ($CDCl_3$): δ 8.17 (1H, br d), 7.64 (1H, br s), 7.52 (1H, br d), 7.38 (1H, app t), 7.30 (1H, app t), 3.78 (2H, s), 1.68 (9H, s).

B. To a stirred solution of (1-*tert*-butoxycarbonylindol-3-yl)acetonitrile (5.30 g, 20.7 mmol) in THF (20 mL, anhyd) chilled to –78°C was added dropwise a 1.0 M solution of LiHMDS in THF (21 mL, 21 mmol). After 40 minutes, iodomethane (1.3 mL, 21 mmol) was added rapidly, and the reaction mixture was allowed to warm to ambient temperature. After 15 hours, the reaction was quenched by addition of 0.2 N HCl (100 mL) and extracted with Et_2O (2 x 100 mL). The combined extracts were washed with brine, dried (Na_2SO_4), concentrated and chromatographed (silica gel, 6% EtOAc/Hex) to give 2-(1-*tert*-butoxycarbonyl indol-3-yl)propionitrile (the title compound) (4.0 g, 71%) as a light yellow oil; ^{1}H-NMR ($CDCl_3$): δ 8.17 (1H, br d), 7.60 (2H, m), 7.37 (1H, br d), 7.30 (1H, app t), 4.10 (1H, q), 1.76 (3H, d), 1.68 (9H, s).

C. To a stirred solution of 2-(1-*tert*-butoxycarbonylindol-3-yl)propionitrile (4.00 g, 14.8 mmol) in DCM (10 mL) was added TFA (10 mL) with caution. After 1 hour, the reaction was diluted with DCM (40 mL), washed with water (2 x 40 mL) and brine, then dried (Na_2SO_4), and concentrated under reduced pressure to give 2-(1*H*-indol-3-yl)propionitrile (2.5 g, 99%) as a pale brown solid; ^{1}H-NMR ($CDCl_3$): δ 8.25 (1H, d), 7.69 (1H, s), 7.65 (1H, d), 7.45 (1H, app t), 7.37 (1H, app t), 4.12 (1H, q), 1.79 (3H, d).

D. To a stirred suspension of LAH (3.4 g, 90 mmol) in THF (40 mL, anhyd) chilled to 0°C was added a solution of 2-(1*H*-indol-3-yl)propionitrile (2.5 g, 14.7 mmol) in THF (40 mL, anhyd). The reaction mixture was allowed to warm to ambient temperature and then heated at reflux. After 1 hour, the reaction mixture was cooled to 0°C and quenched cautiously with wet THF (5-10% H_2O) until gas evolution had ceased. The resulting mixture was filtered through Celite™ and concentrated to give a brown residue. The filtering agent was rinsed with Et_2O (100 mL), which was combined with the residue, dried (Na_2SO_4), and concentrated under reduced pressure to yield 2-(1*H*-indol-3-yl)propylamine (2.1 g, 82%) as a pale amber oil; ^{1}H-NMR

($CDCl_3$): δ 8.28 (1H, br s), 7.61 (1H, d), 7.36 (1H, d), 7.16 (1H, app t), 7.08 (1H, app t), 6.96 (1H, br s), 3.41 (2H, br s), 3.19 (1H, q), 2.95 (2H, app d), 1.35 (3H, d).

E. In a manner similar to Example 1A, but replacing tryptamine hydrocholoride with 2-(1*H*-indol-3-yl)propylamine hydrochloride, prepared *in situ* with one equivalent of anhydrous HCl/dioxane, ethyl 1-methyl-1,2,3,6-tetrahydroazepino[4,5-b]indole-5-carboxylate was prepared; MS(ESI): 271 (MH^+).

F. In a manner similar to Example 2A, but replacing ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with ethyl 1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate, the title compound was prepared; ^1H-NMR ($CDCl_3$): δ 10.54 (1H, br s), 7.97 (1H, s), 7.63-7.68 (2H, m), 7.58 (1H, d), 7.39 (1H, d), 7.09-7.23 (4H, m), 5.28 (1H, dd), 4.25 (2H, m), 3.85 (1H, m), 3.18 (1H, d), 1.34 (3H, d), 1.22 (3H, t); MS(ESI): 393 (MH^+).

G. In a manner similar to that described in Step F, but replacing 4-fluorobenzoyl chloride with the appropriate acyl chloride, the following compounds were prepared:

ethyl 3-(4-chlorobenzoyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^1H-NMR ($CDCl_3$): δ 10.53 (1H, br s), 7.95 (1H, br s), 7.55-7.60 (3H, m), 7.46 (2H, d), 7.38 (1H, d), 7.21 (1H, app t), 7.12 (1H, app t), 5.26 (1H, dd), 4.25 (2H, m), 3.85 (1H, m), 3.18 (1H, d), 1.34 (3H, d), 1.22 (3H, t); MS (ESI): 409 (MH^+); The racemic sample was submitted to chiral separation using (Chiralcel OD 10mmx250 mm, 10% IPA/Hex mobile phase) to afford the two enantiomers.

ethyl 3-(3,4-difluorobenzoyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS(ESI): 411 (MH^+);

ethyl 3-(4-anisoyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 405 (MH^+); and

ethyl 3-piperonyloyl-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 419 (MH^+).

H. In a manner similar to that described in Steps A through E, but using 2 equivalents of iodomethane during the alkylation of (1-*tert*-butoxycarbonyl indol-3-yl)acetonitrile at Step B, the following compound was prepared:

ethyl 1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 285 (MH^+).

I. In a manner similar to that described in Example 2A, but replacing ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with ethyl 1,1-

dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate, the following compound was prepared:

ethyl 1,1-dimethyl-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR (DMSO-d_6): δ 10.82 (1H, s), 7.76 (1H, d), 7.65 (1H, s), 7.61 (2H, dd), 7.54 (1H, d), 7.35 (2H, app t), 7.09 (1H, app t), 6.98 (1H, app t), 4.22 (2H, q), 3.97 (2H, br s), 1.52 (6H, s), 1.17 (3H, t); MS(ESI): 407 (MH^+).

J. In a manner similar to Step I, but replacing 4-fluorobenzoyl chloride with the appropriately substituted benzoyl chloride, the following compounds were prepared:

ethyl 3-(4-chlorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR (DMSO-d_6): δ 10.81 (1H, s), 7.76 (1H, d), 7.63 (1H, s), 7.51-7.61 (5H, m), 7.09 (1H, app t), 6.98 (1H, app t), 4.22 (2H, q), 3.96 (2H, br s), 1.52 (6H, s), 1.18 (3H, t); MS (ESI): 423 (MH^+);

ethyl 3-(3,4-difluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 425 (MH^+);

ethyl 3-(4-anisoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 419 (MH^+); and

ethyl 1,1-dimethyl-3-piperonyloyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 433 (MH^+).

K. In a manner similar to that described in Steps A through E, but replacing iodomethane with bromoethane during alkylation of (1-*tert*-butoxycarbonyl indol-3-yl)acetonitrile at Step B, the intermediate ethyl 1-ethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate was prepared. In manner similar to Step F but replacing ethyl 1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with ethyl 1-ethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate, the following compound was prepared:

ethyl 1-ethyl-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR (DMSO-d_6): δ 10.87 (1H, s), 7.94 (1H, s), 7.69 (2H, m), 7.52 (2H, app t), 7.41 (2H, app t), 7.08 (1H, app t), 7.00 (1H, app t), 5.13 (1H, d), 4.20 (2H, m), 3.56 (1H, m), 3.08 (1H, d), 1.48 (1H, m), 1.14 (3H, t), 0.93 (3H, t); MS(ESI): 407 (MH^+).

L. In a manner similar to Step K, but replacing 4-fluorobenzoyl chloride with the appropriately substituted acyl chloride, the following compounds were prepared:

ethyl 3-(4-chlorobenzoyl)-1-ethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS(ESI): 423 (MH^+);

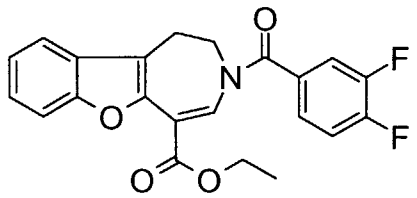
ethyl 3-(3,4-difluorobenzoyl)-1-ethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 425 (MH^+);

ethyl 3-(4-anisoyl)-1-ethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 419 (MH^+); and

ethyl 1-ethyl-3-piperonyloyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; MS (ESI): 433 (MH^+).

EXAMPLE 33

PREPARATION OF 7-(3,4-DIFLUOROBENZOYL)-6,7-DIHYDRO-5H-10-OXA-7-AZA-BENZO[A]AZULENE-9-CARBOXYLIC ACID ETHYL ESTER



A. In a manner similar to that described in Step D of Example 32, but replacing 2-(1-*tert*-butoxycarbonyl indol-3-yl) propionitrile with 3-benzofuranylacetonitrile, the intermediate 3(2-aminoethyl) benzofuran was prepared; MS (ES): 162 (MH^+).

B. In a manner similar to that described in Step E of Example 32, but replacing 2-(1*H*-indol-3-yl)propylamine with 3(2-aminoethyl) benzofuran, the intermediate 6,7-dihydro-5*H*-10-oxa-7-azabenzo[a]azulene-9-carboxylic acid ethyl ester was prepared; MS (ES): 258 (MH^+).

C. In a manner similar to Step F of Example 32, but using the intermediate 6,7-dihydro-5*H*-10-oxa-7-azabenzo[a]azulene-9-carboxylic acid ethyl ester and 3,4-difluorobenzoyl chloride, the title compound was prepared; ^{1}NMR ($CDCl_3$): δ 7.46-7.53 (4H, m), 7.34 (2H, m), 7.25 (2H, m), 4.33 (2H, q), 4.21 (2H, t), 3.17 (2H, t), 1.32 (3H, t). MS (ES): 398 (MH^+).

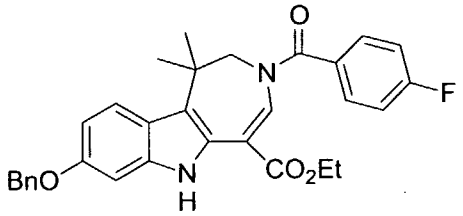
D. In a manner similar to Step A through C, but replacing 3-benzofuranylacetonitrile with 3-benzothiopheneacetonitrile at Step A, the following compound was prepared:

7-(3,4-Difluorobenzoyl)-6,7-dihydro-5H-10-thia-7-aza-benzo[a]azulene-9-carboxylic acid ethyl ester; ^{1}NMR ($CDCl_3$): δ 8.15 (1H, s), 7.84 (1H, m), 7.67 (1H, m),

7.50 (1H, m), 7.38 (3H, m), 7.30 (1H, m), 4.24-4.30 (3H, m), 3.34 (2H, t), 1.27 (3H, t). MS (ES): 414 (MH^+).

EXAMPLE 34

PREPARATION OF 8-BENZYLOXY-3-(4-FLUOROBENZOYL)-1,1-DIMETHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. Methyl iodide (15 mL) was added to a stirred mixture of 6-benzyloxygramine (10 g, 35.66 mmol) in dry benzene (150 mL) at ambient temperature. The mixture was stirred at ambient temperature for 30 minutes, then allowed to stand in the dark overnight. The solid was collected by filtration, then dried in high vaccum to give (6-benzyloxy-1*H*-indol-3-ylmethyl)trimethylammonium iodide (17.5 g).

B. A mixture of (6-benzyloxy-1*H*-indol-3-ylmethyl)-trimethylammonium iodide (2.2 g, 5 mmol), sodium cyanide (500 mg, 10.2 mmol), and 95% EtOH (50 mL) was refluxed under nitrogen for 5 hours. The solvent was removed in vacuo, and the residue was taken in DCM, and washed with water, then dried with sodium sulfate, and evaporated *in vacuo* to afford a white solid, which was recrystallized from EtOH to give (6-benzyloxy-1*H*-indol-3-yl)-acetonitrile (1.25 g, 86%). MS (ES): 263 (MH^+).

C. (6-Benzyloxy-1*H*-indol-3-yl)-acetonitrile was protected by di-*tert*-butyldicarbonate (BOC_2O) to give 6-benzyloxy-3-cyanomethylindole-1-carboxylic acid *tert*-butyl ester using the same conditions as described in Example 32A; MS (ES): 363 (MH^+).

D. Methylation of 6-benzyloxy-3-cyanomethylindole-1-carboxylic acid *tert*-butyl ester was carried out in a manner similar to that described in Step B of Example 32, but using 2 equivalents of iodomethane during alkylation to give 6-benzyloxy-3-(2-cyano(2-propyl)indole-1-carboxylic acid *tert*-butyl ester; MS (ES): 391 (MH^+).

E. 6-Benzyloxy-3-(cyano(dimethyl)methyl)indole-1-carboxylic acid *tert*-butyl ester was deprotected to give 2-(6-benzyloxy-1*H*-indol-3-yl)-2-methyl-

propionitrile in a manner similar to that described in Step C of Example 32; MS (ES): 291 (MH^+).

F. 2-(6-benzyloxy-1*H*-indol-3-yl)-2-methyl-propionitrile was reduced with LAH to give 2-(6-benzyloxy-1*H*-indol-3-yl)-2-methyl-propylamine hydrochloride in a manner similar to that as described in Step D of Example 32; MS (ES): 295 (MH^+).

G. 8-benzyloxy-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester was prepared in a manner similar to that described in Example 1A by using 2-(6-benzyloxy-1H-indol-3-yl)-2-methyl-propylamine hydrochloride generated *in situ*.

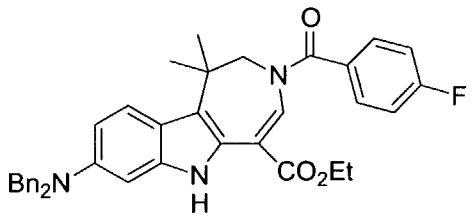
H. The title compound was prepared in a manner similar to that described in Example 2A by using 4-fluorobenzoyl chloride; MS (ES): 513 (MH^+).

I. In a manner similar to that described in Steps C-H, but replacing (6-benzyloxy-1*H*-indol-3-yl)acetonitrile with 5-benzyloxyindole-3-acetonitrile in Step C, the following compound was prepared:

9-benzyloxy-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino [4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 513 (MH^+).

EXAMPLE 35

PREPARATION OF 8-DIBENZYLAMINO-3-(4-FLUOROBENZOYL)-1,1-DIMETHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER AND VARIATIONS



A. To prepare 8-dibenzylamino-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester: Benzyl bromide (10 mL, 84.2 mmol) was added to a stirred mixture of (6-amino-1*H*-indol-3-yl)acetonitrile (Brown, R. K.; Garrison, R.A., *J. Am. Chem. Soc.* (1955), Vol. 77, pp. 3839-3842) (5.16 g, 30.14 mmol), potassium carbonate (10.83 g, 78.36 mmol), sodium iodide (560 mg, 3.74 mmol) and anhydrous DMF (150mL) at ambient temperature under nitrogen. The resulting mixture was stirred at ambient temperature overnight, then poured into a mixture of water, and extracted with ethyl acetate. The combined extracts were washed with ammonium chloride solution, and evaporated *in vacuo*. The residue was purified by chromatography on silica gel eluting with hexane-ethyl acetate (85:15) to

give (6-dibenzylamino-1*H*-indol-3-yl)-acetonitrile (8.8 g); MS (ES): 352 (MH^+), which was then treated in a manner similar to that described in Example 34C-G but replacing (6-benzyloxy-1*H*-indol-3-yl)acetonitrile with (6-dibenzylamino-1*H*-indo-3-yl)acetonitrile at Step C.

B. To prepare 6-(benzyl(methyl)amino)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester: To a solution of 6-amino-1H-indol-3-yl]-acetonitrile (10.8 g, 63.1 mmol) in DCM-MeOH (4:1, 100 mL) was added benzaldehyde (6.8 mL, 1.05 equiv) and the mixture was stirred for 2 h at 20°C. Solvent was removed to give a solid, which was purified by trituration with DCM-hexane (1:4) to give a solid (16. 3 g), which was used in the next step without further purification.

C. To a suspension of all of the above solid in DCM (200 mL) was added $(Boc)_2O$ (20.32 g, 1.5 equiv) and TEA (13.2 mL, 1.5 equiv) and 4-(dimethylamino)pyridine (1 g, 7.8 mmol) and the mixture was stirred for 1 h at 20°C. It was then washed by 1% hydrochloric acid, water, saturated aqueous sodium bicarbonate and water and dried over $MgSO_4$. Evaporation of solvent gave a solid, which was used in the next step without further purification.

D. To a solution of all of the above solid in EtOH-AcOH (10:3, 100mL) was added $NaBH_3CN$ (6g, 94 mmol) and the mixture was stirred for 1 h at 20°C. It was then basified with 28% aqueous ammonium hydroxide and extracted with DCM (3x100 mL). The combined organic layer was washed with water and dried over $MgSO_4$. Evaporation of solvent gave 6-(benzylamino)-3-cyanomethyl-indole-1-carboxylic acid tert-butyl ester as a solid (20.4 g). MS (ES): 362 (MH^+).

E. To a solution of 6-(benzylamino)-3-cyanomethyl-indole-1-carboxylic acid tert-butyl ester (20.4 g, 56.5 mmol) in DMF (100 mL) was added iodomethane (21.2 mL, 6 equiv) and sodium hydride (60%, 13.54g, 6 equiv) at 10°C under nitrogen. The reaction mixture was stirred for 3 h at 0°C. The reaction was quenched with aqueous ammonium chloride and the mixture was extracted with DCM (3x100 mL). The combined organic layer was washed with aqueous ammonium chloride and dried over $MgSO_4$. Evaporation of solvent gave a crude, which was purified by column chromatography on silica gel eluting with hexane-EtOAc (9:1) to give 6-(benzylmethylamino)-3-(cyanodimethylmethyl)indole-1-carboxylic acid tert-butyl ester as a solid (10. 6 g). MS (ES): 404 (MH^+).

F. A solution of 6-(benzyl-methyl-amino)-3-(cyano-dimethyl-methyl)-indole-1-carboxylic acid tert-butyl ester (26.4 g, 90%, 58.9 mmol) in DCM-TFA (2:1, 180 mL) was stirred for 20 h at 20°C. Evaporation of solvent gave a crude, which

was redissolved in DCM and the solution was washed with water, aqueous sodium bicarbonate and water and dried over $MgSO_4$. Evaporation of solvent gave a solid, which was triturated with hexane to give [6-(benzyl-methyl-amino)-1H-indol-3-yl]-acetonitrile as a solid (14.3 g). MS (ES): 304 (MH^+). [6-(benzyl-methyl-amino)-1H-indol-3-yl]-acetonitrile was then treated in a manner similar to that described in Step 34D-H, but using greater than three equivalents of iodomethane, to give 6-(benzyl(methyl)amino)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester.

G. In a similar manner to steps A-F, but replacing (6-amino-1*H*-indol-3-yl)-acetonitrile with (5-amino-1*H*-indol-3-yl)acetonitrile, the following compound was prepared:

9-dibenzylamino-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester.

H. In a manner similar to that described in Example 2A, but replacing ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with the appropriate compounds, the following compounds were prepared:

8-dibenzylamino-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester MS (ES): 602 (MH^+);

8-(benzyl(methyl)amino)-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 526 (MH^+); and

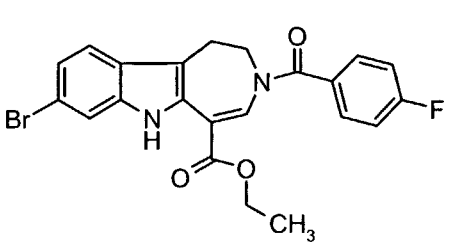
9-dibenzylamino-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 602 (MH^+).

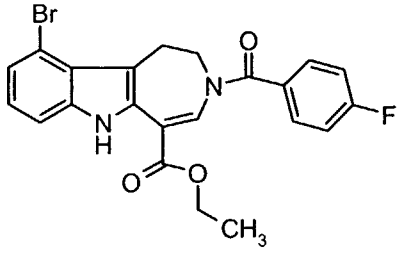
I. In a manner similar to Example 2A, but using ethyl 8-(benzyl(methyl)amino)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate and 3,4-difluorobenzoyl chloride, the following compound was prepared:

8-(benzyl(methyl)amino)-3-(3,4-difluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester. MS (ES): 544 (MH^+).

EXAMPLE 36

PREPARATION OF 10-BROMO-3-(4-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER AND 8-BROMO-3-(4-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



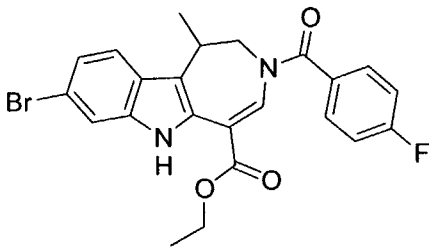


36a 36b

To a solution of ethyl 3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (0.38 g, 1 mmol) in carbon tetrachloride (10 mL) was added *N*-bromosuccinimide (0.28 g, 1.55 mmol) and benzoyl peroxide (10 mg). The mixture was heated to reflux under nitrogen for 30 minutes. After cooling, solid was removed by filtration and washed with carbon tetrachloride. The filtrate was concentrated to give a crude product, which was purified by chromatography on silica gel eluting with MeOH-DCM (1:19) to afford 36a (1.8 mg) and 36b.(6.6 mg): 36a ^{1}H-NMR ($CDCl_3$): δ 10.58 (1H, s), 8.04 (1H, s), 7.62 (2H, m), 7.53 (1H, d), 7.37 (1H, d), 7.18 (3H, m), 4.24 (4H, m), 3.23 (2H, m), 1.23 (3H, t). MS (ES): 457 (MH^+); 36b. ^{1}H-NMR ($CDCl_3$): δ 10.81 (1H, s), 8.11 (1H, s), 7.62 (2H, m), 7.31 (1H, m), 7.24 (1H,m), 7.18 (2H, m), 6.98 (1H, m), 4.25 (2H, q), 4.20 (2H, t), 3.78 (2H, t), 1.23 (3H, t); MS (ES): 457 (MH^+).

EXAMPLE 37

PREPARATION OF 8-BROMO-3-(4-FLUOROBENZOYL)-1-METHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. To a stirred solution of 3-(4-fluorobenzoyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester (compound in Example 32F) (110 mg, 0.28 mmol) in 6 mL of DCM was added NBS (48 mg, 0.27 mmol) at ambient temperature. The reaction mixture was stirred at ambient temperature under N_2 for 1.5 hours and samples monitored by LC-MS. The solution was concentrated and purified by flash chromatograph on silica gel, eluting with EtOAc-hexane (0-30%) to yield the title compound (124 mg) as a yellow solid; ^{1}H-NMR ($CDCl_3$): δ 10.54 (1H, s), 7.98 (1H, d), 7.63 (2H, m), 7.50 (1H, d), 7.39 (1H, m), 7.16 (3H, m), 5.26 (1H, dd), 4.22 (2H, m), 3.78 (1H, m), 3.12 (1H, m), 1.28 (3H, d), 1.18 (3H, t). MS (ESI): 471, 473 (MH^+).

B. In a similar manner, but using excess NBS, the following compound was prepared:

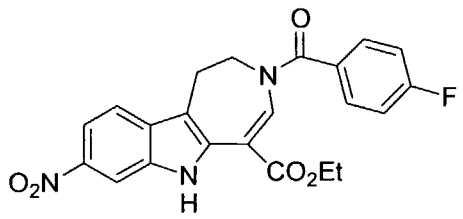
8,10-dibromo-3-(4-fluorobenzoyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 550 (MH^+).

C. In a similar manner as in Step A, but replacing 3-(4-fluorobenzoyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester with ethyl 3-(4-fluororobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate, the following compound was prepared:

8-bromo-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; ^{1}H-NMR ($CDCl_3$): δ 10.81 (1H, s), 7.95 (1H, s), 7.73 (3H, m), 7.65 (1H, d), 7.26 (3H, m), 4.36 (2H, dd), 1.72 (6H, s), 1.31 (3H, t); MS (ESI): 485, 487 (MH^+).

EXAMPLE 38

PREPARATION OF 3-(4-FLUOROBENZOYL)-8-NITRO-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



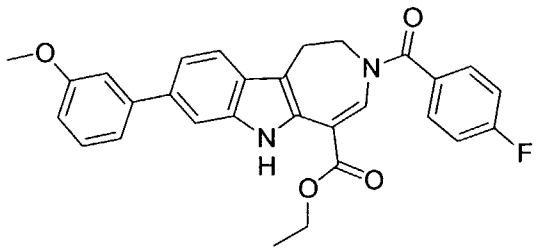
A. A solution of nitric acid (90%, 50 µL, 1 mmol) in acetic acid (3 mL) was added dropwise to a stirred solution of ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (256 mg, 1 mmol) in acetic acid (5mL) at

10°C. The mixture was allowed to warm to ambient temperature and stirred for another 1.5 hours, then poured into a mixture of ammonium hydroxide and ice and extracted with DCM. The combined extracts was washed with brine, dried with sodium sulfate, and evaporated *in vacuo*. The crude product was purified by chromatography on silica gel eluting with hexane-EtOAc (75:25) to give 8-nitro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester (25mg); ^{1}H-NMR ($CDCl_3$): δ 11.52 (1H, s), 8.78 (1H, d), 8.43 (1H, m), 7.92 (1H, d), 7.82 (1H, dd), 7.46 (1H, d), 4.24 (2H, q), 3.52 (2H, m), 3.07 (2H, m), 1.27 (3H, t); MS (ES): 301 (MH^+).

B. The title compound was prepared in a manner similar to that described in Example 2A by using 8-nitro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester and 4-fluorobenzoyl chloride; MS (ES): 424 (MH^+).

EXAMPLE 39

PREPARATION OF 3-(4-FLUOROBENZOYL)-8-(3-METHOXYPHENYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. To a stirred solution of 8-bromo-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester (compound in Example 37A, 70 mg, 0.15 mmol), 3-methoxyphenylboronic acid (58 mg, 0.38 mmol), and (o-tolyl)$_3$P (24 mg, 0.077 mmol) in toluene/EtOH (2:1, 3 mL) was added 0.55 mL of 1M $NaHCO_3$ solution and $Pd(OAc)_2$ (7 mg) at ambient temperature. The reaction mixture was heated at 80°C under N_2 for 1.5 hours and samples monitored by LC-MS. The solution was diluted with DCM (10 mL) and washed with brine. The aqueous phase was extracted with DCM (10 mL) twice. The combined organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatograph on silica gel, eluting with EtOAc-hexane (0-30%) to yield the title compound (68 mg) as a light yellow solid; ^{1}H-NMR ($CDCl_3$): δ 10.76 (1H, s), 8.20 (1H, s), 7.78 (4H, m), 7.52 (2H, m), 7.42 (1H, d), 7.36 (3H, m), 7.04 (1H, m), 4.43 (4H, m), 4.05 (3H, s), 3.45 (2H, m), 1.39 (3H, t). MS (ESI): 485 (MH^+).

B. In a similar manner, but replacing 3-methoxyphenylboronic acid with 3-furanboronic acid or 4-(2-aminoethyl)-morpholine, the following compounds were prepared:

3-(4-fluorobenzoyl)-8-furan-3-yl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 445 (MH^+); and

3-(4-fluorobenzoyl)-8-(2-morpholin-4-yl-ethylamino)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 507 (MH^+).

C. In a manner similar to Step A, but replacing 8-bromo-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester with 8-bromo-3-(4-fluorobenzoyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester, the following compound was prepared:

3-(4-fluorobenzoyl)-8-(3-methoxyphenyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; ^{1}H-NMR ($CDCl_3$): δ 10.52 (1H, s), 7.92 (1H, d), 7.56 (4H, m), 7.29 (2H, m), 7.17 (1H, m), 7.11 (3H, m), 6.81 (1H, m), 5.22 (1H, dd), 4.20 (2H, m), 3.81 (4H, m), 3.12 (1H, m), 1.28 (3H, d), 1.15 (3H, t); MS (ESI): 499 (MH^+).

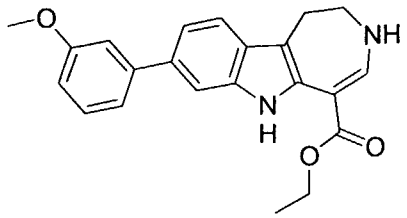
D. In a manner similar to Steps A and B, but replacing 8-bromo-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester with 8-bromo-3-(4-fluorobenzoyl)-1,1-dimethyl-2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester, the following compounds were prepared:

3-(4-fluorobenzoyl)-8-(3-methoxyphenyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; ^{1}H-NMR ($CDCl_3$): δ 10.71 (1H, s), 7.85 (1H, d), 7.81 (1H, s), 7.63 (3H, m), 7.35 (2H, m), 7.23 (1H, m), 7.20 (1H, m), 7.13 (2H, m), 6.88 (1H, m), 4.26 (2H, dd), 3.89 (3H, s), 1.68 (6H, s), 1.23 (3H, t). MS (ESI): 513 (MH^+); and

3-(4-fluorobenzoyl)-8-furan-3-yl-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; ^{1}H-NMR ($CDCl_3$): δ 10.67 (1H, s), 7.81 (2H, m), 7.76 (1H, t), 7.63 (2H, m), 7.48 (2H, m), 7.23 (1H, m), 7.13 (2H, m), 6.76 (1H, m), 4.26 (2H, dd), 3.89 (3H, s), 1.62 (6H, s), 1.21 (3H, t). MS (ESI): 473 (MH^+).

EXAMPLE 40

PREPARATION OF 8-(3-METHOXYPHENYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. To a stirred solution of 3-(4-fluorobenzoyl)-8-(3-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester (48 mg, 0.10 mmol) in 2 mL of EtOH was added 0.30 mL of 1M Na_2CO_3 solution at ambient temperature. The reaction mixture was heated at 93°C reflux under N_2 for 3.5 hours and samples monitored by LC-MS. The solution was diluted with DCM (10 mL), washed with brine. The aqueous phase was extracted with DCM (10 mL) twice. The combined organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatograph on silica gel, eluting with EtOAc-hexane (0-30%) to yield the title compound (33 mg) as a yellow solid; ^{1}H-NMR ($CDCl_3$): δ 10.46 (1H, s), 7.73 (1H, d), 7.47 (1H, d), 7.37 (1H, d), 7.26 (2H, m), 7.12 (1H, m), 7.00 (1H, m), 6.79 (1H, m), 5.25 (1H, s), 4.21(2H, m), 3.80 (3H, s), 3.55 (2H, m), 3.11 (2H, m), 1.26 (3H, t). MS (ESI): 363 (MH^+).

B. In a similar manner, but replacing 3-(4-fluorobenzoyl)-8-(3-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester with the compounds prepared in Steps C and D of Example 39, the following compounds were prepared:

8-(3-ethoxyphenyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 377 (MH^+);

8-(3-methoxyphenyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 391 (MH^+); and

8-furan-3-yl-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 351 (MH^+).

C. In a manner similar to Example 2A, but replacing ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with 8-(3-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester and 4-fluorobenzoyl chloride with 3,4-difluorobenzoyl chloride, the following compound was prepared:

3-(3,4-difluorobenzoyl)-8-(3-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 503 (MH^+).

D. In a similar manner to Step C, but replacing 8-(3-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester with 8-(3-methoxyphenyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester, the following compound was prepared:

3-(3,4-difluorobenzoyl)-8-(3-methoxyphenyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 517 (MH^+).

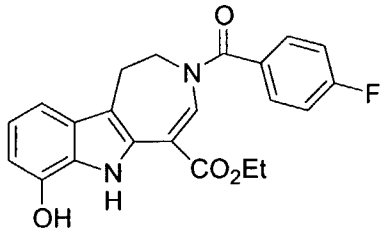
E. In a manner similar to Step C, but replacing 8-(3-methoxyphenyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester with 8-(3-methoxyphenyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester or 8-furan-3-yl-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester, the following compounds were prepared:

3-(3,4-difluorobenzoyl)-8-(3-methoxyphenyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 531 (MH^+); and

3-(3,4-difluorobenzoyl)-8-furan-3-yl-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 491 (MH^+).

EXAMPLE 41

PREPARATION OF 3-(4-FLUOROBENZOYL)-7-HYDROXY-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. A mixture of 7-benzyloxy-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester (82 mg, 0.17 mmol) and 10% Pd/C (82 mg) and 1,4-cyclohexadiene (0.15 mL, 1.58 mmol) was stirred at 50°C for 2 hours. The catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with hexane-EtOAc (85:15) to give the title compound as a yellow solid (42mg, 62%); ^{1}H-NMR ($CDCl_3$): δ 10.56 (1H, s), 8.0 (1H, s), 7.64-7.59 (2H, m), 7.20-7.11(3H, m), 6.97-6.93 (1H, m),

6.61-6.55 (1H, m), 5.33 (1H, brs), 4.27-4.20 (4H, m), 3.26-3.23 (2H, m), 1.25 (3H, t); MS (ES): 395 (MH^+).

B. In a manner similar to that described above in Step A, but replacing the 7-benzyloxy-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester with 10-benzyloxy 3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester, the following compound was prepared:

3-(4-fluorobenzoyl)-10-hydroxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 395 (MH^+).

C. In a manner similar to that described above in Step A, but replacing 7-benzyloxy-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester with 8-benzyloxy-3-(4-fluorobenzoyl)1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester, 9-benzyloxy-3-(4-fluorobenzoyl)1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester or 9-dibenzylamino-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester, the following compounds were prepared:

3-(4-fluorobenzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; ^{1}H-NMR ($CDCl_3$): δ 10.45 (1H, s), 7.72 (1H, s), 7.66-7.59 (3H, m), 7.15-7.10 (2H, m), 6.81 (1H, d), 6.66 (1H, dd), 4.84 (1H, s), 4.24 (2H, q), 4.08 (2H, brs), 1.59 (6H, s), 1.24 93H, t); MS (ES): 423 (MH^+);

3-(4-fluorobenzoyl)-9-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 423 (MH^+);

9-benzylamino-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 512 (MH^+); and

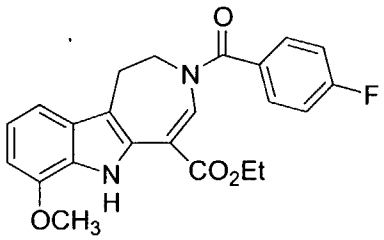
9-amino-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester; MS (ESI): 422 (MH^+).

D. For the preparation of 9-fluoro-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester, to a stirred solution of 9-amino-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester (Example 41C) (0.024 g, 0.055 mmol) in 1.0 mL of MeCN was added 11 µL of 48% HBF_4 water solution at –10°C under N_2 for 10 minutes. 9 µL of ^{t}BuONO (90%, 0.066 mmol) was added to the reaction mixture and

stirred at –10°C for 20 minutes. The reaction mixture was warmed to room temperature for 1 hour and monitored by LC-MS. The solvents were removed in vacuo, and the residue was washed with Et_2O/hexane (1:1) once and benzene twice. After having dried in high vacuo for several hours, a brown solid was obtained. The solid in 1.5 mL of xylenes was heated at 145°C reflux under N_2 for 1 hour and then concentrated. The crude product was purified by flash chromatograph on silica gel, eluting with EtOAc- hexane (0-30%) to yield the title compound (0.012 g) as a light yellow solid. ^{1}H-NMR ($CDCl_3$): δ10.68 (1H, s), 7.83 (1H, s), 7.62 (2H, m), 7.44 (1H, dd), 7.29 (1H, m), 7.13 (2H, m), 6.93 (1H, m), 4.23 (2H, q), 1.56 (6H, s), 1.22 (3H, t). MS (ESI): 425 (MH^+).

EXAMPLE 42

PREPARATION OF 3-(4-FLUOROBENZOYL)-7-METHOXY-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. A mixture of 3-(4-fluorobenzoyl)-7-hydroxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester (65 mg, 0.16 mmol), potassium carbonate (54 mg, 0.39 mmol), methyl iodide (0.4 mL, 6.4 mmol) and dry acetone (5 mL) was stirred at 60°C for 13 hours. The potassium carbonate solid was filtered off, and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel eluting with hexane-EtOAc (90:10) to give the title compound as a yellow solid (36mg, 55%); ^{1}H-NMR ($CDCl_3$): δ 10.56 (1H, s), 7.98 (1H, s), 7.64-7.59 (2H, m), 7.18-7.12 (3H, m), 7.03 (1H, t), 6.64 (1H, d), 4.28-4.19 (4H, m), 3.96 (3H, s), 3.26-3.24 (2H, m), 1.24 (3H, t); MS (ES): 409 (MH^+).

B. In a similar manner, but replacing 3-(4-fluorobenzoyl)-7-hydroxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester with 3-(4-fluorobenzoyl)-10-hydroxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester, the following compound was prepared:

3-(4-fluorobenzoyl)-10-methoxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 409 (MH^+).

C. In a manner similar to that described in Step A, but replacing methyl iodide with 4-(2-chloroethyl)morpholine hydrochloride, the following compound was prepared:

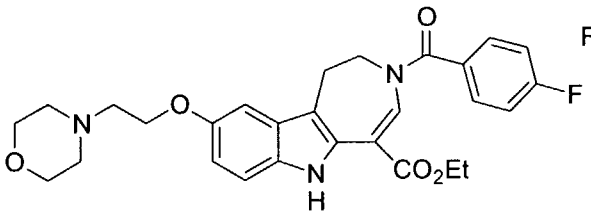
3-(4-fluorobenzoyl)-7-(2-morpholin-4-yl-ethoxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 508 (MH^+).

D. In a manner similar to that described in Step A, but methylating 9-amino-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester, the following compound was prepared:

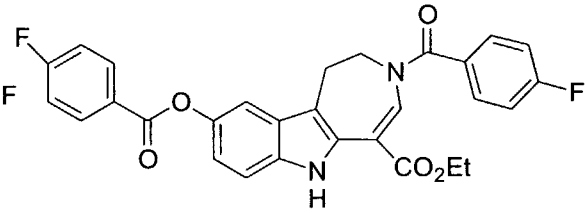
9-Dimethylamino-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester; MS (ESI): 450 (MH^+).

EXAMPLE 43

PREPARATION OF 3-(4-FLUOROBENZOYL)-9-(2-MORPHOLIN-4-YL-ETHOXY)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER AND 3-(4-FLUOROBENZOYL)-9-(4-FLUOROBENZOYLOXY)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



43a



43b

A. A mixture of 9-hydroxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester (109 mg, 0.4 mmol) , potassium carbonate (280 mg, 2.0 mmol), sodium iodide (60 mg, 0.4 mmol) and 4-(2-chloroethyl)morpholine hydrochloride (224 mg, 1.2 mmol) in dry acetone (10 mL) was stirred at 80°C for 5 days. The solid was filtered off, and the filtrate was concentrated *in vacuo*, and then dried in high vacuum for several hours, which was used in the next reaction without further purification; MS (ES): 386 (MH^+).

B. The above crude product was dissolved in dry DCM (15 mL), and triethylamine (0.9 mL) was added followed by 4-fluorobenzoyl chloride (0.3 mL) at 0°C. The resulting mixture was stirred at ambient temperature overnight. The solvent was removed *in vacuo*, and the residue was purified by chromatography on silica gel

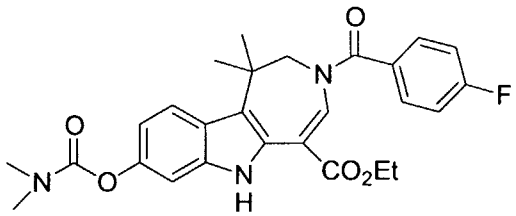
eluting with DCM-50% MeOH/DCM (80:20) to give the title compounds 43a (52mg) and 43b (26 mg); 43a, ^{1}H-NMR ($CDCl_3$): δ 10.43 (1H, s), 7.97 (1H, s), 7.64-7.60 (2H, m), 7.27 (1H, m), 7.19-7.09 (2H, m), 6.95 (1H, d), 6.88 (1H, dd), 4.28-4.17 (6H, m), 3.78-3.69 (5H, m), 3.22-3.20 (2H, m), 2.84 (2H, m), 2.66-2.51 (4H, m), 1.24 (3H, t); MS (ES): 506 (MH^+); 43b, ^{1}H-NMR (DMSO-d_6): δ 11.00 (1H, s), 8.24-8.20 (2H, m), 8.05-7.99 (1H, m), 7.72-7.68 (2H, m), 7.59 (1H, d), 7.47-7.30 (5H, m), 6.97 (1H, d), 4.23 (2H, q), 4.07-4.02 (2H, m), 3.18 (2H, m), 1.20 (3H, t); MS (ES): 517 (MH^+).

C. In a similar manner, but replacing 4-(2-chloroethyl)morpholine hydrochloride with 1-(2-chloroethyl)piperidine hydrochloride, the following compound was prepared:

3-(4-fluorobenzoyl)-9-(2-piperidin-1-ylethoxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 506 (MH^+).

EXAMPLE 44

PREPARATION OF 8-DIMETHYLCARBAMOYLOXY-3-(4-FLUOROBENZOYL)-1,1-DIMETHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. Dimethylcarbamoyl chloride (0.2 mL, 2.17 mmol) was added dropwise to a stirred solution of 3-(4-fluorobenzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester (199 mg, 0.47 mmol), 4-dimethylaminopyridine (DMAP) (20 mg), and triethylamine (0.8 mL, 5.74mmol) in anhydrous DCM (15 mL) at 0°C under nitrogen, and the resulting mixture was stirred at 50°C for 5 hours. The solvents were removed *in vacuo*, and the residue was purified by chromatography on silica gel eluting with DCM-20%MeOH/DCM (90:10) to give the title compound (171 mg, 74%); ^{1}H-NMR ($CDCl_3$): δ 10.62 (1H, s), 7.78 (s, 1H), 7.74 (1H, d), 7.63-7.59 (2H, m), 7.16-7.10 (3H, m), 6.84 (1H, dd), 4.24 (2H, q), 4.08 (2H, brs), 3.14 (3H, s), 3.03 (3H, s), 1.59 (6H, s), 1.23 (3H, t); MS (ES): 494 (MH^+).

B. In a similar manner, but replacing dimethylcarbamoyl chloride with the appropriate carbamoyl chloride, acid chloride or chloroformate, the following compounds were prepared:

8-diethylcarbamoyloxy-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 522 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(morpholine-4-carbonyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 536 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(piperidine-1-carbonyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 534 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(pyrrolidine-1-carbonyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 520 (MH^+);

8-diisopropylcarbamoyloxy-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 550 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(2-oxo-imidazolidine-1-carbonyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 535 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(methyl-phenyl-carbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 556 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(4-methyl-piperazine-1-carbonyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 549 (MH^+);

8-ethoxycarbonyloxy-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 495 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-phenoxycarbonyloxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 543 (MH^+);

8-benzyloxycarbonyloxy-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 557 (MH^+);

8-acetoxy-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 465 (MH^+); and

8-(ethyl-isopropyl-carbamoyloxy)-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 536 (MH^+).

C. In a manner similar to that described in Step A above, but replacing 3-(4-fluorobenzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester with 3-(4-fluorobenzoyl)-9-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl

ester, and dimethylcarbamyl chloride with 1-pyrrolidinecarbonyl chloride, the following compound was prepared:

3-(4-fluorobenzoyl)-1,1-dimethyl-9-(pyrrolidine-1-carbonyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 520 (MH^+).

D. In a manner similar to that described in Step C, but replacing 1-pyrrolidinecarbonyl chloride with 4-morpholine carbonyl chloride or dimethylcarbamyl chloride, the following compounds were prepared:

3-(4-fluorobenzoyl)-1,1-dimethyl-9-(morpholine-1-carbonyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 536 (MH^+); and

9-dimethylcarbamoyloxy-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 494 (MH^+).

E. In a manner similar to Step A, but replacing 3-(4-fluorobenzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester with 9-amino-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester and dimethylcarbamyl chloride with methoxyacetyl chloride, the following compound was prepared:

9-(2-methoxy-acetylamino)-3-(4-Fluorobenzoyl)- 1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 494 (MH^+).

F. In a manner similar to Step E, but replacing methoxyacetyl chloride with the appropriate acyl chloride or carbamyl chloride, the following compounds were prepared:

9-acetylamino-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 464 (MH^+);

3-(4-fluorobenzoyl)-9-(4-fluorobenzoylamino)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 544 (MH^+);

9-(3,3-dimethyl-ureido)-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 493 (MH^+);

3-(4-fluoro-benzoyl)-1,1-dimethyl-9-[(morpholine-4-carbonyl)-amino]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester, MS (ESI): 535 (MH^+);

3-(4-fluoro-benzoyl)-1,1-dimethyl-9-(2-thiophen-2-yl-acetylamino)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester; MS (ESI): 546 (MH^+); and

3-(4-fluoro-benzoyl)-9-(3-isopropyl-ureido)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester, MS (ESI): 507 (MH^+).

G. In a manner similar to Step A, but replacing 3-(4-fluorobenzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester with 9-benzylamino-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester, the following compound was prepared:

9-(1-benzyl-3,3-dimethyl-ureido)-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ESI): 583 (MH^+).

H. To prepare 3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-propylcarbamoyloxy) -1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester, a mixture of 3-(3,4-difluoro-benzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-*b*]-indole-5-carboxylic acid ethyl ester (45 mg, 0.1 mmol), triethylamine (0.1 mL), and propylisocyanate (0.2 mL) in dry DCM (5 mL) was refluxed at 60°C for 20 hours. The solvent was removed in vacuo, and the residue was purified by preparative reverse-phase HPLC to give the title compound, which was then acylated in the manner described in Example 2A; ^{1}HNMR ($CDCl_3$): δ 10.62 (1H, s), 7.76-7.73 (2H, m), 7.52-7.47 (1H, m), 7.36-7.31 (1H, m), 7.24-7.19 (1H, m), 7.16 (1H, d), 6.86 (1H, m), 5.04 (1H, t), 4.26 (2H, q), 4.09 (2H, brs), 3.25 (2H, q), 1.66-1.54 (8H, m), 1.25 (3H, t), 0.99 (3H, t). MS (ES): 526 (MH^+).

I. In a manner similar to step H but using 3-(3,4-difluoro-benzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]-indole-5-carboxylic acid isopropyl ester and isopropyl isocyanate the following compound was prepared:

3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-isopropylcarbamoyloxy-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid isopropyl ester MS (ES): 540(MH^+).

J. In a manner similar to step H but using 3-(3,4-difluoro-benzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]-indole-5-carboxylic acid isopropyl ester and 4-fluorobenzyl isocyanate the following compound was prepared:

3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-[1-(4-fluorobenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid isopropyl ester MS (ES): 606 (MH^+).

K. In a manner similar to step H but using 3-(3,4-difluoro-benzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]-indole-5-carboxylic acid isopropyl ester and (S)-α-methylbenzyl isocyanate the following compound was prepared:

3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-[1-(S)-α-methylbenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid isopropyl ester MS (ES): 602(MH^+).

L. In a manner similar to step H but using 3-(3,4-difluoro-benzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]-indole-5-carboxylic acid ethyl ester and phenyl isocyanate the following compound was prepared:

3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-(1-phenylcarbamoyloxy)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester MS (ES): 560 (MH^+).

M. In a manner similar to step H but using 3-(3,4-difluoro-benzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]-indole-5-carboxylic acid ethyl ester and 4-fluorobenzyl isocyanate the following compound was prepared:

3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-[1-(4-fluorobenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester MS (ES): 592 (MH^+).

N. In a manner similar to step H but using 3-(3,4-difluoro-benzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]-indole-5-carboxylic acid ethyl ester and (R)-α-methylbenzyl isocyanate the following compound was prepared:

3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-[1-(R)-α-methylbenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester . MS (ES): 588 (MH^+).

O. In a manner similar to step H but using 3-(3,4-difluoro-benzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]-indole-5-carboxylic acid ethyl ester and (S)-α-methylbenzyl isocyanate the following compound was prepared:

3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-[1-(S)-α-methylbenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl MS (ES): 588 (MH^+).

P. In a manner similar to step H but using 3-(4-fluoro-benzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]-indole-5-carboxylic acid ethyl ester and (S)-α-methylbenzyl isocyanate the following compound was prepared:

3-(4-fluoro-benzoyl)-1,1-dimethyl-8-[1-(S)-α-methylbenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester MS (ES): 570 (MH^+).

Q. In a manner similar to step H but using 3-(4-fluoro-benzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]-indole-5-carboxylic acid ethyl ester and benzyl isocyanate the following compound was prepared:

3-(4-fluoro-benzoyl)-1,1-dimethyl-8-(1-benzylcarbamoyloxy)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester MS (ES): 556 (MH^+).

R. In a manner similar to step H but using 3-(4-fluoro-benzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]-indole-5-carboxylic acid ethyl ester and 2,3-dihydrobenzofuran-5-yl isocyanate the following compound was prepared:

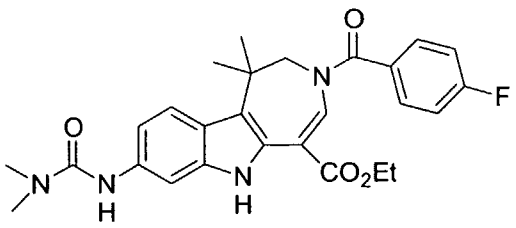
3-(4-fluoro-benzoyl)-1,1-dimethyl-8-[1-(2,3-dihydrobenzofuran-5-yl-carbamoyloxy)]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester. MS (ES): 584 (MH^+).

S. In a manner similar to step H but using 3-(4-fluoro-benzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]-indole-5-carboxylic acid ethyl ester and benzyl isothiocyanate the following compound was prepared:

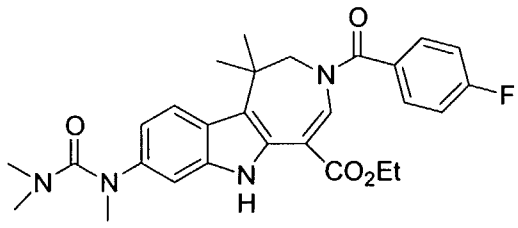
3-(4-fluoro-benzoyl)-1,1-dimethyl-8-(1-benzylcarbamoyloxy)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester MS (ES): 585 (MH^+).

EXAMPLE 45

PREPARATION OF 8-(3,3-DIMETHYL-UREIDO)-3-(4-FLUOROBENZOYL)-1,1-DIMETHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER AND 3-(4-FLUOROBENZOYL)-1,1-DIMETHYL-8-(1,3,3-TRIMETHYL-UREIDO)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



45a



45b

A. The product of Example of 35B was debenzylated to give a mixture of 8-amino-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester and 8-methylamino-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid

ethyl ester (ca.1:1) using the same conditions as described in Example 41. The mixture was used in the next reaction without further purification.

B. The title compounds were prepared in a manner similar to that described in Example 44A using the above mixture of 8-amino-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester and 8-methylamino-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; 45a: MS (ES): 493 (MH^+); 45b: MS (ES): 507 (MH^+).

C. In a manner similar to Example 44H but using 8-methylamino-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]-indole-5-carboxylic acid ethyl ester prepared above and isopropyl isocyanate the following compound was prepared:

3-(4-fluoro-benzoyl)-1,1-dimethyl-8-(1-methyl-3-isopropyl-ureido)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester MS (ES): 521 (MH^+).

D. In a manner similar to Example 44H, but using 8-methylamino-3-(3,4-difluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]-indole-5-carboxylic acid ethyl ester prepared in a similar manner as in Example 45, and methyl isocyanate the following compound was prepared:

3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-(1-methyl-3-methyl-ureido)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester. MS (ES): 493 (MH^+).

E. In a manner similar to Example 44H but using 8-methylamino-3-(3,4-difluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]-indole-5-carboxylic acid ethyl ester prepared in a similar manner to step B and 2-fururyl isothiocyanate the following compound was prepared:

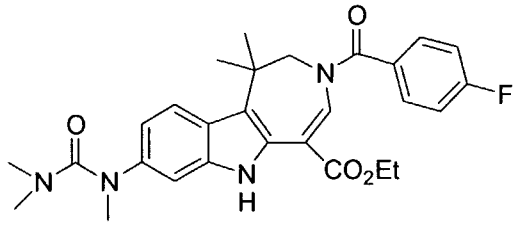
3-(3, 4-difluoro-benzoyl)-1,1-dimethyl-8-(1-methyl-3-furan-2-ylmethyl-thioureido)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester. MS (ES): 575 (MH^+).

F. In a manner similar to Example 44H but using 8-methylamino-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]-indole-5-carboxylic acid ethyl ester prepared in step B, and 2-fururyl isothiocyanate the following compound was prepared:

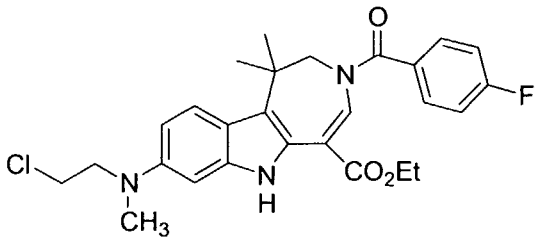
3-(4-fluoro-benzoyl)-1,1-dimethyl-8-(1-methyl-3-benzyl-thioureido)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester MS (ES): 575 (MH^+).

EXAMPLE 46

PREPARATION OF 3-(4-FLUOROBENZOYL)-1,1-DIMETHYL-8-(1,3,3-TRIMETHYL-UREIDO)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER AND 8-[(N-2-CHLORO-ETHYL)-N-METHYL-AMINO]-3-(4-FLUOROBENZOYL)-1,1-DIMETHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



46a



46b

A. 8-(Benzyl(methyl)amino)-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester was debenzylated to give 8-methylamino-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino [4,5-*b*]indole-5-carboxylic acid ethyl ester in a manner similar to that described in Example 41; MS (ES): 436 (MH^+).

B. 8-Methylamino-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro azepino[4,5–b] indole-5-carboxylic acid ethyl ester was reacted with dimethylcarbamoyl chloride in a manner similar to that described in Example 44 using 1,2-dichloroethane instead of DCM as solvent to give 3-(4-fluorobenzoyl)-1,1-dimethyl-8-(trimethylureido)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester. At the same time, 8-[(2-chloroethyl)methylamino]-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester was also obtained as a minor by-product; MS (ES): 498 (MH^+).

C. In a manner similar to that described in Steps A and B, but replacing 8-(benzyl(methyl)amino)-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester with 8-(benzyl(methyl)amino)-3-(3,4-difluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester at Step B and 1,2-dichloroethane with chloroform, the following compound was prepared:

3-(3,4-difluorobenzoyl)-1,1-dimethyl-8-(trimethylureido)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester.

D. In a manner similar to that described in Step C, but replacing dimethylcarbamoyl chloride with the appropriate carbamoyl chloride or acid chloride the following compounds were prepared:

3-(4-fluorobenzoyl)-1,1-dimethyl-8-[methyl(pyrrolidine-4-carbonyl)amino]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 533 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-[methyl(morpholine-4-carbonyl)-amino]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 549 (MH^+);

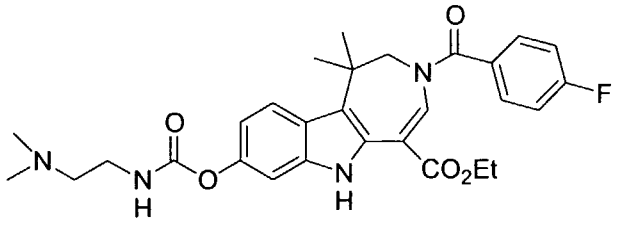
8-(4-fluorobenzoylmethylamino)-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 558 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(1-methyl-3-pyridin-2-ylmethylureido)- 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 570 (MH^+); and

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(1-methyl-3-pyridin-2-yl-ethylureido)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester.

EXAMPLE 47

PREPARATION OF 8-(2-DIMETHYLAMINO-ETHYLCARBAMOYLOXY)-3-(4-FLUOROBENZOYL)-1,1-DIMETHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. Triphosgene (58 mg, 0.195 mmol) was added to a stirred solution of 3-(4-fluorobenzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester (49 mg, 0.116 mmol) and diisopropylethylamine (0.8 mL, 4.01 mmol) in dry DCM (10mL) at 0°C under N_2. The resulting mixture was stirred at ambient temperature for 1.5 hours, and *N,N*-dimethylethylenediamine (0.1 mL, 0.91 mmol) was added. The mixture was stirred at ambient temperature overnight. The solvents were removed *in vacuo*, and the residue

was purified by preparative reverse-phase HPLC to give the title compound (18mg); ^{1}H-NMR ($CDCl_3$): 10.63 (1H, s), 7.76 (2H, m), 7.63-7.60 (2H, m), 7.16-7.11 (3H, m), 6.88-6.86 (1H, dd), 5.61 (1H, t), 4.24 (2H, q), 4.10 (2H, brs), 3.37 (2H, m), 2.48 (2H, m), 2.27 (6H, s), 1.59 (6H, s), 1.24 (3H, t); MS (ES): 537 (MH^+).

B. In a similar manner, but replacing *N, N*-dimethylethylenediamine with the appropriately substituted alcohol or amine, the following compounds were prepared:

8-(2-dimethylaminoethoxycarbonyloxy)-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 538 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(2-pyridin-2-yl-ethylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 538 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(pyridin-4-yl-methylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 557 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(pyridin-2-yl-methylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 557 (MH^+);

8-cyclopropylcarbamoyloxy-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 506 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(4-pyridin-2-yl-piperazine-1-carbonyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 557 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(pyridin-3-yl-methylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 557 (MH^+);

8-(azetidine-1-carbonyloxy)-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 506 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(4-methylpiperazin-1-ylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 564 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-phenethylcarbamoyloxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 570(MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(thiophen-2-ylmethylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 557(MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(furan-2-ylmethylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 546(MH^+);

8-cyclobutylcarbamoyloxy-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; (ES): 520 (MH^+);

8-cyclopentylcarbamoyloxy-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; (ES): 534 (MH^+);

8-cyclohexylcarbamoyloxy-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 548 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(5-methylpyrazin-2-ylmethylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 572 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-isopropylcarbamoyloxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 508 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-8-methylcarbamoyloxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 481 (MH^+);

8-(3-cyclopropyl-1-methylureido)-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester;) MS (ES): 519 (MH^+);

3-(4-fluorobenzoyl)-1,1-dimethyl-9-(pyridin-2-yl-methylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester;)

3-(4-fluorobenzoyl)-1,1-dimethyl-9-(2-pyridin-2-yl-ethylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; and

3-(4-fluorobenzoyl)-1,1-dimethyl-9-(thiophen-2-ylmethylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester.

C. In a manner similar to Step A, but replacing 3-(4-fluorobenzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester with 3-(3,4-difluorobenzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester and using the appropriate amine, the following compounds were prepared:

8-cyclopropylcarbamoyloxy-3-(3,4-difluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 524 (MH^+);

3-(3,4-difluorobenzoyl)-1,1-dimethyl-8-methylcarbamoyloxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 499 (MH^+);

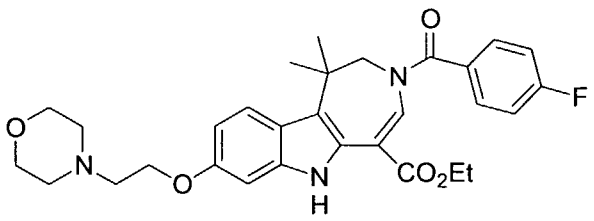
3-(3,4-difluorobenzoyl)-1,1-dimethyl-8-(pyridin-2-yl-methylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 575 (MH^+);

3-(3,4-difluorobenzoyl)-1,1-dimethyl-8-benzylcarbamoyloxy)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester MS (ES): 574 (MH^+); and

3-(3,4-difluorobenzoyl)-1,1-dimethyl-8-phenylcarbamoyloxy-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester MS (ES): 560 (MH^+).

EXAMPLE 48

PREPARATION OF 3-(4-FLUOROBENZOYL)-1,1-DIMETHYL-8-(2-MORPHOLIN-4-YL-ETHOXY)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. A mixture of 3-(4-fluorobenzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester (85 mg, 0.2 mmol), sodium iodide (30 mg), potassium carbonate (140 mg, 1.01 mmol) and 4-(2-chloroethyl)morpholine (free base, 300 mg, 2 mmol) and acetone (8 mL) was heated at 75°C for 24 hours. The solid was filtered off, and the filtrate was concentrated *in vacuo*, and the crude product was purified by reverse-phase preparative HPLC to give the title compound (11mg); ^{1}H-NMR ($CDCl_3$): δ 10.51 (1H, s), 7.72 (1H, s), 7.67 (1H, d), 7.66-7.59 (2H, m), 7.15-7.10 (2H, m), 6.86 (1H, d), 6.76 (1H, dd), 4.27-4.17 (4H, m), 4.08 (2H, brs), 3.77 (4H, m), 2.88 (2H, brs), 2.65 (4H, brs), 1.59 (6H, s), 1.25 (3H, t); MS (ES): 536 (MH^+).

B. In a similar manner, but replacing 4-(2-chloroethyl)morpholine with1-(2-chloroethyl)piperidine, ethyl bromoacetate or 2-bromoacetamide, the following compounds were prepared:

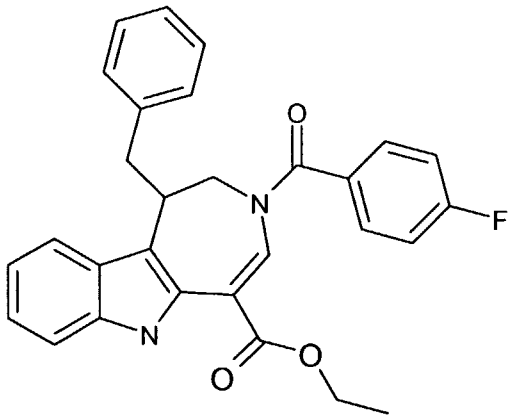
3-(4-fluorobenzoyl)-1,1-dimethyl-8-(2-piperidin-1-ylethoxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 534 (MH^+);

8-ethoxycarbonylmethoxy-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 509 (MH^+); and 8-carbamoylmethoxy-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 480 (MH^+).

C. To prepare 3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-(3-hydroxy-propoxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester, a mixture of 3-(4-fluorobenzoyl)-8-hydroxy-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]-indole-5-carboxylic acid ethyl ester (46 mg, 0.11 mmol), diisopropylethylamine (0.5mL), and 3-bromo-1-propanol (1.4mL) in dry acetonitrile (1mL) was stirred at 75°C for 10 hours. The solvent was removed in vacuo, and the residue was purified by preparative reverse-phase HPLC, which was then acylated in the manner described in Example 2A. ^{1}HNMR ($CDCl_3$): δ 10.51 (1H, s), 7.86 (1H, s), 7.82 (1H, d), 7.66-7.59 (2H, m), 7.15-7.09 (2H, m), 6.87 (1H, d), 6.74 (1H, m), 4.27-4.15 (4H, m), 4.09 (2H, brs), 3.90 (2H, m), 2.11-2.05 (2H, m), 1.60 (6H, s), 1.26-1.21 (3H, m). MS (ES): 481 (MH^+).

EXAMPLE 49

1-BENZYL-3-(4-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. 2-(1*H*-Indol-3-yl)-3-phenylacrylonitrile was prepared by the addition of 3-indolylacetonitrile (2.02 g, 12.9 mmol), MeOH (18mL), benzaldehyde (1.60 mL, 15.5 mmol), and a 25 % wt solution of sodium methoxide in MeOH (3.2 mL, 14.2 mmol) to a 50 mL flask. The solution was allowed to stir at ambient temperature under N_2 for 16 h. The reaction solution was diluted with DCM (20 mL), molecular sieves (250 mg) were added, and the solution was allowed to reflux for 1 hour. The reaction was quenched with the addition of sat. NH_4Cl (20 mL). The organic phase

was partitioned, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude material was chromatographed (SiO_2, 100 % hexane to 5% EtOAc) to yield 1.4 g (44 % yield) of 2-1*H*-indol-3-yl-3-phenyl-acrylonitrile; ^1H NMR ($CDCl_3$) δ 8.42 (1H, br s), 7.97 (1H, d), 7.87 (2H, m), 7.63 (1H, s), 7.60 (1H, d), 7.37-7.48 (4H, m), 7.25-7.33 (2H, m); TLC (SiO_2 plate, 5:1 hexane/EtOAc) R_f = 0.35; MS (ESI): 245 (MH^+).

B. β-Benzyltryptamine was prepared by the addition of 2-1*H*-indol-3-yl-3-phenylacrylonitrile (500 mg, 2.04 mmol) and EtOH (25 mL) to a N_2 purged 100 mL flask. To the solution was added approximately 2 g of Raney-Ni slurry. To the reaction solution, dropwise with stirring, was added hydrazine monohydrate (2.5 mL). The reaction solution was allowed to stir at 65°C for 4 hours. The slurry was filtered through a pad of Celite to remove excess Raney-Ni. The filtrate was concentrated under reduced pressure, and the crude product was used without further purification; MS (ESI): 251 (MH^+).

C. 1-Benzyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester was prepared in a manner similar to that described in Example 1A by using β-benzyl-tryptamine; MS (ESI): 347(MH^+).

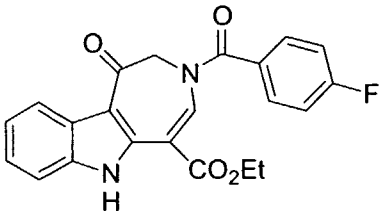
D. The title compound was prepared in a manner similar to that described in Example 2A by using 1-benzyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester and 4-fluorobenzoyl chloride; ^1H NMR ($CDCl_3$) δ 10.58 (1H, s), 8.07 (1H, s), 7.62-7.66 (2H, m), 7.36 (1H, d), 7.13-7.23 (9H, m), 6.99 (1H, t), 5.25 (1H, dd), 4.26 (2H, m), 3.94 (1H, d), 2.99 (1H, dd), 2.83 (1H, dd), 1.22 (3H, t); MS (ESI): 469 (MH^+).

E. In a manner similar to Steps A-D, but replacing benzaldehyde with furfural in Step A, the following compound was prepared:

3-(4-fluorobenzoyl)-1-furan-2-ylmethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS(ESI): 459(MH^+).

EXAMPLE 50

PREPARATION OF 3-(4-FLUOROBENZOYL)-1-OXO-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



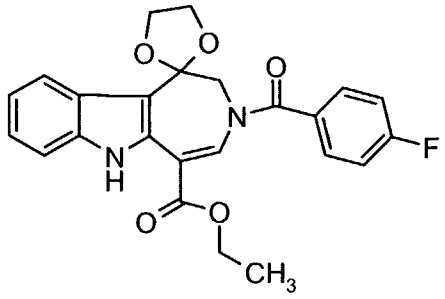
A. To a mixture of ethyl 3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (190 mg, 0.5 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (139 mg, 0.6 mmol) was added a mixture of THF-H_2O (9:1, 8 mL) at ambient temperature. The reaction mixture was allowed to stir at ambient temperature for 2 hours. Additional DDQ (139 mg, 0.6 mmol) was added, and the mixture was stirred at ambient temperature for another 2 hours. The solvent was removed *in vacuo*, and the residue was taken up in EtOAc and washed thoroughly with saturated sodium bicarbonate solution and then with brine. The organic phase was dried with sodium sulfate, and concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with hexane-EtOAc (85:15) to give the title compound as a yellow solid (180mg, 92%); ^{1}H-NMR ($CDCl_3$): δ 11.4 (1H, s), 8.52-8.48 (2H, m), 7.66-7.62 (2H, m), 7.48-7.46 (1H, m), 7.37-7.31 (2H, m), 7.22-7.17 (2H, m), 4.53 (2H, s), 4.38 (2H, q), 1.35 (3H, t); MS (ES): 393 (MH^+).

B. In a similar manner, but replacing ethyl 3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with 10-benzyloxy-3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester, the following compound was prepared:

10-benzyloxy-3-(4-fluorobenzoyl)-1-oxo-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 499 (MH^+).

EXAMPLE 51

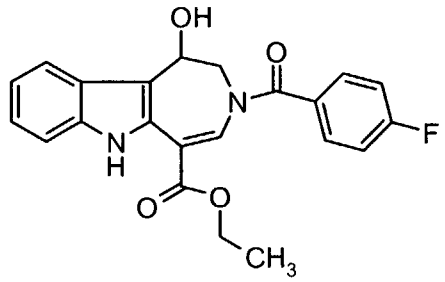
PREPARATION OF 1,1-ETHYLENEDIOXY-3-(4-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A mixture of 3-(4-fluorobenzoyl)-1-oxo-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester (39 mg, 10.1 mmol) and TsOH (10 mg) and ethylene glycol (0.2 mL) in toluene (10 mL) was heated to reflux overnight under nitrogen. After cooling, the reaction was diluted with DCM. It was then washed with saturated aqueous $NaHCO_3$ and water and dried over $MgSO_4$. Evaporation of solvent gave a crude product, which was purified by column chromatography on silica gel eluted with MeOH-DCM (2:98) to give the title compound (7.5 mg); ^{1}H-NMR ($CDCl_3$): δ 9.68 (1H, s), 8.24 (1H, d), 7.08 (2H, m), 7.57 (1H, s), 7.41 (2H, m), 7.12 (2H, m), 4.77 (2H, m), 4.55 (2H, m), 4.46 (2H, q), 1.46 (3H, t). MS (ES): 437 (MH^+).

EXAMPLE 52

PREPARATION OF 3-(4-FLUOROBENZOYL)-1-HYDROXY-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER

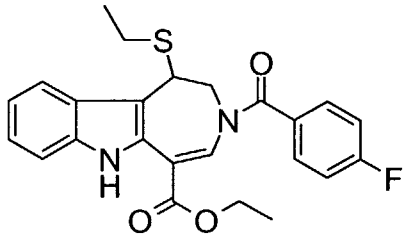


To a suspension of 3-(4-fluorobenzoyl)-1-oxo-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester (784 mg, 2 mmol) in EtOH (11 mL) and AcOH (3 mL) was added $NaBH_3CN$ (500 mg, 8 mmol) and the mixture was stirred at 20°C overnight. It was then basified with 28% ammonium hydroxide and

extracted with DCM. The combined organic layer was washed with water and dried over $MgSO_4$. Evaporation of solvent gave a crude product, which was purified by column chromography on silica gel and eluted with MeOH-DCM (1:19) to give the title compound (450 mg); ^{1}H-NMR ($CDCl_3$): δ 9.61 (1H, s), 8.41 (1H, m), 7.41 (1H, m), 7.25-7.36 (5H, m), 7.05 (2H, m), 4.93 (1H, m), 4.57 (1H, d), 4.42 (3H, m), 3.85 (1H, m), 1.35 (3H, d). MS (ES): 395 (MH+).

EXAMPLE 53

PREPARATION OF 1-ETHYLSULFANYL-3-(4-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



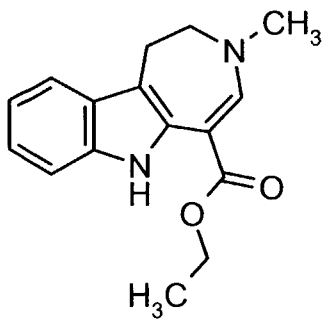
A. To a solution of 3-(4-fluorobenzoyl)-1-hydroxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester (60 mg, 0.3 mmol) in DCM (2 mL) was added trifluoromethanesulfonic anhydride (50 mL, 0.6 mmol) at 0°C and the mixture was stirred for 1 hour at 0°C. Ethanethiol (34 mL, 0.9 mmol) was added and the reaction mixture was stirred overnight at 20°C. Water was added and organic layer was separated. The aqueous layer was extracted with DCM. The combined organic layer was then washed with water and dried over $MgSO_4$. Evaporation of solvent gave a crude product, which was purified by column chromatography on silica gel, eluted with MeOH-DCM (1:19) to give the title compound (2 mg); ^{1}NMR ($CDCl_3$): δ 8.59 (1H, s), 8.77 (1H, d), 7.54 (2H, m), 7.36 (1H), 7.19 (1H, m), 7.06 (2H, m), 6.73 (1H, s), 4.41 (2H, m), 4.21-4.30 (3H, m), 2.59-2.69 (2H, m), 1.28 (3H, t), 1.19 (3H, t). MS (ES): 439 (MH^+).

B. In a similar manner, but replacing ethanethiol with *n*-propylamine, the following compound was prepared:

3-(4-fluorobenzoyl)-1-propylamino-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 436 (MH^+).

EXAMPLE 54

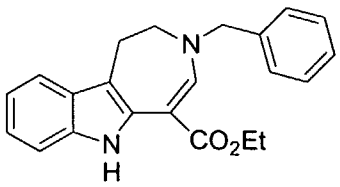
PREPARATION OF 3-METHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



To a solution of ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (0.15 g, 0.6 mmol) in DMF (2 mL) was added sodium hydride (60%, 28 mg, 0.7 mmol) at 0°C and a solution of MeI (38 μL, 0.7 mmol). The mixture was stirred for 30 min at 0°C. Water was added to the reaction mixture, which was then extracted by DCM. The combined organic layer was washed with water and dried over magnesium sulfate. Evaporation of solvent gave a crude product, which was purified by column chromatography on silica gel eluting with MeOH-DCM (5:95) and then further purified by preparative HPLC to afford the title compound (86 mg); ^{1}H-NMR ($CDCl_3$): δ 10.50 (1H, s), 8.26 (1H, m), 7.77 (1H, s), 7.40 (1H, d), 7.31 (1H, d), 7.05 (2H, m), 5.35 (1H, s), 4.28 (2H, q), 3.54 (2H, t), 3.26 (3H, s), 3.14 (2H, m), 1.36 (3H, t). MS (ES): 271 (MH^+).

EXAMPLE 55

PREPARATION OF 3-BENZYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. Sodium hydride (60% in mineral oil, 320 mg, 8 mmol) was added to a stirred solution of ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (520 mg, 2 mmol) in anhydrous DMF (8 mL) at 0°C under nitrogen, and the resulting mixture was stirred at ambient temperature for 30 minutes. Benzyl bromide (345 mg, 2 mmol) was then added dropwise to the above mixture at 0°C. The resulting mixture was

stirred at ambient temperature for 6 hours. Ammonium chloride solution was added carefully to quench the reaction at 0°C. The mixture was extracted with DCM. The combined extracts were washed with saturated ammonium chloride solution, water and brine, dried over sodium sulfate, and evaporated *in vacuo* to give a brown oil, which was purified by chromatography on silica gel eluting with EtOAc-Hexane (5:95) to give the title compound (421 mg); ^{1}H-NMR ($CDCl_3$): δ 10.53 (1H, s), 7.96 (1H, s), 7.41-7.25 (7H, m), 7.08-6.99 (2H, m), 4.57 (2H, s), 4.33-4.27 (2H, q), 3.48 (2H, m), 3.01 (2H, m), 1.36 (3H, t); MS (ES): 347 (MH^+).

B. In a similar manner as described above in Step A, but replacing benzyl bromide with the appropriately substituted haloalkane or halo ether, the following compounds were prepared:

3-(2-methoxyethyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 315 (MH^+); and 3,6-bis-(2-methoxyethyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 373 (MH^+);

3-(3-fluoropropyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 317 (MH^+);

3-cyclohexylmethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 353 (MH^+); and 3,6-bis-cyclohexylmethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 449 (MH^+);

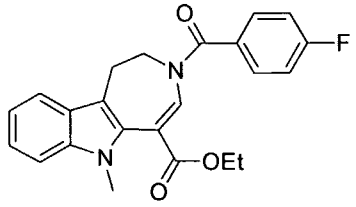
3-pyridin-2-ylmethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 348 (MH^+);

3-(2-morpholin-4-ylethyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 370 (MH^+);

3-pyridin-3-ylmethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 348 (MH^+).

EXAMPLE 56

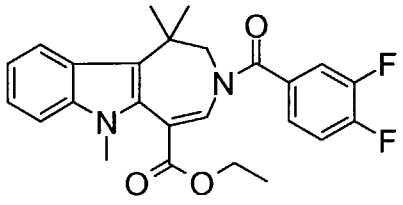
PREPARATION OF ETHYL 3-(4-FLUOROBENZOYL)-6-METHYL-3-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



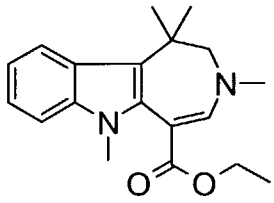
LDA (1.2 mmol) was added to a solution of ethyl 3-(4-Fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (the compound of Example 2A: 378 mg, 1 mmol) in THF at –78°C and the reaction mixture slowly warmed to 0°C and stirred for 30 minutes at 0°C. MeI (125 mL, 2 mmol) was added and stirred at 20°C for 1 hour. The reaction mixture was quenched with water. The organic layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with water and dried over $MgSO_4$. Evaporation of solvent gave a crude product, which was purified by chromatography on silica gel eluting with EtOAc-Hexane (1:4) to give the title compound (27 mg). ^{1}H-NMR ($CDCl_3$): δ (1H, s), 7.54-7.60 (3H, m), 7.32 (1H, d), 7.25 (1H, m), 7.14-7.17 (3H, m), 4.14-4.28 (4H, m), 3.61 (3H, s), 3.17 (2H, m), 1.25 (3H, t); MS (ES): 392 (M^+), 415 (MNa^+).

EXAMPLE 57

PREPARATION OF 3-(3,4-DIFLUOROBENZOYL)-1,1,6-TRIMETHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5B]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER AND 1,1,3,6-TETRAMETHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



57a



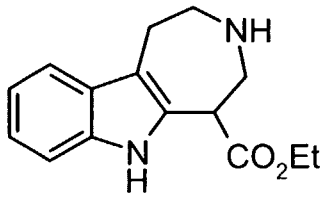
57b

To a solution of ethyl 3-(3,4-difluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (21 mg, 0.05 mmol) in DMF (2 mL) was added NaH (60%, 4 mg, 2 equiv) at 0°C and the reaction mixture stirred for 30 minutes at 0°C. Iodomethane was added and the reaction mixture was stirred for 15 minutes at 0°C and then quenched with water/AcOH. The mixture was diluted with DCM and washed with water and dried over $MgSO_4$. Evaporation of solvent gave a crude product, which was purified by chromatography on silica gel, eluted with MeOH-DCM (1:19) to give 57a (2 mg) and 57b (5 mg); 57a: ^{1}NMR ($CDCl_3$): δ 7.85 (1H,d), 7.46 (2H, m), 7.33 (2H, m), 7.24 (2, m), 7.12 (1H, m), 4.20 (2H, q), 4.00 (2H, s), 3.56 (3H, s), 1.63 (6H, s), 1.39 (3H, t). MS (ES): 439 (MH^+); 57b: ^{1}NMR ($CDCl_3$): δ 7.81(1H,), 7.71

(1H, , 7.24 (1, m), 7.11(1H, m), 7. 00 (1H, m), 4.24 (2H, q), 3.40 (3H, s), 3.19 (3H, s), 1.62 (6H, s), 1.27 (3H, t). MS (ES): 313 (MH^+).

EXAMPLE 58

PREPARATION OF 1,2,3,4,5,6-HEXAHYDRO-AZEPINO [4,5-B] INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. The title compound was prepared in a manner similar to that described in Kuehne *et al.* (*J. Org. Chem.* 1985, *50*, 919-924) and in European Patent No. EP 064 317 B1; MS (ES): 259 (MH+).

B. In a manner similar to Example 2A, but replacing ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate with ethyl 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate, the following compound was prepared:

ethyl 3-(4-fluorobenzoyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate; ^{1}H-NMR ($CDCl_3$): δ 8.43 (1H, m), 7.31-7.52 (4H, m), 6.96-7.19 (4H, m), 3.96-4.33 (6H, m), 3.67 (2H, m), 3.14 (1H, m), 2.94 (1H, m), 1.15-1.36 (3H, m); MS (ES): 381 (MH^+).

C. In a manner similar to Step B, but replacing 4-fluorobenzoyl chloride with the appropriately substituted acyl chloride, isocyanate or chloroformate, the following compounds were prepared:

3-benzoyl-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 363 (MH^+);

3-(4-*tert*-butyl-benzoyl)-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 363 (MH^+);

3-phenylacetyl-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 377 (MH^+);

3-(3-phenyl-propionyl)-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 391 (MH^+);

3-(4-chlorobenzoyl)-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 391 (MH^+);

3-(2,4-dichlorobenzoyl)-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 431 (MH^+);

3-(3-methoxybenzoyl)-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 393 (MH^+);

3-piperonyloyl-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 407 (MH^+);

3-(4-nitrobenzoyl)-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 408 (MH^+);

3-(4-methoxybenzoyl)-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 393 (MH^+);

3-(4-methyl-3-nitrobenzoyl)-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 444 (MNa^+);

3-(4-methoxycarbonyl-benzoyl)-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 421 (MH^+);

3-(4-chlorophenoxycarbonyl) 1,4,5,6-tetrahydro-2*H*-azepino[4,5-*b*]indole-5-carboxylic acid ester 5-ethyl ester; MS (ES): 435 (MNa^+);

3-(4-chlorophenylcarbamoyl)-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 434 (MNa^+); and

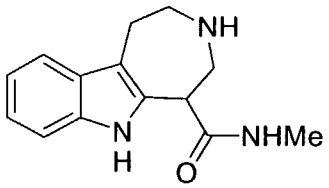
3-p-tolylcarbamoyl-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 392 (MH+).

D. In a manner similar to that described in Step B, but using 3,4-difluorobenzoyl chloride and ethyl 1,1-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate which was prepared in a similar manner as described in Step A, the following compound was prepared:

ethyl 3-(3,4-difluorobenzoyl)-1,1-dimethyl-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylate; MS(ESI): 427 (MH^+).

EXAMPLE 59

PREPARATION OF *N*-METHYL 1,2,3,4,5,6-HEXAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBAMIDE



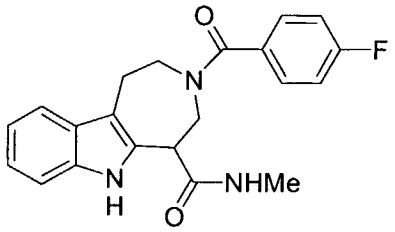
A. Ethyl 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (1.29 g, 5 mmol; European Patent No. EP 064 317 B1) and methylamine hydrochloride (0.67 g, 10 mmol) were added to a solution of methylamine in THF (2 M, 15 mL) and the suspension was heated to 80°C in a sealed tube under nitrogen stirring for 72 hours. Solvent was evaporated to give a crude product, which was purified by chromatography on silica gel eluting with MeOH-DCM (1:9 to 1:4) to give the title compound (0.8g); ^{1}H-NMR ($CDCl_3$): δ 8.46 (1H, br s), 8.24 (1 H, s), 7.48 (1H, d),), 7.30 (1H, d), 7.16 (1H, m), 7.10 (1H, m), 3.70 (1H, d), 3.66 (1H, dd), 3.46 (1H, dd), 3.08 (2H, m), 2.87 (2H, m), 2.73 (3H, d), 1.9 (1H, br s); MS (ES): 244 (MH^+).

B. In a similar manner, but replacing methylamine and its hydrochloride salt with ethylamine and its hydrochloride salt, the following compound was prepared:

N-ethyl 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carbamide; ^{1}H-NMR ($CDCl_3$): δ 8.70 (1H, br s), 8.37 (1H, br s), 7.48 (1H, d), 7.47 (1H, d), 7.14 (1H, m), 7.08 (1H, m), 3.64-3.68 (2H, m), 3.44 (1H, m), 3.20 (2H, m), 3.08 (2H, m), 1.08 (3H, t); MS (ES): 258 (MH^+).

EXAMPLE 60

PREPARATION OF N-METHYL 3-(4-FLUOROBENZOYL)-1,2,3,4,5,6-HEXAHYDROAZEPINO[4,5-B]INDOLE-5-CARBAMIDE



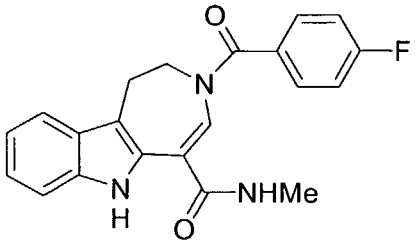
A. The title compound was prepared in a manner similar to that described in Example 2A by using *N*-methyl 1,2,3,4,5,6-hexahydroazepino[4,5-b]indole-5-carbamide and 4-fluorobenzoyl chloride; ^{1}H-NMR (CDCl3): δ 9.49 (1H, br s), 7.35 (3H, m), 7.24 (1H, m), 7.14 (4H, m), 4.30 (2H, m), 4.19 (1H, m), 3.69 (2H, m), 3.07 (1H, m), 2.91 (1H, m), 2.78 (3H, br s); MS (ES): 366.2 (MH^+).

B. In a similar manner, the above *N*-methyl 1,2,3,4,5,6-hexahydroazepino[4,5-b]indole-5-carbamide was replaced with *N*-ethyl 1,2,3,4,5,6-

hexahydroazepino[4,5-b]indole-5-carbamide to give *N*-ethyl 3-(4-fluorobenzoyl)-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole-5-carbamide.

EXAMPLE 61

PREPARATION OF N-METHYL 3-(4-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-B]INDOLE-5-CARBAMIDE



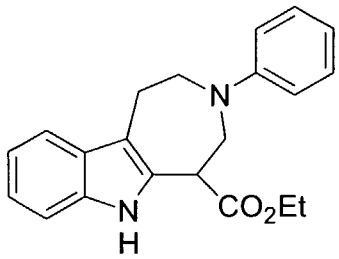
A. To a solution of *N*-methyl 3-(4-fluorobenzoyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carbamide and TEA in DCM at 0°C was added a cooled (0°C) solution of *tert*-butyl hypochloride (57 mL, 0.5 mmol) in DCM. The reaction mixture was stirred for 1.5 hours at 0°C. Cold water was added to wash the solution. Organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were washed by water and dried over $MgSO_4$. Evaporation of solvent gave a crude product, which was purified by chromatography on silica gel eluting with MeOH-DCM to give the title compound (14 mg); ^{1}H-NMR ($CDCl_3$): δ 10.04 (1H, br s), 7.57 (2H, m), 7.52 (1H, d), 7.37 (1H, d), 7.24 (1H, m), 7.12 (4H, m) 5.9 (1H, br s), 4.15 (2H, t), 3.27 (2H, t), 2.92 (3H, d); MS (ES): 378 (MH^+).

B. In a similar manner, but replacing *N*-methyl 3-(4-fluorobenzoyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carbamide with *N*-ethyl 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carbamide, the following compound was prepared:

N-ethyl 3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino [4,5-*b*]indole-5-carbamide; ^{1}H-NMR ($CDCl_3$): δ 10.05 (1H, br s), 7.57 (2H, m), 7.52 (1H, d), 7.37 (1H, d), 7.21 (1H, m), 7.12 (5H, m) 5.88 (1H, br s), 4.15 (2H, t), 3.27 (2H, t), 3.40 (2H, m), 1.19 (3H, t); MS (ES): 378 (MH^+).

EXAMPLE 62

PREPARATION OF 3-PHENYL-1,2,3,4,5,6-HEXAHYDRO-AZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. The mixture of ethyl 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (520 mg, 2 mmol), cupric acetate (728 mg, 4 mmol), phenyl boronic acid (490 mg, 4 mol) and pyridine (0.35 mL, 4 mmol) in dry DCM (20 mL) was stirred at ambient temperature for 3 days. The mixture was filtered though a pad of celite. The filtrate was concentrated *in vacuo* and then purified by chromatography on silica gel eluting with EtOAc-Hexane (7:93) to give the title compound (53 mg); ^{1}H-NMR ($CDCl_3$): δ 8.66 (1H, s), 7.42 (1H, d), 7.26-7.18 (4h, m), 7.10-7.00 (2H, m), 7.69 (2H, m), 6.67 (1H, t), 5.22 (1H, m), 4.40-4.18 (3H, m), 4.04-4.01 (1H, m), 3.98-3.88 (1H, m), 3.58-3.52 (1H, m), 3.22-3.15 (1H, m), 3.08-3.02 (1H, m), 1.27 (3H, t); MS (ES): 335 (MH^+).

B. In a similar manner as that described in Example 61A using 3-phenyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester derived in Step A, the following compound was prepared:

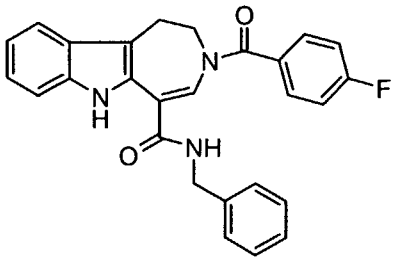
3-phenyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 333 (MH^+).

C. In a similar manner as described in Step A, but replacing phenyl boronic acid with 3-methoxyphenyl boronic acid, the following compound was prepared:

3-(3-methoxyphenyl)-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 365 (MH^+).

EXAMPLE 63

PREPARATION OF 3-(4-FLUOROBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID BENZYLAMIDE



A. To a solution of ethyl 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate (0.46 g, 1.8 mmol) in DCM (6 mL) was added 4-fluorobenzoyl chloride (0.26 mL, 1.2 equiv) and TEA (0.38 mL, 1.5 equiv) and the mixture was stirred for 1 hour at 20 °C. Evaporation of solvent gave a crude product, which was purified by column chromatography on silica gel eluting with MeOH-DCM (1:9) to afford 3-(4-fluorobenzoyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; (543 mg, 80%) MS (ES): 381 (MH^+).

B. To a solution of 3-(4-fluorobenzoyl)-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester (543 mg, 1.42 mmol) in 1,4-dioxane (8 mL) was added aqueous sodium hydroxide (114 mg in 2 mL 0f water). The mixture was stirred for 1 hour at 20°C. Solvent was then removed under high vacuum to give a crude product, which was redissolved in water and acidified with AcOH. Solid was collected by filtration and washed with water and dried under high vacuum to give 3-(4-fluorobenzoyl)-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid (421 mg, 84%); MS (ES): 353 (MH^+).

C. To a suspension of 3-(4-fluorobenzoyl)-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylic acid (176 mg, 0.5 mmol) in DCM (3 mL) was added carbonyldiimidazole (97 mg, 0.6 mol) and the mixture was stirred for 1 hour at 20°C. Benzylamine (109 μL, 1 mmol) was added and the mixture was stirred overnight. Solid was collected by filtration and washed by DCM and dried under high vacuum to give the title compound (90 mg); 93% MS (ES): 442 (MH^+).

D. In a manner similar to that described in Example 61, but replacing *N*-methyl 3-(4-fluorobenzoyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carbamide with 3-(4-fluorobenzoyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylic acid benzylamide, the following compound was prepared:

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid benzylamide; ^{1}H-NMR ($CDCl_3$): δ 10.13 (1H, s), 7.45 (3H, m), 7.37 (1H, d), 7.30 (3H, m), 7.22 (4H, m), 7.12 (4H, m), 6.16 (1H, s), 4.53 (1H, d), 4.15 (2H, t), 3.27 (2H, t); MS (ES): 440 (MH^+).

E. The following compounds were prepared in a manner similar to that described in Steps A through D, by using the appropriate amine, hydrazine, alcohol, phenol or thiol at step C:

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid cyclobutylamide; ^{1}H-NMR ($CDCl_3$): δ 10.00 (1H, s), 7.58 (2H, m), 7.51 (1H, d), 7.36 (1H, d), 7.09-7.24 (5H, m), 6.04 (1H, m), 4.45 (1H, q), 4.14 (2H, t), 3.26 (2H, t), 2.40 (2H, m), 1.86 (2H, m), 1.76 (2H, m); MS (ES): 404 (MH^+);

[3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indol-5-yl]piperidin-1-yl-methanone; MS (ES): 418 (MH^+);

[3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indol-5-yl]morpholin-4-yl-methanone; MS (ES): 420 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid (1-methyl-1*H*-benzoimidazol-2-yl)amide; MS (ES): 479 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid propylamide; MS (ES): 392 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid *tert*-butylamide;MS (ES): 406 (MH^+);

[3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indol-5-yl]-(4-methyl-piperazin-1-yl)-methanone; MS (ES): 433 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid cyclohexylamide; MS (ES): 432 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid pyridin-2-ylamide; MS (ES): 427 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid (2-dimethylamino-ethyl)amide; MS (ES): 421 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropylamide; MS (ES): 392 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid dimethylamide; MS (ES): 378 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid cyclohexylmethylamide; MS (ES): 446 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid (pyridin-2-ylmethyl)amide; MS (ES): 441 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid allylamide; MS (ES): 390 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid cyclopropylamide MS (ES): 390 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid (2-fluoro-ethyl)amide; MS (ES): 396 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid (2-methoxyethyl)amide; MS (ES): 408 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid cyclopropylmethylamide; MS (ES): 404 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isobutylamide; MS (ES): 406 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid *sec*-butylamide; MS (ES): 406 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid phenylamide; MS (ES): 426 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid (2,2,2-trifluoroethyl)amide;MS (ES): 432 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid thiazol-2-ylamide; MS (ES): 433 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid cyclopentylamide; MS (ES): 418 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid cyclobutyl ester; ^{1}H-NMR ($CDCl_3$): δ 10.50 (1H, s), 8.03 (1H, s), 7.63 (2H, m), 7.52 (1H, d), 7.28 (1H, d), 7.15-7.22 (3H, m), 7.11 (1H, dd), 5.10 (1H, m), 4.21 (2H, t), 3.27 (2H, t), 1.96 (2H, m), 1.81 (2H, m), 1.66 (2H, m); MS (ES): 405 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid *sec*-butyl ester; MS (ES): 407 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid 2-dimethylaminoethyl ester; MS (ES): 422 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid 1-methyl-allyl ester; MS (ES): 405 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid 2-methoxyethyl ester; MS (ES): 409 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid 2,2-dimethylpropyl ester; MS (ES): 421 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isobutyl ester; MS (ES): 407 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid 3-dimethylaminopropyl ester; MS (ES): 436 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid butyl ester; MS (ES): 407 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid cyclopentyl ester; MS (ES): 419 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid cyclohexyl ester; MS (ES): 433 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid allyl ester; MS (ES): 391 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid 1-ethylallyl ester; MS (ES): 419 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid phenyl ester; MS (ES): 427 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid benzyl ester; MS (ES): 444 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carbothioic acid S-ethyl ester; ^{1}H-NMR ($CDCl_3$): δ 10.13 (1H, s), 7.99 (1H, s), 7.64 (2H, m), 7.53 (1H, d), 7.37 (1H, d), 7.10-7.24 (4H, m), 4.23 (2H, t), 3.28 (2H, t), 2.94 (2H, m), 1.63 (3H, t); MS (ES): 395 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carbothioic acid S-propyl ester; MS (ES): 409 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carbothioic acid S-isopropyl ester; MS (ES): 395 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carbothioic acid S-butyl ester; MS (ES): 423 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carbothioic acid S-sec-butyl ester; MS (ES): 423 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carbothioic acid S-isobutyl ester; MS (ES): 423 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carbothioic acid S-*tert*-butyl ester; MS (ES): 423 (MH^+);

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid *N',N'*-dimethylhydrazide; ^{1}H-NMR ($CDCl_3$): δ 9.88 (1H, s), 7.58 (2H, m), 7.51 (1H, d), 7.37 (1H, d), 7.23 (1H, m), 7.09-7.16 (4H, m), 6.62 (1H, s), 4.14 (2H, t), 3.25 (2H, t), 2.62 (6H, s); MS (ES): 393 (MH^+); and

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*] indole-5-carboxylic acid (2,2,2-trifluoroethylidene)hydrazide; ^{1}H-NMR ($CDCl_3$): δ 9.65 (1H, s), 9.39 (1H, s), 8.15 (1H, s), 7.51-7.57 (3H, m), 7.45 (1H, m), 7.23 (1H, d), 7.12-7.19 (4H, m), 4.16 (2H, t), 3.27 (2H, t); MS (ES): 445 (MH^+).

F. In a manner similar to that described in Steps A through D, but replacing ethyl 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate with 2-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; and benzylamine with cyclobutylamine, the following compound was prepared:

3-(4-fluorobenzoyl)-2-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid cyclobutylamide; ^{1}H-NMR ($CDCl_3$): δ 9.93 (1H, s), 7.58 (2H, m), 7.49 (1H, d), 7.35 (1H, d), 7.09-7.23 (5H, m), 5.92 (1H, d), 5.45 (1H, s), 4.45 (2H, m), 3.34 (1H,dd), 3.12 (1H, dd), 2.40 (2H, m), 1.72-1.89 (4H, m), 1.08 (3H, d); MS (ES): 418 (MH^+).

G. In a manner similar to Step F, but replacing 4-fluorobenzoyl chloride with 3,4-difluorobenzoyl chloride in Step A, the following compound was prepared:

3-(3,4-difluorobenzoyl)-2-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid cyclobutylamide; ^{1}H-NMR ($CDCl_3$): δ 9.90 (1H, s), 7.47 (2H, m), 7.36 (1H, d), 7.25-7.33 (6H, m), 7.22 (1H, m), 7.10 (2H, m), 5.94 (1H, d), 5.42 (1H, s), 4.46 (2H, m), 3.34 (1H,dd), 3.12 (1H, dd), 2.42 (2H, m), 1.88 (2H, m), 1.76 (2H, m), 1.09 (3H, d); MS (ES): 436 (MH^+).

H. In a manner similar to that described in Steps A through D, but replacing ethyl 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate with 1-methyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester in Step A, the following compound was prepared:

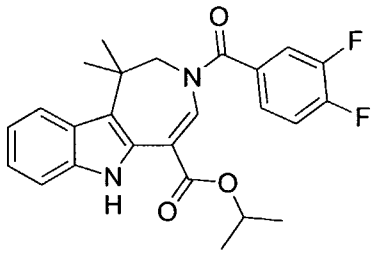
3-(3,4-difluorobenzoyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid cyclobutylamide; ^{1}H-NMR ($CDCl_3$): δ 9.99 (1H, s), 7.56 (1H, d), 7.49 (1H, m), 7.31-7.37 (2H, m), 7.19-7.27 (2H, m), 7.11 (1H, m), 7.05 (1H, br s), 5.97 (1H, m), 5.09 (1H, br s), 4.45 (2H, m), 3.75 (1H, m), 3.24 (1H, d), 2.40 (2H, m), 1.86 (2H, m), 1.76 (2H, m), 1.35 (3H, d); MS (ES): 436 (MH^+).

I. In a manner similar to that described in Step H, but replacing cyclobutamine at Step D with *iso*-propanol, the following compound was prepared:

3-(3,4-difluorobenzoyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid isopropyl ester; ^{1}H-NMR ($CDCl_3$): δ 10.54 (1H, s), 7.58 (1H, d), 7.52 (1H, m), 7.37-7.42 (2H, m), 7.19-7.31 (5H, m), 7.12 (1H, m), 5.26 (1H,dd), 5.14 (1H, m), 3.85 (2H, m), 3.18 (1H, d), 1.33 (3H, d), 1.23 (3H, d), 1.20 (3H, d); MS (ES): 425 (MH^+).

EXAMPLE 64

PREPARATION OF ISOPROPYL 3-(3,4-DIFLUOROBENZOYL)-1,1-DIMETHYL-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLATE



A. Ethyl 3-(3,4-difluorobenzoyl)-1,1-dimethyl-1,2,3,4,5,6-hexahydro-azepino[4,5-*b*]indole-5-carboxylate was saponified, converted to the corresponding isopropyl ester using CDI and isopropanol, and then oxidized as described previously in Step D of Example 63 to give the title compound; ^{1}H-NMR (DMSO-d_6): δ 10.83 (1H, s), 7.76 (1H, d), 7.71 (1H, app t), 7.64 (1H, s), 7.52-7.61 (2H, m), 7.40 (1H, m), 7.08 (1H, app t), 6.98 (1H, app t), 5.05 (1H, sept), 1.52 (6H, s), 1.18 (6H, d); MS(ESI): 439 (MH^+).

B. In a similar manner, ethyl 3-(3,4-difluorobenzoyl)-1,1-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate was saponified, converted to the corresponding carboxamide using CDI and the appropriate amine, and then oxidized as described previously in Example 63 to give the following compounds:

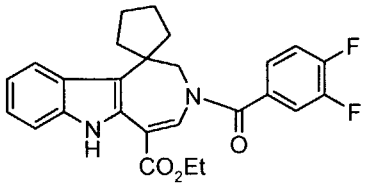
cyclobutyl 3-(3,4-difluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino-[4,5-*b*]indole-5-carboxamide; MS(ESI): 450 (MH^+); and

isopropyl 3-(3,4-difluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino-[4,5-*b*]indole-5-carboxamide; MS(ESI): 438 (MH^+).

C. In a similar manner, ethyl 9-fluoro-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole-5-carboxylate was saponified, converted to the corresponding carboxamide using CDI and isopropylamine, and then oxidized to give 9-fluoro-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino-[4,5-b]indole-5-carboxylic acid isopropylamide MS (ESI): 438 (MH^+).

EXAMPLE 65

PREPARATION OF 3-(3,4-DIFLUOROBENZOYL)-1,1-TETRAMETHYLENE-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



A. A mixture of 3-indolylacetonitrile (5 g, 32 mmol), triton B (40% in MeOH, 0.5 g), benzyl bromide (7. 8 mL, 2 eq.) and aqueous NaOH (50%, 12.6 mL) was stirred for 2 hours at 20°C. Water was added. Solid was collected by filtration and washed with water and hexane and dried under high vacuum to give [1-benzyl-1*H*-indol-3-yl]acetonitrile (6.97 g). MS (ES): 247 (MH^+).

B. To a suspension of sodium hydride (60%, 2.26 g, 56 mmol) was added a solution of 1-benzyl-1*H*-indol-3-ylacetonitrile (5.7g, 22 mmol) and 1,4-dibrombutane (2.6 ml) in DMSO-ether (10ml: 80 mL) dropwise and the mixture was stirred for 5 hours at 20°C. Water and hexane were added. Solid was collected by filtration and washed with water and hexane to give 1-(1-benzyl-1*H*-indol-3-yl)cyclopentanecarbonitrile (5.3 g). MS (ES): 301 (MH^+).

C. C-[1-(1*H*-Indol-3-yl)cyclopentyl]methylamine was prepared in a manner similar to that described in Example 32 D by using 1-(1-benzyl-1H-indol-3-yl)-cyclopentanecarbonitrile; MS (ES): 305 (MH^+).

D. To a solution of liquid ammonia (60 mL) in anhydrous THF (20 mL) was added metal sodium (1.64 g, 71 mmol) in portions. A solution of C-[1-(1*H*-indol-3-yl)cyclopentyl]methylamine (3.58 g, 11.8 mmol) in THF (20 mL) was added dropwise to the above solution and refluxed for 1.5 hours at –33°C. The reaction mixture was quenched with saturated aqueous ammonium chloride. After ammonia

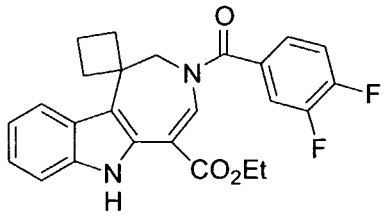
was purged with nitrogen, more water was added and extracted with DCM. The combined organic layer was washed with brine and dried over $MgSO_4$. Evaporation of solvent gave C-[1-(1*H*-indol-3-yl)cyclopentyl]methylamine as a white solid (2.5 g); MS (ES): 215 (MH^+).

E. 1,1-Tetramethylene-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester was prepared in a manner similar to that described in Example 1A by using C-[1-(1*H*-Indol-3-yl)cyclopentyl]methylamine; MS (ES): 311 (MH^+).

F. The title compound was prepared in a manner similar to that described in Example 2A by using 1,1-tetramethylene-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester;. ^{1}NMR ($CDCl_3$): δ 10.74 (1H, s), 7.74 (1H, m), 7.49 (1H, m), 7.40 (1H, d), 7.34 (1H, m), 7.21 (2H, m), 7.08 (1H, m), 4.27 (2H, q), 3.50-4.60 (2H, br s), 2.46 (2H, m), 2.05 (4H, m), 1.69 (2H, m), 1.25 (2H, t). MS (ES): 451 (MH^+).

EXAMPLE 66

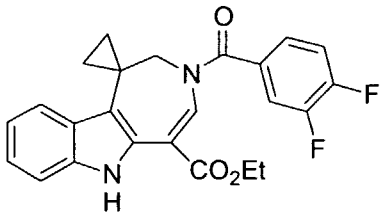
PREPARATION OF 3-(3,4-DIFLUORO-BENZOYL)-1,1-TRIMETHYLENE-1,2,3,6-TETRAHYDRO-AZEPINO[4,5-B]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER.



The title compound was prepared in a manner similar to that described above in Example 65 and Example 32 by using 1,3-dibromopropane in place of iodomethane. ^{1}HNMR ($CDCl_3$): δ 10.62 (1H, s), 8.04 (1H, d), 7.74 (1H,d), 7.51-7.13 (6H, m), 4.30-4.24 (2H, q), 3.04 (2H, brs), 2.41-2.21 (2H,m), 2.07-2.01 (2H,m), 1.25 (3H, 3H). MS (ES): 437 (MH^+).

EXAMPLE 67

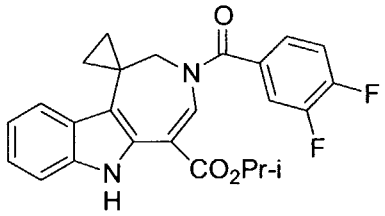
PREPARATION OF 3-(3,4-DIFLUORO-BENZOYL)-1,1-DIMETHYLENE-1,2,3,6-TETRAHYDRO-AZEPINO[4,5-B]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER



The title compound was prepared in a manner similar to that described in Example 66 by using 1,2-dichloroethane instead of 1,3-dibromopropane. ^{1}HNMR ($CDCl_3$): δ 10.52 (1H, s), 7.96 (1H, d), 7.54-7.47 (2H,d), 7.38-7.36 (2H, m), 7.29-7.24 (1H, m), 7.18-7.14 (1H, m), 7.05-7.01 (1H, m), 4.27 (2H, q), 4.02 (2H, s), 1.67 (2H, brs),1.26 (3H, m), 1.08 (2H, brs). MS (ES): 423 (MH^+).

EXAMPLE 68

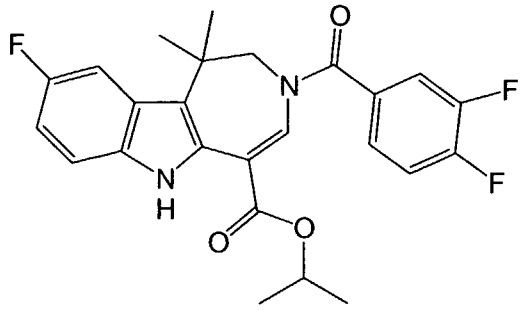
PREPARATION OF 3-(3,4-DIFLUORO-BENZOYL)-1,1-DIMETHYLENE-1,2,3,6-TETRAHYDRO-AZEPINO[4,5-B]INDOLE-5-CARBOXYLIC ACID ISOPROPYL ESTER.



The title compound was prepared in a manner similar to that described in 66 by using isopropyl bromopyvurate instead of ethyl bromopyruvate at the appropriate point in sysnthesis. ^{1}HNMR ($CDCl_3$): δ 10.55 (1H, s), 7.96 (1H, d), 7.55-7.48 (2H,d), 7.39-7.36 (2H, m), 7.29-7.25 (1H, m), 7.18-7.14 (1H, m), 7.05-7.01 (1H, m), 5.17-5.11 (1H, m), 4.03 (2H, s), 1.66 (2H, brs),1.27-1.21 (3H, m), 1.08 (2H, brs). MS (ES): 437 (MH^+).

EXAMPLE 69

PREPARATION OF 9-FLUORO-3-(3,4-DIFLUORO-BENZOYL)-1,1-DIMETHYL-1,2,3,6-TETRAHYDRO-AZEPINO[4,5-B]INDOLE-5-CARBOXYLIC ACID ISOPROPYL ESTER



A. To a chilled solution of dimethylamine (Aldrich, 40% aqueous, 15.6 mL, 123.4 mmol) and formaldehyde (Aldrich, 37% aqueous, 8.1 mL, 108.9 mmol) in 60 mL of acetic acid was added 5-fluoroindole (Lancaster, 10.0 g, 72.6 mmol) in 5 mL of acetic acid at 0°C under N_2. The reaction mixture was warmed to room temperature and stirred for 3 hours and monitored by LC-MS. The solution was poured into ice water (200 mL) and basified with 50% NaOH. The mixture was extracted with Et_2O (3 x 250 mL), dried with Na_2SO_4, and concentrated. After having dried in high vacuo for several hours, crude product (16.3 g, >100%) was obtained as a white solid. The product was used in the next step without further purification. MS (ESI): 193 (MH^+).

B. The product from step A (72.6 mmol) in 300 mL of EtOH was treated with methyl iodide (Aldrich, 5.0 mL, 80.0 mmol) at room temperature and placed in the dark under N_2 for 16 hours. Sodium cyanide (Aldrich, 7.1 g, 145.2 mmol) was added at room temperature, and then the reaction mixture was heated at 90.5°C reflux under N_2 for 10 hours. The solvent was removed in vacuo, and the residue was dissolved in EtOAc (300mL). The organic phase was wash with brine x 1 and water x 1, dried with Na_2SO_4, and concentrated. Brown oily crude indole acetonitrile (16.8 g, >100%) was obtained. The product was used in the next step without further purification. MS (ESI): 175 (MH^+).

C. The indole acetonitrile from step B (72.6 mmol) in 300 mL of CH_2Cl_2 was treated with DMAP (Aldrich, 36 mmol), triethylamine (Aldrich, 49.6 mL, 362 mmol), and $(Boc)_2O$ (Aldrich, 31.6 g, 145 mmol) at room temperature under N_2 for 15 hours. The organic phase was washed with brine x 1, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatograph on silica gel, eluting with EtOAc- hexane (0-30%) to yield the corresponding Boc-indole acetonitrile

(13.98 g, 70% yield for 4 steps from 5-Fluoro indole) as a light yellow solid. ^{1}H-NMR ($CDCl_3$): δ 8.12 (1H, b), 7.67 (1H, s), 7.17 (1H, dd), 7.09 (1H, m), 3.74 (2H, s), 1.67 (9H, s). MS (ESI): 275 (MH^+).

D The chilled Boc-indole acetonitrile from step C (5.0 g, 18.2 mmol) and methyl iodide (Aldrich, 6.8 mL, 109.4 mmol) in 100 mL of DMF was treated with NaH (Aldrich, 60%, 5.1 g, 127.6 mmol) at – 10°C under Argon for 30 minutes. The reaction was quenched by 24 mL of saturated NH_4Cl aqueous solution at –10°C and diluted with 100 mL of ether. The aqueous phase was extracted with ether (100 x 2). The organic phase was washed with brine x 1, dried over Na_2SO_4, and concentrated. The top oil layer was separated. The bottom crude product (a brown film) was used without further purification. The top oil layer was purified by flash chromatograph on silica gel, eluting with EtOAc- hexane (0-30%) to yield the desired compound as a white film. ^{1}H-NMR ($CDCl_3$): δ 8.12 (1H, b), 7.55 (1H, s), 7.45 (1H, dd), 7.09 (1H, m), 1.82 (6H, s), 1.67 (9H, s). MS (ESI): 303 (MH^+).

E. The crude compound from step D (18.2 mmol) in 10 mL of CH_2Cl_2 was treated with TFA (Aldrich, 10.0 mL, 130 mmol) at room temperature under N_2 for 3 hours. The reaction mixture was diluted with 50 mL of EtOAc and 30 mL of water and neutralized with solid $NaHCO_3$. The aqueous phase was extracted with EtOAc (80 x 2). The organic phase was washed with brine x 1, dried over Na_2SO_4, and concentrated. The crude product was purified by flash chromatograph on silica gel, eluting with EtOAc- hexane (0-30%) to yield the α-Me_2-indole acetonitrile (3.50 g, 95% yield) as brown oil. ^{1}H-NMR ($CDCl_3$): δ 8.24 (1H, s), 7.46 (1H, dd), 7.30 (1H, m), 7.17 (1H, d), 6.97 (1H, m), 1.81 (6H, s). MS (ESI): 203 (MH^+).

F. The α-Me_2-indole acetonitrile from step E (3.67 g, 18.2 mmol) in 150 mL of ether was treated with LAH (Aldrich, 2.0 g, 52.7 mmol) at 0°C under N_2 for 10 minutes. The reaction mixture was heated at 41.5°C reflux for 1 hour and then cooled to 0°C. The reaction was quenched by 25 mL of MeOH and 20 mL of 10% Rochelle salt solution at 0 °C. The aqueous phase was extracted with EtOAc (50 x 4). The organic phase was washed with brine x 1 and water x 1, dried over Na_2SO_4, and concentrated. After having dried in high vacuo for several hours, crude product (3.45 g, 89% yield) was obtained as a light yellow solid. The tryptamine was used in the next step without further purification. ^{1}H-NMR ($CDCl_3$): δ 8.50 (1H, s), 7.40 (1H, dd), 7.21 (1H, m), 6.97 (1H, d), 6.91 (1H, m), 2.95 (2H, s), 1.35 (6H, s). MS (ESI): 207 (MH^+).

G. The solution of crude tryptamine obtained from step F (9.69 mmol), HCl (Aldrich, 4M in dioxane, 2.7 mL, 10.7 mmol), and charcoal (Aldrich, 2.0 g) in 60 mL of ^{i}PrOH was treated with isopropyl bromopyruvate (home made, 5.26 g, 25.2 mmol) at room temperature under Ar for 10 minutes. The reaction mixture was heated at 91°C reflux for 16 hours and then cooled to room temperature. The solvent was removed in vacuo. To the above residue, 21 mL of pyridine was added at room temperature. The reaction mixture was heated at 105°C reflux under Ar for 16 hours, and then the solvent was removed in vacuo. MeOH (50mL) was added, and the solution was filtered and concentrated. The crude product was purified by flash chromatograph on silica gel, eluting with CH_2Cl_2- hexane (0-80%) to yield the indoleazepine product (1.34 g, 43.5% yield) as a light yellow solid. ^{1}H-NMR ($CDCl_3$): δ 11.01 (1H, s), 7.87 (1H, d), 7.39 (1H, d), 7.19 (1H, m), 6.78 (1H, m), 5.32 (1H, s), 5.15 (1H, m), 3.27 (2H, s), 1.52 (6H, s), 1.29 (6H, d). MS (ESI): 317 (MH^+).

H. The solution of indoleazepine from step G (1.0 g, 3.16 mmol) and DIPEA (Aldrich, 0.99 mL, 5.69 mmol) in 30 mL of 1,2-dichloroethane was treated with 3,4-difluorobenzoylchloride (Aldrich, 0.61 mL, 4.74 mmol) at room temperature under N_2 for 10 minutes. The reaction mixture was heated at 70°C reflux for 5 hours and then quenched by 1 mL of MeOH at room temperature. Diluted with 50 mL of DCM, washed with brine x 1, and solvent was removed in vacuo. The crude product was purified by flash chromatograph on silica gel, eluting with EtOAc- hexane (0-30%) to yield the title compound (1.43 g, 99% yield) as a yellow solid. ^{1}H-NMR ($CDCl_3$): δ 10.69 (1H, s), 7.77 (1H, s), 7.48 (1H, m), 7.42 (1H, dd), 7.33 (1H, m), 7.28 (1H, m), 7.20 (1H, m), 6.92 (1H, m), 5.13 (1H, m), 4.03 (2H, b), 1.56 (6H, s), 1.20 (6H, d). MS (ESI): 457 (MH^+).

I In a similar manner to above, but replacing 3,4-difluorobenzoylchoride with 4-fluorobenzoylchoride the following compound was made:

9-fluoro-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid isopropyl ester. MS (ESI): 439 (MH^+).

J. In a similar manner, but replacing isopropyl bromopyruvate with ethyl 3-bromopyruvate in step G, the following compound was made:

9-fluoro-3-(3,4-difluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester MS (ESI): 443 (MH^+).

K. In a similar manner to step J, but also replacing 3,4-difluorobenzoylchoride with 4-fluorobenzoylchoride in step H the following compound was made:

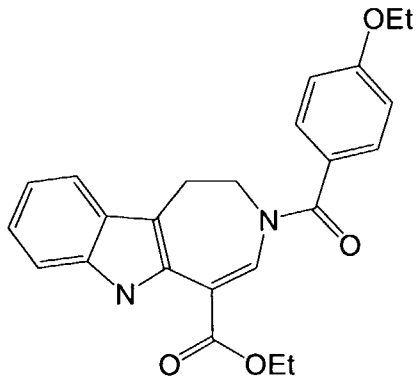
9-fluoro-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester. MS (ESI): 425 (MH^+).

L In a similar manner to step K but replacing 4-fluorobenzoylchoride with cyclohexanecarbonyl chloride the following compound was made:

9-fluoro-3-cyclohexanecarbonyl-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester MS (ESI): 413 (MH^+).

EXAMPLE 70

PREPARATION OF 3-(4-ETHOXYBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER;



A. To a solution of ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (250 μl of a 0.2 M solution (~13 mg), 0.05 mmol) in THF was added 4-ethoxybenzoyl chloride (500 μl of a 0.2 M solution (~18mg), 0.1 mmol) and TEA (28 μL, 0.2 mmol) using a robotic pipette. The mixture was shaken overnight at 55°C using a circulating oil bath. Trisamine resin (~30 mg) was added and the suspension was shaken for 0.5 hours at 20°C. The resin was removed by filtration through the reaction block. Evaporation of solvent gave a crude product, which was purified by HPLC-MS to give the compound (~0.5 mg, estimated weight based on ELSD calibration curve); MS (ES): 405 (MH^+).

B. The following compounds were prepared in this manner using the appropriately substituted acyl chloride:

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 379 (MH^+);

3-(4-chlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 395 (MH^+);

3-(4-ethoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 405 (MH^+);

3-(4-ethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 389 (MH^+);

3-(4-propylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 403 (MH^+);

3-(2-phenoxyacetyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 391(MH^+);

3-[2-(4-methoxyphenyl)-acetyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES); 405 (MH^+);

3-(2-methoxyacetyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 329 (MH^+);

3-(3-phenylpropionyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 389 (MH^+);

3-(3-methoxycarbonylpropionyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 371 (MH^+);

3-(4-chlorobutyryl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester;MS (ES): 361(MH^+);

3-nonanoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 397(MH^+);

3-(2-chloro-2-phenyl-acetyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 409 (MH^+);

3-(3,4,5-trimethoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 451(MH^+);

3-cyclopropanecarbonyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 325 (MH^+);

3-cyclopentanecarbonyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 353 (MH^+);

3-cyclohexanecarbonyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 367 (MH^+);

3-(3-cyclopentylpropionyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 381 (MH^+);

3-(furan-2-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 351(MH^+);

3-(2-nitrobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 406 (MH^+);

3-[2-(3-methoxy-phenyl)-acetyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl esterMS (ES): 405 (MH^+);

3-(2-benzyloxy-acetyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 405 (MH^+);

3-(3-nitrobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 406 (MH^+);

3-(benzo[1,3]dioxole-5-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 405 (MH^+);

3-(2-phenylbutyryl)-1,2, 3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 403 (MH^+);

3-(2-methylbutyryl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 341(MH^+);

3-(2-chloropyridine-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 396 (MH^+);

3-(2,4,6-trifluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+);

3-(2-chlorobutyryl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 361(MH^+);

3-(benzo[b]thiophene -2-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 417 (MH^+);

3-(2-phenylsulfanyl-acetyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 407(MH^+);

3-(thiophene-2-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 367(MH^+);

3-propionyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 313 (MH^+);

3-(3,5-bis-trifluoromethylbenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 533 (MH^+);

3-(toluene-4-sulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 411(MH^+);

3-benzenesulfonyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 397(MH^+);

3-(thiophene-2-sulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 403 (MH^+);

3-(naphthalene-2-sulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 447(MH^+);

3-(3-chloro-4-fluorobenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 449 (MH^+);

3-(2-chlorobenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 431(MH^+);

3-(4-trifluoromethylbenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 465 (MH^+);

3-(4-isopropylbenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 439 (MH^+);

3-(3-methylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 375 (MH^+);

3-(3-chlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 395 (MH^+);

3-(2,4-dichlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 429 (MH^+);

3-(2-chlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 395 (MH^+);

3-benzoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 361 (MH^+);

3-(3,4-difluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 397 (MH^+);

3-(2,5-difluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 397 (MH^+);

3-(4-cyanobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 386 (MH^+);

3-phenylacetyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 375 (MH^+);

3-(4-methylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 375 (MH^+);

3-(4-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 391 (MH^+);

3-(2,5-bis-trifluoromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 497 (MH^+);

3-[3-(2-chloro-6-fluorophenyl)-5-methyl-isoxazole-4-carbonyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 494 (MH^+);

3-[2-(4-chlorophenyl)acetyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 409 (MH^+);

3-(4-chloromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 409 (MH^+);

3-(3-chloromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 409 (MH^+);

3-(2-thiophen-2-yl-acetyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 381 (MH^+);

1,6-dihydro-2*H*-azepino[4,5-*b*]indole-3,5-dicarboxylic acid 3-benzyl ester; 5-ethyl ester; MS (ES): 391 (MH^+);

3-(2-phenylcyclopropanecarbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 401 (MH^+);

3-(4-sulfamoylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 440 (MH^+);

3-(3-fluoro-4-trifluoromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 447 (MH^+);

3-(2-fluoro-6-trifluoromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 447 (MH^+);

3-(2-bromobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 439 (MH^+);

3-[2-(4-chlorophenoxy)acetyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 425 (MH^+);

3-[3-(3-trifluoromethylphenyl)acryloyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 455 (MH^+);

3-(3-ethoxycarbonylpropionyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 385 (MH^+);

3-(2-acetoxy-2-phenylacetyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 433 (MH^+); 0

3-(2-acetoxyacetyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 357 (MH^+);

3-(4-butoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 433 (MH^+);

3-(methyl(phenyl)carbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 390 (MH^+);

3-(2-chloro-2,2-diphenylacetyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 485 (MH^+);

3-(2-formyloxy-2-phenylacetyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 419 (MH^+);

3-(5-fluoro-2-trifluoromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 447 (MH^+);

3-(4-butylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 417 (MH^+);

3-(6-chloropyridine-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 396 (MH^+);

3-(3-dichloromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 443 (MH^+);

3-(4-pentylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 431 (MH^+);

3-(3-phenylacryloyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 387 (MH^+);

3-diethylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 356 (MH^+);

3-(2-Iodobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 487 (MH^+);

3-diphenylacetyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 451 (MH^+);

3-(4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 437 (MH^+);

3-(4-trifluoromethoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 445 (MH^+);

3-(3-methylbenzofuran-2-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+);

3-(4-phenylazobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 465 (MH^+);

3-(3-bromobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 439 (MH^+);

3-(4-*tert*-butylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 417 (MH^+);

3-(2-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 391 (MH^+);

3-(4-fluoro-3-trifluoromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 447 (MH^+);

3-acryloyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 311 (MH^+);

3-(3-cyanobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 386 (MH^+);

3-(3,4-dichlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 429 (MH^+);

3-(4-methoxycarbonylbutyryl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 385 (MH^+);

3-(2-ethylhexanoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 383 (MH^+);

3-(2,6-dichlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 429 (MH^+);

3-(naphthalene-1-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 411 (MH^+);

3-(2-fluoro-3-trifluoromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 447 (MH^+);

3-(3-fluoro-5-trifluoromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 447 (MH^+);

3-(4-fluoro-2-trifluoromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 447 (MH^+);

3-(2-fluoro-4-trifluoromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 447 (MH^+);

3-(2-acetoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 419 (MH^+);

3-(2-acetoxy-2-methylpropionyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 385 (MH^+);

3-(3,5,5-trimethylhexanoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 397 (MH^+);

3-[2-(4-chlorophenoxy)-pyridine-3-carbonyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 488 (MH^+);

3-(2-naphthalen-1-ylacetyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 425 (MH^+);

3-(2,4,5-trifluoro-3-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 445 (MH^+);

3-(2,5-dichlorothiophene-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 435 (MH^+);

3-(2*H*-chromene-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 415 (MH^+);

3-(furan-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 351 (MH^+);

3-(thiophene-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 367 (MH^+);

3-(2,2'-bithiophenyl-5-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 449 (MH^+);

3-(2,3-dihydrobenzofuran-5-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 403 (MH^+);

3-(2,3-dihydrobenzo[1,4]dioxine-6-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 419 (MH^+);

3-(2-benzyl-5-tert-butyl-2*H*-pyrazole-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 497(MH^+);

3-(3,4-dimethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 389 (MH^+);

3-[3-(4-trifluoromethoxyphenyl)-acryloyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 471 (MH^+);

3-(2,3-dimethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 389 (MH^+);

3-(2-chloropyridine-4-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 396 (MH^+);

3-(2,6-difluoro-3-nitrobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 442 (MH^+);

3-(2-methyl-3-phenylacryloyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 401 (MH^+);

3-[1-(4-trifluoromethylpyrimidin-2-yl)-piperidine-4-carbonyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 514 (MH^+);

3-[2-(4-chlorophenoxy)-2-methylpropionyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 453 (MH^+);

3-(2-chloro-6-methoxypyridine-4-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 426 (MH^+);

3-[1-(4-chlorophenyl)-5-propyl-1*H*-pyrazole-4-carbonyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 503 (MH^+);

3-(5-chloro-4-methoxythiophene-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 431 (MH^+);

3-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 429 (MH^+);

3-(2-*tert*-butyl-5-methyl-2*H*-pyrazole-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 421 (MH^+);

3-(benzo[1,2,5]thiadiazole-5-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 419 (MH^+);

3-(4-pyrazol-1-ylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 427 (MH^+);

3-(2-propylsulfanylpyridine-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES):436 (MH^+);

3-(2-thiophen-2-ylthiazole-4-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 450 (MH^+);

3-(6-phenoxypyridine-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 454 (MH^+);

3-(5-phenyloxazole-4-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 428 (MH^+);

3-(4,6-dichloro-1*H*-indole-2-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 468 (MH^+);

3-(1-methyl-1H-benzotriazole-5-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 416 (MH^+);

3-(quinoxaline-6-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl esterMS (ES): 413 (MH^+);

3-(5-phenylthiophene-2-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 443 (MH^+);

3-(6-morpholin-4-ylpyridine-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 447 (MH^+);

3-(4-thiophen-2-ylbenzoyl)-1,2,3,6- tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 443 (MH^+);

3-(2-phenylthiazole-4-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 444(MH^+);

3-(4-methyl-2-pyrazin-2-ylthiazole-5-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 460 (MH^+);

3-(2-phenyl-2*H*-pyrazole-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 427 (MH^+);

3-(2-phenylsulfanylpyridine-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 470 (MH^+);

3-(2-*p*-tolyloxypyridine-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 468 (MH^+);

3-[5-(2-methylthiazol-4-yl)-isoxazole-3-carbonyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 449 (MH^+);

3-(5-bromopyridine-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 440 (MH^+);

3-[3-(5-ethyl-[1,3,4]-oxadiazol-2-yl)-benzenesulfonyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 479 (MH^+);

3-[4-(3-trifluoromethylpyrazol-1-yl)benzoyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 495 (MH^+);

3-(5,3'-dimethyl-[3,5']-biisoxazolyl-4'-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 447 (MH^+);

3-[2-(4-chlorophenylsulfanyl)pyridine-3-carbonyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 504 (MH^+);

3-(2-phenoxypyridine-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 454 (MH^+);

3-[3-chloro-4-(propane-2-sulfonyl)thiophene-2-carbonyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 507 (MH^+);

3-[5-(4-chlorophenyl)-2-methylfuran-3-carbonyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 475 (MH^+);

3-(2-p-tolylsulfanylpyridine-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 484 (MH^+);

3-(2,5-dichloropyridine-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 430 (MH^+);

3-(5-tert-butyl-2-methyl-furan-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 421 (MH^+);

3-[1-(4-methoxy-phenyl)-5-methyl-1*H*-pyrazole-4-carbonyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 471(MH^+);

3-(5-pyridin-2-ylthiophene-2-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 444 (MH^+);

3-(5-methyl-3-phenylisoxazole-4-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 442 (MH^+);

3-(5-methyl-1-phenyl-1*H*-pyrazole-4-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 441 (MH^+);

3-(4-methyl-2-phenylthiazole-5-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 458 (MH^+);

3-(1,3-dimethyl-1*H*-thieno[2,3-*c*]pyrazole-5-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 435 (MH^+);

3-(benzo[*b*]thiophene-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 417 (MH^+);

3-(3-methyl-5-phenylisoxazole-4-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 442 (MH^+);

3-(3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepine-7-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 433 (MH^+);

3-(5-methyl-2-phenyl-2*H*-[1,2,3]-triazole-4-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 442 (MH^+);

3-(2-methyl-5-phenylfuran-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 441 (MH^+);

3-(5-thiophen-2-ylpyridine-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 444 (MH^+);

3-(3-methylbutyryl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 341 (MH^+);

3-(3,3-dimethylbutyryl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 355 (MH^+);

3-isobutyryl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 327 (MH^+);

3-butyryl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 327 (MH^+);

3-(2,2-dimethylpropionyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 341 (MH^+);

3-(3-chloro-2,2-dimethylpropionyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 375 (MH^+);

3-(2-chloropropionyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 347 (MH^+);

3-(adamantane-1-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 419 (MH^+);

3-dimethylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 328 (MH^+);

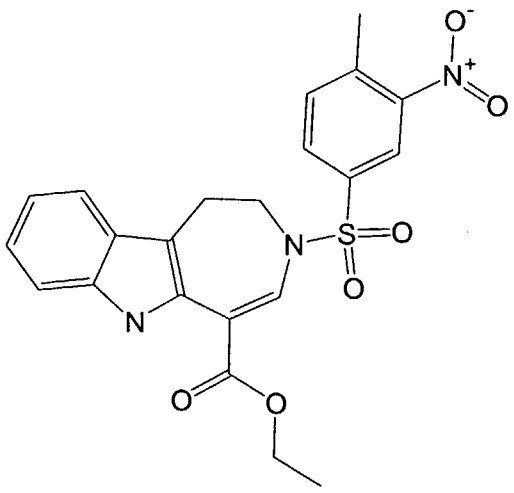
3-(2,4,6-trimethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 403 (MH^+);

3-(4-chloro-3-nitrobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 440 (MH^+); and

3-(pyridine-3-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 362 (MH^+).

EXAMPLE 71

PREPARATION OF 3-(4-METHYL-3-NITROBENZENESULFONYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER;



A. The title compound was prepared in a manner similar to that described in Example 70 by using ethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate and 4-methyl-3-nitrobenzenesulfonyl chloride (~3.4mg); MS (ES): 456 (MH^+).

B. The following compounds were prepared in this manner using the appropriately substituted sulfonyl chloride:

3-(3,5-dimethylisoxazole-4-sulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 416 (MH^+).

3-(2-cyanobenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 422 (MH^+);

3-(3-chloro-2-methylbenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 445 (MH^+);

3-(4-butylbenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 453 (MH^+);

3-(4-methyl-3-nitrobenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; 456 (MH^+);

3-(biphenyl-4-sulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 473 (MH^+);

3-(2,5-dichlorobenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 465 (MH^+);

3-(3,5-dimethylisoxazole-4-sulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 416 (MH^+);

3-(2-cyanobenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 422 (MH^+);

3-(3-chloro-2-methylbenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 445 (MH^+);

3-(4-butylbenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 453 (MH^+);

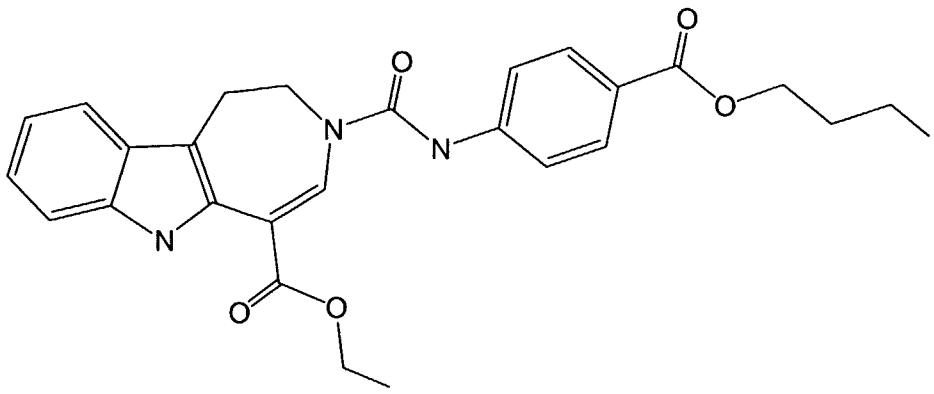
3-(4-methyl-3-nitrobenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 456 (MH^+);

3-(biphenyl-4-sulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 473 (MH^+); and

3-(2,5-dichlorobenzenesulfonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 465 (MH^+).

EXAMPLE 72

PREPARATION OF 3-(4-N-BUTOXYCARBONYL-PHENYLCARBAMOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER;



A. The title compound was prepared in a manner similar to that described in Example 71 by using ethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate and 4-(carbobutoxy)phenyl isocyanate (~2.0mg); MS (ES): 476 (MH^+).

B. The following compounds were prepared in this manner using an appropriately substituted isocyanate:

3-(2-fluoro-5-trifluoromethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 462 (MH^+);

3-(2-benzylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 466 (MH^+);

3-(3-fluorobenzylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 408 (MH^+);

3-(2-bromophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 454 (MH^+);

3-(3-phenoxyphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 468 (MH^+);

3-(2,4-dichlorobenzylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 458 (MH^+);

3-(4-butoxycarbonylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 476 (MH^+);

3-(2,3-dihydrobenzo[1,4]dioxin-6-ylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 434 (MH^+);

3-(4-methylsulfanylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 422 (MH^+);

3-(3,4-dimethoxyphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 436 (MH^+);

3-(2,5-dimethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 404 (MH^+);

3-(3-cyclopentyloxy-4-methoxyphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 490 (MH^+);

3-(2-chloroethylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 362 (MH^+);

3-(4-methylbenzylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 404 (MH^+);

3-(2-propylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 418 (MH^+);

3-(2-ethyl-6-methylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 418 (MH^+);

3-(3-methylbenzylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 404 (MH^+);

3-(2-methylbenzylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 404 (MH^+);

3-(2-chlorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 410 (MH^+);

3-(2,3,4-trifluorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 430 (MH^+);

3-(4-fluoro-3-trifluoromethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 462 (MH^+);

3-pentafluorophenylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 466 (MH^+);

3-(2-methoxycarbonylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 434 (MH^+);

3-(3-cyanophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 401 (MH^+);

3-(benzhydrylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 466 (MH^+);

3-(4-fluorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 394 (MH^+);

3-(2,4-dimethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 404 (MH^+);

3-(4-methoxybenzylcarbamoyl)-1,2,3 ,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 420 (MH^+);

3-(2-chloro-4-trifluoromethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 478 (MH^+);

3-(2-phenoxyphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 468 (MH^+);

3-(4-methoxy-2-methyphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 420 (MH^+);

3-phenylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 376 (MH^+);

3-(3-chloro-2-methylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 424 (MH^+);

3-(2-trifluoromethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 444 (MH^+);

3-*p*-tolylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 390 (MH^+);

3-(2-chlorobenzylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 424 (MH^+);

3-(4-butoxyphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 448 (MH^+);

3-(2,6-diethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 432 (MH^+);

3-(4-isopropylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 418 (MH^+);

3-(3-trifluoromethyl-phenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 444 (MH^+);

3-(3,5-dimethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 404 (MH^+);

3-(biphenyl-2-ylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 452 (MH^+);

3-(5-fluoro-2-methylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 408 (MH^+);

3-(3-chloro-4-fluorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 428 (MH^+);

3-(2-isopropyl-6-methylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 432 (MH^+);

3-(4-phenoxyphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 468 (MH^+);

3-(2-methoxyphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 406 (MH^+);

3-(2-chloro-5-trifluoromethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 478 (MH^+);

3-(1-methoxycarbonyl-2-phenylethylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 462 (MH^+);

3-(2-fluoro-3-trifluoromethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 462 (MH^+);

3-(1-naphthalen-1-ylethylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*] indole-5-carboxylic acid ethyl ester; MS (ES): 454 (MH^+);

3-(naphthalen-1-ylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 426 (MH^+);

3-(indan-5-ylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 416 (MH^+);

3-benzylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 390 (MH^+);

3-(3,4-difluorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 412 (MH^+);

3-(4-ethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 404 (MH^+);

3-(2,5-difluorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 412 (MH^+);

3-(3,4-dimethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 404 (MH^+);

3-(2-fluorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 394 (MH^+);

3-(4-thoxyphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 420 (MH^+);

3-(3-chloropropylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 376(MH^+);

3-(2-ethoxycarbonylethylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 400 (MH^+);

3-(3-chlorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 410 (MH^+);

3-pentylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 370 (MH^+);

3-(2-isopropylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 418 (MH^+);

3-(3-acetylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 418 (MH^+);

3-(3,4-dichlorobenzylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 458 (MH^+);

3-(2-fluoro-5-methylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 408 (MH^+); 3-(1-naphthalen-1-ylethylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 454 (MH^+); 3-(butoxycarbonylmethylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 414 (MH^+); 3-(4-*tert*-butylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 432 (MH^+);

3-(ethoxycarbonylmethylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 386 (MH^+);

3-(3-methylsulfanylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 422 (MH^+);

3-(4-methoxyphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 406 (MH^+);

3-(thiophen-3-ylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 382 (MH^+);

3-(3,5-dimethylisoxazol-4-ylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 395 (MH^+);

3-(2-butoxycarbonylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 476 (MH^+);

3-(2-ethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 404 (MH^+);

3-(3-ethoxycarbonylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 448 (MH^+);

3-butylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 356 (MH^+);

3-(4-fluorobenzylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 408 (MH^+);

3-(2-fluoro-6-trifluoromethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 462 (MH^+);

3-(3-ethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 404 (MH^+);

3-m-Tolylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 390 (MH^+);

3-(4-benzylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 466 (MH^+);

3-phenethylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 404 (MH^+);

3-(2-ethoxyphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 420 (MH^+);

3-(4-trifluoromethylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 444 (MH^+);

3-(3-fluoro-4-methylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 408 (MH^+);

3-(biphenyl-4-ylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 452 (MH^+);

3-(2,6-difluorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 412 (MH^+);

3-(4-ethoxycarbonylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 448 (MH^+);

3-(3-chloro-4-methylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 424 (MH^+);

3-(2,5-dimethoxyphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 436 (MH^+);

3-(3,5-dichlorophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 444 (MH^+);

3-(2-*tert*-butyl-6-methylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 446 (MH^+);

3-*o*-tolylcarbamoyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 390 (MH^+);

3-(1-methoxycarbonyl-2-methylpropylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 414 (MH^+);

3-(6-fluoro-4*H*-benzo[1,3]dioxin-8-ylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 452 (MH^+);

3-(3,4-dihydro-2*H*-benzo[*b*][1,4]dioxepin-7-ylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 448 (MH^+);

3-(4-bromophenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 454 (MH^+);

3-(1-benzyloxycarbonylpiperidin-4-ylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 517 (MH^+);

3-(2,4-dimethoxyphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 436 (MH^+);

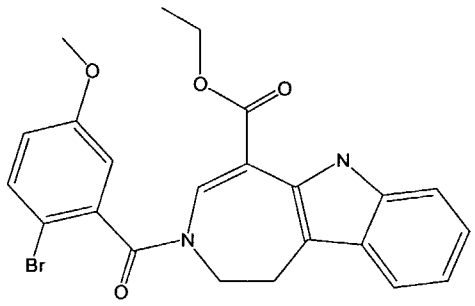
3-(9*H*-fluoren-9-ylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 464 (MH^+);

3-(4-chloro-2-methylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 424 (MH^+); and

3-(4-bromo-3-methylphenylcarbamoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 468 (MH^+).

EXAMPLE 73

PREPARATION OF 3-(2-BROMO-5-METHOXYBENZOYL)-1,2,3,6-TETRAHYDROAZEPINO[4,5-*B*]INDOLE-5-CARBOXYLIC ACID ETHYL ESTER;



A. To a solution of 2-bromo-5-methoxybenzoic acid (240 μL, 0.25M in 1.0 M DIEA in DMF); was added (120μL of a 0.50 M solution, ~ 23mg); of HBTU and

ethyl 1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate (80 μL of a 0.25 M solution(~5 mg), 0.02 mmol); in DMF using a robotic pipette. The mixture was shaken overnight at 20°C. Evaporation of solvent gave a crude product, which was redissolved in EtOAc and purified by aqueous workup. Evaporation of solvent then gave a crude product, which was further purified by ion exchange (250 mg SCX). The compound was then further purified by HPLC-MS to give the compound (~2.75 mg, estimated weight based on ELSD calibration curve); MS (ES): 469 (MH^+).

B. The following compounds were prepared in this manner, using an appropriately substituted carboxylic acid:

3-[2-(4-pyridin-4-ylmethylpiperazin-1-yl)acetyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 474 (MH^+);

3-[2-(4-naphthalen-1-ylmethylpiperazin-1-yl)acetyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 523 (MH^+);

3-{2-[4-(2-morpholin-4-yl-2-oxoethyl)piperazin-1-yl]acetyl}-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 510 (MH^+);

3-[2-(4,4-dimethyl-4,5-dihydroimidazol-1-yl)acetyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 395 (MH^+);

3-{2-[4-(1-phenylethyl)piperazin-1-yl]acetyl}-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 487 (MH^+);

3-{2-[4-(2-methoxyethyl)piperazin-1-yl]-acetyl}-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 441 (MH^+);

3-[2-(1,2-dimethyl-propylamino)-acetyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 384(MH^+);

3-[2-(3-methylpiperidin-1-yl)acetyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 396 (MH^+);

3-(2-benzylaminoacetyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 404 (MH^+);

3-(2-piperidin-1-ylacetyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 382 (MH^+);

3-(2-morpholin-4-ylacetyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 384 (MH^+);

3-(2-methyl-3-trifluoromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 443 (MH^+);

3-[2-(2-bromophenyl)acetyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 453 (MH^+);

3-acetyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 299 (MH^+);

3-(2,4-dimethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 389 (MH^+);

3-(4-benzylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 451 (MH^+);

3-(2,5-dimethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 389 (MH^+);

3-(5-chloro-2-methylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 409 (MH^+);

3-(2-bromo-4-methylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 453 (MH^+);

3-[1-(4-chlorophenyl)-cyclopropanecarbonyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 435 (MH^+);

3-(benzofuran-2-carbonyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 401 (MH^+);

3-[2-(3,4-dimethoxyphenyl)-acetyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 435 (MH^+);

3-(4-*p*-tolylbutyryl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 417 (MH^+);

3-(2-bromo-6-methylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 453 (MH^+);

3-[3-(3-bromophenyl) acryloyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 465 (MH^+);

3-(2-bromo-5-methoxybenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 469 (MH^+);

3-(2,3-dichlorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 429 (MH^+);

3-[2-(4-methoxy-phenoxy)-acetyl]-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 421 (MH^+);

3-(3-nitro-5-trifluoromethylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 474 (MH^+);

3-(2-chloro-3-methylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 409 (MH^+);

3-(2-bromo-3-methylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 453 (MH^+);

3-(3-methoxy-2-methylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 405 (MH^+);

3-(4-methoxycarbonyl-3-nitrobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 464 (MH^+);

3-(3-chloro-2-methylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 409 (MH^+);

3-(2-*p*-tolyl-propionyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 403 (MH^+);

3-(4-benzoylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 465 (MH^+);

3-(5-methoxy-2-nitrobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 436 (MH^+);

3-(2-bromo-5-methylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 453 (MH^+);

3-(4-dhloro-2-methylbenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 409 (MH^+); and

3-(4-acetylbenzoyl)-1,2,3,6-tetrahydro-azepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; MS (ES): 403 (MH^+).

EXAMPLE 74

TIME RESOLVED FLUORESCENCE RESONANCE ENERGY TRANSFER (TR-FRET) ASSAY

The TR-FRET assay was performed by incubating 8 nM of GST-farnesoid X receptor -LBD (comprising glutathione-S-transferase fused in frame to the farnesoid X receptor ligand binding domain , (amino acids 244-471 of the human farnesoid X receptor)), 8 nM of Europium-labeled anti-GST antibody (Wallac/PE Life Sciences Cat#AD0064), 16 nM biotin-SRC-1 peptide [5'-biotin-CPSSHSSLTERHKILHRLLQEGSPS-CONH2], 20 nM APC-SA [allophycocyanin conjugated streptavidin] (Wallac/PE Life Sciences, Cat# AD0059A) in FRET assay buffer (20 mM KH_2PO_4/K_2HPO_4 (pH 7.3), 150 mM NaCl, 2 mM CHAPS, 2 mM EDTA, 1 mM DTT) in the presence of the test compound(s) for 2-4 hours at room temperature in a 384 well assay plate. Data was collected using an LJL Analyst using the standard operating instructions and conditions with readings at emission wavelengths of 615 nm

and 665 nm after a delay of 65 μs and an excitation wavelength of 330 nm.

EXAMPLE 75

CO-TRANSFECTION ASSAY

The basic co-transfection protocol for measuring the farnesoid X receptor activity is as follows. CV-1 African Green Monkey Kidney cells were plated 24 hours before transfection to achieve approximately 70-80 percent confluency. Cells were transfected with the following expression vectors, CMX- farnesoid X receptor (full length human farnesoid X receptor), CMX-RXRα (full length human RXR), Luc12 ((ECREx7-Tk-Luciferase) luciferase reporter gene construct. (See WO 00/76523, Venkateswaran et al., (2000) J. Biol. Chem. 275 14700-14707). A CMX-β-Galactosidase expression vector was used as a transfection control. The transfection reagent used was DOTAP (Boehringer Mannheim). Cells were incubated with the DOTAP/DNA mixture for 5 hours after which the cells were harvested and plated onto either 96 well or 384 well plates containing the appropriate concentration of test compound. The assay was allowed to continue for an additional 18-20 hours, after which the cells were lysed, with lysis buffer (1 % triton X 100, 10 % glycerol, 5 mM Dithiothreitol, 1 mM EGTA, 25 mM Tricine, pH 7.8) and the luciferase activity measured in the presence of Luciferase assay buffer (0.73 mM ATP, 22.3 mM Tricine, 0.11 mM EGTA, 0.55 mM Luciferin, 0.15 mM Coenzyme A, 0.5 mM HEPES, 10 mM Magnesium sulphate) on a standard luminomter plate reader (PE Biosystems, NorthStar Reader), using recommended operating instructions and conditions

EXAMPLE 76

IN VIVO STUDIES

General Methods

Young adult male mice (~8 weeks of age) were purchased from conventional vendors and group housed (3-4/cage) with *ad libitum* access to chow and water, in a temperature- and light-controlled vivarium (lights on at 06:00 hours, off at 18:00 hours). Compounds were administered daily by oral gavage in the morning (~08:00 hrs), in a final volume of 0.1 ml/mouse, with the first dose of compound delivered on study day 0. Compounds were solubilized by gentle mixing in PEG400:Tween80 (4:1) for at least several hours and usually overnight prior to

initiation of dosing. When necessary, solutions were sonicated briefly to ensure complete compound solubilization.

Blood samples (~0.15 ml/mouse) were obtained from the retro-orbital sinus of non-fasted isoflurane-anesthetized mice, 3 hours after drug dosing. Blood samples were collected into heparin-coated tubes, and plasma was recovered following centrifugation. Plasma total cholesterol and triglyceride levels were determined by colorimetric enzymatic commercially available assays that were adapted to 96-well plate formats. Plasma HDL cholesterol (HDL-C) was determined by removing non-HDL-C from the plasma with a precipitating reagent, and then determining the plasma cholesterol levels in the remaining HDL-C fraction. Plasma triglycerides concentrations, determined from a blood sample obtained in the 24 hours prior to the first dose, were used to group the mice such that the pre-study triglyceride levels between groups were equivalent prior to initiation of the dosing regimen.

Representative data from these experiments are shown in Figures 1,2 and 3 for the effect of Compound A (ethyl 3-(3,4-difluorobenzoyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate), Compound B (Ethyl 3-(3,4-difluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-*b*]indole-5-carboxylate) and Compound C (isopropyl 3-(3,4-difluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate).

Compound Effects in Normolipidemic mice

Male C57BL/6 mice (Harlan Sprague Dawley, San Diego, CA) consumed standard laboratory chow (~4.5% fat w/w) *ad libitum* and were treated with Compound A (Figure 1A) or Compound B (Figure 1B) daily by oral gavage at doses of 0.1, 1.0 or 10 mg/kg/day for seven days (n=6/group).

Figure 1 shows plasma triglyceride levels in the C57BL/6 mice either treated with Compound A (Figure 1A) or Compound B (Figure 1B) daily by oral gavage at doses of 0.1 (filled triangles), 1.0 (Upside down filled triangles) or 10 mg/kg/day (Diamonds) for seven days (n=6/group) compared to vehicle alone (filled squares).

Surprisingly across this dose range, both compounds significantly reduced plasma triglycerides ~25-30% on study day 7 (*$p<0.05$ vs. vehicle-treated controls within treatment day). Even at the lowest dose tested (0.1 mg/kg) the compounds unexpectedly exhibit the ability to dramatically reduce plasma triglyceride levels.

Compound Effects in Diet-Induced Hyperlipidemic $LDLR^{-/-}$ Mice

Male $LDLR^{-/-}$ mice (JAX Mice, Bar Harbor, ME) consumed a purified "Western" diet (~21% fat, 0.02% cholesterol w/w) *ad libitum*, for two weeks prior to and during treatment with Compound C daily by oral gavage at a dose of 10 mg/kg/day for 7 days (n=9-10/group).

The results, (Figure 2) show that by study day 7, the compound had reduced plasma triglyceride concentrations to the level observed prior to introduction of the high-fat chow. Surprisingly, Compound C also significantly lowered plasma total cholesterol levels ~40% by study day 7, despite continued consumption of the high-fat, cholesterol-supplemented chow (Figure 2B, *$p<0.05$ vs. vehicle-treated controls within treatment day).

In a separate study utilizing the same mouse model (n=12-16/group) subjected to the dietary lead-in for 8 weeks, $LDLR^{-/-}$ mice were treated with Compound B at a dose of 10 mg/kg/day for 6 weeks. Surprisingly Compound B also lowered both plasma triglyceride and cholesterol concentrations with a time course similar to that observed with Compound C (Figure 3A and B). Daily dosing with Compound C resulted in a sustained normalization of plasma lipid profiles throughout the 6 weeks of study, despite continued consumption of the "Western" diet.

The data demonstrate in sum that the claimed compounds exhibit unexpectedly high potency and efficacy in modulating plasma triglyceride and cholesterol in both normal animals and animal models of hyperlipidemia. Accordingly such compounds show great potential for the development of therapeutic agents and specific utility for use in the various methods disclosed herein.

RESULTS OF EXAMPLES 74 AND 75

Both the farnesoid X receptor /ECREx7 co-transfection assay (Example 74) and the TR-FRET assay (Example 75) can be used to establish the EC_{50}/IC_{50} values for potency and percent activity or inhibition for efficacy. Efficacy defines the activity of a compound relative to a high control (chenodeoxycholic acid, CDCA) or a low control (DMSO/vehicle). The dose response curves are generated from an 8 point curve with concentrations differing by ½ LOG units. Each point represents the average of 4 wells of data from a 384 well plate. A curve for the data is generated by using the equation:

Y = Bottom + (Top-Bottom)/(1+10^((LogEC50-X)*HillSlope))

The EC_{50}/IC_{50} is therefore defined as the concentration at which an agonist or antagonist elicits a response that is half way between the Top (maximum) and Bottom (baseline) values. The EC_{50}/IC_{50} values represented are the averages of at least 3 independent experiments. The determination of the relative efficacy or % control for an agonist is by comparison to the maximum response achieved by chenodeoxycholic acid that is measured individually in each dose response experiment.

For the antagonist assay, CDCA is added to each well of a 384 well plate to elicit a response. The % inhibition for each antagonist is therefore a measurement of the inhibition of the activity of CDCA. In this example, 100% inhibition would indicate that the activity of CDCA has been reduced to baseline levels, defined as the activity of the assay in the presence of DMSO only.

Most of the compounds disclosed herein and tested exhibited activity in at least one of the above assays (EC_{50} or IC_{50} less than 10 uM). Most showed activity at below 1 μM. For example, the following exemplary compounds exhibited agonist activity with less than 1 μM EC_{50} and greater than 100 % efficacy as measured via the co-transfection assay:

n-propyl 3(4-fluorobenzoyl)-2-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate;

3-(3-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester;

3-(4-fluorobenzoyl)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid cyclobutylamide; and

n-propyl 3(4-fluorobenzoyl)-2-methyl-8-fluoro-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate.

The following exemplary compounds exhibited agonist activity with less than 250 nM EC_{50} and greater than 100 %efficacy as measured via one or more of the in vitro assays described herein:

diethyl 3-(4-fluorobenzoyl-1,2,3,6-tetrahydroazepino[4,5-b]indole-2,5-dicarboxylate;

ethyl 3-(3,4-difluorobenzoyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate;

ethyl 3-(3,4-difluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate;

9-fluoro-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

9-fluoro-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid isopropyl ester;

9-fluoro-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid isopropyl ester;

9-fluoro-3-(3,4-difluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

9-fluoro-3-cyclohexanecarbonyl-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

9-fluoro-3-(3,4-difluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid isopropylamide;

3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid isopropylamide;

3-(4-fluorobenzoyl)-2-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid cyclobutylamide;

3-(3,4-difluorobenzoyl)-1,1-tetramethylene-1,2,3,6-tetrahydroazepino [4,5-*b*]indole-5-carboxylic acid ethyl ester;

3-(3,4-difluoro-benzoyl)-1,1-trimethylene-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

3-(3,4-difluoro-benzoyl)-1,1-dimethylene-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

3-(3,4-difluoro-benzoyl)-1,1-dimethylene-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid isopropyl ester;

isopropyl 3-(3,4-difluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate; and

isopropyl 3-(3,4-difluorobenzoyl)-1-methyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylate.

The following exemplary compounds exhibited antagonist activity with IC_{50} less than 250 nM and 100% inhibition, or partial agonist activity with less than 200nM EC_{50} or IC_{50} and 10-30% efficacy and 70-90% inhibition as measured via one or more of the in vitro assays described herein:

8-(3-cyclopropyl-1-methylureido)-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester;

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(1-methyl-3-pyridin-2-ylmethylureido)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester;

3-(4-fluorobenzoyl)-1,1-dimethyl-8-isopropylcarbamoyloxy-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester;

8-cyclopropylcarbamoyloxy-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; and

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(thiophen-2-ylmethylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester;

9-(1-benzyl-3,3-dimethyl-ureido)-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

8-cyclohexylcarbamoyloxy-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester;

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(5-methylpyrazin-2-ylmethylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester;

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(2-pyridin-2-yl-ethylcarbamoyl oxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester;

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(pyridin-2-yl-methylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester; and

3-(4-fluorobenzoyl)-1,1-dimethyl-8-(pyridin-3-ylmethylcarbamoyloxy)-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester.

3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-(1-phenylcarbamoyloxy)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

3-(4-fluoro-benzoyl)-1,1-dimethyl-8-[1-(2,3-dihydrobenzofuran-5-yl-carbamoyloxy)]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

3-(4-fluoro-benzoyl)-1,1-dimethyl-8-(1-benzylcarbamoyloxy)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-benzylcarbamoyloxy)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-[1-(4-fluorobenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-[1-(R)-α-methylbenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-[1-(S)-α-methylbenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

3-(4-fluoro-benzoyl)-1,1-dimethyl-8-[1-(S)-α-methylbenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

3-(4-fluoro-benzoyl)-1,1-dimethyl-8-(1-methyl-3-methyl-ureido)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

3-(4-fluoro-benzoyl)-1,1-dimethyl-8-(1-methyl-3-isopropyl-ureido)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

9-(acetyl-methyl-amino)-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

3-(4-fluoro-benzoyl)-1,1-dimethyl-9-phenylacetylamino-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

3-(4-fluoro-benzoyl)-1,1-dimethyl-9-(3-methyl-butyrylamino)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

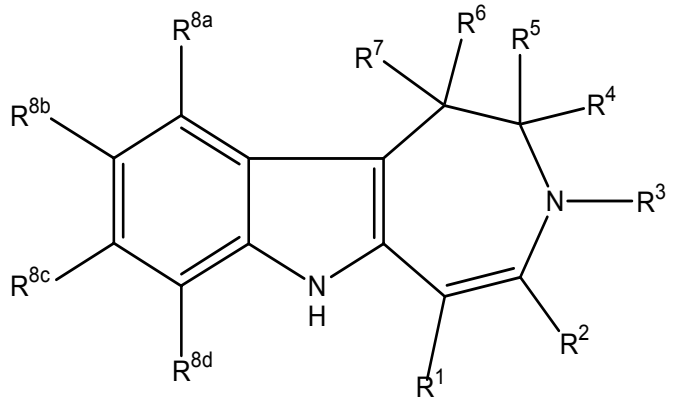
9-[benzyl-(2-thiophen-2-yl-acetyl)-amino]-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

9-(2,2-dimethyl-propionylamino)-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester; and

9-dimethylamino-3-(4-fluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino[4,5-*b*]indole-5-carboxylic acid ethyl ester.

Since modifications will be apparent to those of skill in this art, it is intended that this invention be limited only by the scope of the appended claims.

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable derivative thereof; wherein:

R^1 is $-C(J)OR^{14}$, $-C(J)SR^{14}$ and $-C(J)N(R^{15})R^{16}$;

J is NR^{17};

R^2 is hydrogen, halo or optionally substituted alkyl;

R^3 is $-C(O)R^9$;

R^4, R^5, R^6 and R^7 are together selected from a), b), c), d), e) or f) below:

a) R^4 and R^5 are each independently selected from hydrogen or halo; and R^6 and R^7 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$, and $-R^{21}-SC(J)R^{10}$; or R^6 and R^7, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene;

b) R^4 and R^5 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; or R^4 and R^5, together with

the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, an optionally substituted cycloalkenyl ring, an optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene; and R^6 and R^7 are each independently selected from hydrogen or halo; or

c) R^4 and R^6 are each independently selected from hydrogen or halo; and R^5 and R^7 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$;

d) R^4 is hydrogen or halo; R^5 is selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; and R^6 and R^7 are each independently selected from a group consisting of hydrogen, halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; or R^6 and R^7, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene;

e) R^4 and R^5 are each independently selected from a group consisting of hydrogen, halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally

substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, -C(J)R^{10}, -R^{21}-OC(J)R^{10}, -R^{21}-N(R^{25})C(J)R^{10} and -R^{21}-SC(J)R^{10}; or R^4 and R^5, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene; R^6 is hydrogen or halo; and R^7 is selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, -C(J)R^{10}, -R^{21}-OC(J)R^{10}, -R^{21}-N(R^{25})C(J)R^{10} and -R^{21}-SC(J)R^{10};

f) R^4 and R^5 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, -C(J)R^{10}, -R^{21}-OC(J)R^{10}, -R^{21}-N(R^{25})C(J)R^{10} and -R^{21}-SC(J)R^{10}; or R^4 and R^5, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, an optionally substituted cycloalkenyl ring, an optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene; and R^6 and R^7 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, -C(J)R^{10}, -R^{21}-OC(J)R^{10}, -R^{21}-N(R^{25})C(J)R^{10}, and -R^{21}-SC(J)R^{10}; or R^6 and R^7, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene;

R^{8a}, R^{8b}, R^{8c} and R^{8d} are each independently selected from the group consisting of hydrogen, halo, pseudohalo, cyano, azido, amidino, guanidino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-R^{21}-OR^{22}$, $-R^{21}-SR^{22}$, $-R^{21}-N(R^{23})(R^{24})$, $-R^{21}-C(J)R^{22}$, $-R^{21}-C(J)OR^{22}$, $-R^{21}-C(J)SR^{22}$, $-R^{21}-C(J)N(R^{23})(R^{24})$, $-R^{21}-N(R^{25})S(O)_2R^{26}$ and $-R^{21}-S(O)_2N(R^{23})(R^{24})$;

R^9 is selected from the group consisting of optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heteroaryl and optionally substituted heterocyclyl;

each R^{10} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-OR^{11}$, $-SR^{11}$ and $-N(R^{12})(R^{13})$;

each R^{11} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, and optionally substituted heteroaralkyl;

R^{12} and R^{13} are each independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, and optionally substituted heteroaralkyl; or R^{12} and R^{13}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

each R^{14} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted

heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-OR^{18}$, $-SR^{18}$ and $-N(R^{19})(R^{20})$;

R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-OR^{18}$, $-SR^{18}$ and $-N(R^{19})(R^{20})$;

or R^{15} and R^{16}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl ring or an optionally substituted heteroaryl ring;

R^{17} is hydrogen, optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl;

each R^{18} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroaralkyl;

R^{19} and R^{20} are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroaralkyl; or

R^{19} and R^{20}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

each R^{21} is independently a direct bond or an alkylene;

each R^{22} independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl,

$-R^{21}-OR^{32}$, $-R^{21}-SR^{32}$, $-R^{21}-N(R^{33})(R^{34})$, $-R^{21}-C(J)R^{32}$, $-R^{21}-C(J)OR^{32}$, $-R^{21}-C(J)SR^{32}$ and$-R^{21}-C(J)N(R^{33})(R^{34})$;

each R^{23} and R^{24} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-R^{21}-OR^{32}$, $-R^{21}-SR^{32}$, $-R^{21}-N(R^{33})(R^{34})$, $-R^{21}-C(J)R^{32}$, $-R^{21}-C(J)OR^{32}$, $-R^{21}-C(J)SR^{32}$, and $-R^{21}-C(J)N(R^{33})(R^{34})$;

or R^{23} and R^{24}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

each R^{25} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

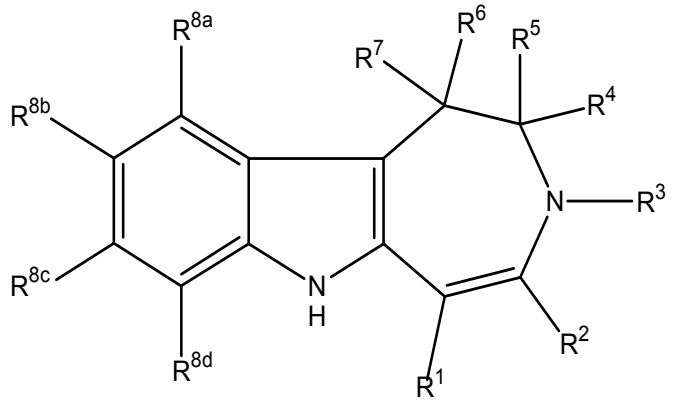
each R^{26} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

each R^{32} is each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; and

R^{33} and R^{34} are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; or

R^{33} and R^{34}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl.

2. A compound of formula (I):



(I)

or a pharmaceutically acceptable derivative thereof; wherein:

R^1 is -C(J)OR^{14}, -C(J)SR^{14} and -C(J)$N(R^{15})R^{16}$;

J is O, S or NR^{17};

R^2 is halo;

R^3 is -C(O)R^9;

R^4, R^5, R^6 and R^7 are together selected from a), b), c), d), e) or f) below:

a) R^4 and R^5 are each independently selected from hydrogen or halo; and R^6 and R^7 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, -C(J)R^{10}, -R^{21}-OC(J)R^{10}, -R^{21}-N(R^{25})C(J)R^{10}, and -R^{21}-SC(J)R^{10}; or R^6 and R^7, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene;

b) R^4 and R^5 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally

substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; or R^4 and R^5, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, an optionally substituted cycloalkenyl ring, an optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene; and R^6 and R^7 are each independently selected from hydrogen or halo; or

c) R^4 and R^6 are each independently selected from hydrogen or halo; and R^5 and R^7 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$;

d) R^4 is hydrogen or halo; R^5 is selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; and R^6 and R^7 are each independently selected from a group consisting of hydrogen, halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; or R^6 and R^7, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene;

e) R^4 and R^5 are each independently selected from a group consisting of hydrogen, halo, optionally substituted alkyl, optionally substituted alkenyl, optionally

substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; or R^4 and R^5, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene; R^6 is hydrogen or halo; and R^7 is selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$;

f) R^4 and R^5 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$ and $-R^{21}-SC(J)R^{10}$; or R^4 and R^5, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, an optionally substituted cycloalkenyl ring, an optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene; and R^6 and R^7 are each independently selected from a group consisting of halo, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-C(J)R^{10}$, $-R^{21}-OC(J)R^{10}$, $-R^{21}-N(R^{25})C(J)R^{10}$, and $-R^{21}-SC(J)R^{10}$; or R^6 and R^7, together with the carbon atom to which they are attached, form an optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkenyl ring, optionally substituted alkylidene, optionally substituted cycloalkylidene, optionally

substituted heterocyclylidene, optionally substituted aralkylidene or an optionally substituted heteroaralkylidene;

R^{8a}, R^{8b}, R^{8c} and R^{8d} are each independently selected from the group consisting of hydrogen, halo, pseudohalo, cyano, azido, amidino, guanidino, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-R^{21}-OR^{22}$, $-R^{21}-SR^{22}$, $-R^{21}-N(R^{23})(R^{24})$, $-R^{21}-C(J)R^{22}$, $-R^{21}-C(J)OR^{22}$, $-R^{21}-C(J)SR^{22}$, $-R^{21}-C(J)N(R^{23})(R^{24})$, $-R^{21}-N(R^{25})S(O)_2R^{26}$ and $-R^{21}-S(O)_2N(R^{23})(R^{24})$;

R^9 is selected from the group consisting of optionally substituted alkyl, optionally substituted aryl, optionally substituted cycloalkyl, optionally substituted heteroaryl and optionally substituted heterocyclyl;

each R^{10} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-OR^{11}$, $-SR^{11}$ and $-N(R^{12})(R^{13})$;

each R^{11} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, and optionally substituted heteroaralkyl;

R^{12} and R^{13} are each independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, and optionally substituted heteroaralkyl; or R^{12} and R^{13}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

each R^{14} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-OR^{18}$, $-SR^{18}$ and $-N(R^{19})(R^{20})$;

R^{15} and R^{16} are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-OR^{18}$, $-SR^{18}$ and $-N(R^{19})(R^{20})$;

or R^{15} and R^{16}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl ring or an optionally substituted heteroaryl ring;

R^{17} is hydrogen, optionally substituted alkyl, optionally substituted substituted alkenyl or optionally substituted alkynyl;

each R^{18} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroaralkyl;

R^{19} and R^{20} are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, or optionally substituted heteroaralkyl; or

R^{19} and R^{20}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

each R^{21} is independently a direct bond or an alkylene;

each R^{22} independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted

heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-R^{21}-OR^{32}$, $-R^{21}-SR^{32}$, $-R^{21}-N(R^{33})(R^{34})$, $-R^{21}-C(J)R^{32}$, $-R^{21}-C(J)OR^{32}$, $-R^{21}-C(J)SR^{32}$ and$-R^{21}-C(J)N(R^{33})(R^{34})$;

each R^{23} and R^{24} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, $-R^{21}-OR^{32}$, $-R^{21}-SR^{32}$, $-R^{21}-N(R^{33})(R^{34})$, $-R^{21}-C(J)R^{32}$, $-R^{21}-C(J)OR^{32}$, $-R^{21}-C(J)SR^{32}$, and $-R^{21}-C(J)N(R^{33})(R^{34})$;

or R^{23} and R^{24}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl;

each R^{25} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

each R^{26} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

each R^{32} is each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; and

R^{33} and R^{34} are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally

substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; or

R^{33} and R^{34}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl.

3. The compound of claim 1 or 2 wherein R^9 is optionally substituted heterocyclyl or optionally substituted aryl.

4. The compound of claim 3 wherein:

R^4, R^5 and R^6 are hydrogen,

R^7 is optionally substituted alkyl, substituted alkenyl, or optionally substituted alkynyl.

5. The compound of claim 3, wherein R^4 and R^5 are independently selected from hydrogen or halo; and R^6 and R^7 are each independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, and optionally substituted alkynyl.

6. The compound of claim 5 wherein R^4 and R^5 are hydrogen and R^6 and R^7 are both optionally substituted alkyl.

7. The compound of claim 6 wherein R^{8b} is $-N(R^{23})(R^{24})$ or $-N(R^{25})S(O)_2R^{26}$;

where R^{23} and R^{24} are each independently hydrogen, optionally substituted alkyl, optionally substituted aralkyl, $-C(J)R^{32}$, $-C(J)N(R^{33})(R^{34})$ or $-C(J)OR^{32}$;

each R^{25} is independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

each R^{26} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl;

each R^{32} is each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl,

optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; and

R^{33} and R^{34} are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; or

R^{33} and R^{34}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl.

8. The compound of claim 6 wherein R^{8c} is $-N(R^{23})(R^{24})$ where R^{23} and R^{24} are each independently selected from hydrogen, optionally substituted alkyl, $-R^{21}-C(J)R^{32}$ or $-R^{21}-C(J)N(R^{33})(R^{34})$;

R^{21} is a direct bond or an alkylene;

each R^{32} is each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; and

R^{33} and R^{34} are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; or

R^{33} and R^{34}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl.

9. The compound of claim 6 wherein R^{8c} is $-R^{21}-OR^{22}$ where R^{21} is a direct bond or an alkylene;

R^{22} is -C(J)N(R^{33})(R^{34}); and

R^{33} and R^{34} are each independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl and optionally substituted heteroaralkyl; or

R^{33} and R^{34}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl.

10. The compound of claim 3 wherein R^5 is -R^{21}-OC(J)R^{10} or -R^{21}-C(J)R^{10} where R^{21} is a direct bond or alkylene;

R^{10} is -OR^{11} or -N(R^{12})R^{13});

R^{11} is independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, and optionally substituted heteroaralkyl; and

R^{12} and R^{13} are each independently selected from the group consisting of optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted cycloalkyl, optionally substituted cycloalkylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, and optionally substituted heteroaralkyl; or R^{12} and R^{13}, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl or an optionally substituted heteroaryl.

11. A compound selected from the group consisting of:

- 3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-isopropylcarbamoyloxy-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid isopropyl ester;
- 3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-[1-(4-fluorobenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid isopropyl ester;
- 3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-[1-(S)-α-methylbenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid isopropyl ester;

- 3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-(1-phenylcarbamoyloxy)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;
- 3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-[1-(4-fluorobenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;
- 3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-[1-(R)-α-methylbenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;
- 3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-[1-(S)-α-methylbenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;
- 3-(4-fluoro-benzoyl)-1,1-dimethyl-8-[1-(S)-α-methylbenzyl)carbamoyloxy]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;
- 3-(4-fluoro-benzoyl)-1,1-dimethyl-8-(1-benzylcarbamoyloxy)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;
- 3-(4-fluoro-benzoyl)-1,1-dimethyl-8-[1-(2,3-dihydrobenzofuran-5-yl-carbamoyloxy)]-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;
- 3-(4-fluoro-benzoyl)-1,1-dimethyl-8-(1-benzylcarbamoyloxy)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;
- 3-(4-fluoro-benzoyl)-1,1-dimethyl-8-(1-methyl-3-isopropyl-ureido)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;
- 3-(3,4-difluoro-benzoyl)-1,1-dimethyl-8-(1-methyl-3-methyl-ureido)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;
- 3-(3, 4-difluoro-benzoyl)-1,1-dimethyl-8-(1-methyl-3-furan-2-ylmethyl-thioureido)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;
- 3-(4-fluoro-benzoyl)-1,1-dimethyl-8-(1-methyl-3-benzyl-thioureido)-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;
- isopropyl 3-(3,4-difluorobenzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino-[4,5-*b*]indole-5-carboxamide;
- 9-fluoro-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydroazepino-[4,5-b]indole-5-carboxylic acid isopropylamide;
- 3-(3,4-difluoro-benzoyl)-1,1-trimethylene-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;
- 3-(3,4-difluoro-benzoyl)-1,1-dimethylene-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester;

- 3-(3,4-difluoro-benzoyl)-1,1-dimethylene-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid isopropyl ester;
- 9-Fluoro-3-(3,4-difluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid isopropyl ester;
- 9-fluoro-3-(4-fluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid isopropyl ester;
- 9-fluoro-3-(3,4-difluoro-benzoyl)-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester; and
- 9-fluoro-3-cyclohexanecarbonyl-1,1-dimethyl-1,2,3,6-tetrahydro-azepino[4,5-b]indole-5-carboxylic acid ethyl ester.

12. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and a compound of any one of claims 1-11 or a pharmaceutically acceptable derivative thereof.

13. The pharmaceutical composition of claim 12 wherein the pharmaceutical composition further comprises at least one additional active agent(s) selected from antihyperlipidemic agents, plasma HDL-raising agents, antihypercholesterolemic agents, cholesterol biosynthesis inhibitors, HMG CoA reductase inhibitors, acyl-coenzyme A cholesterol acytransferase (ACAT) inhibitors, probucol, raloxifene, nicotinic acid, niacinamide, cholesterol absorption inhibitors, bile acid sequestrants, low density lipoprotein receptor inducers, clofibrate, fenofibrate, benzofibrate, cipofibrate, gemfibrizol, vitamin B_6, vitamin B_{12}, vitamin C, vitamin E, β-blockers, anti-diabetes agents, sulfonylureas, biguanides, thiazolidinediones, activators of PPARα, PPARβ, and PPARγ, dehydroepiandrosterone, antiglucocorticoids, TNFα inhibitors, α-glucosidase inhibitors, pramlintide, amylin, insulin, angiotensin II antagonists, angiotensin converting enzyme inhibitors, platelet aggregation inhibitors, fibrinogen receptor antagonists, LXR α agonists, antagonists or partial agonists, LXR β agonists, antagonists or partial agonists, phenylpropanolamine, phentermine, diethylpropion, mazindol, fenfluramine, dexfenfluramine, phentiramine, β_3 adrenoceptor agonist agents, sibutramine, gastrointestinal lipase inhibitors, neuropeptide Y, enterostatin, cholecytokinin, bombesin, amylin, histamine H_3 receptor agonists or antagonists, dopamine D_2 receptor agonists or

antagonists, melanocyte stimulating hormone, corticotrophin releasing factor, leptins, galanin or gamma amino butyric acid (GABA), aspirin or fibric acid derivatives.

14. Use of a compound according to anyone of claims 1-11 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for the treatment, prevention, or amelioration of one or more symptoms of a disease or disorder in which nuclear receptor activity is implicated.

15. The use of claim 14 wherein said nuclear receptor is farnesoid X receptor.

16. The use of claim 15, wherein themedicament further comprises administering at least one additional active agent selected from antihyperlipidemic agents, plasma HDL-raising agents, antihypercholesterolemic agents, cholesterol biosynthesis inhibitors, HMG CoA reductase inhibitors, acyl-coenzyme A:cholesterol acytransferase (ACAT) inhibitors, probucol, raloxifene, nicotinic acid, niacinamide, cholesterol absorption inhibitors, bile acid sequestrants, low density lipoprotein receptor inducers, clofibrate, fenofibrate, benzofibrate, cipofibrate, gemfibrizol, vitamin B_6, vitamin B_{12}, vitamin C, vitamin E, β-blockers, anti-diabetes agents, sulfonylureas, biguanides, thiazolidinediones; activators of PPARα, PPARβ and PPARγ, dehydroepiandrosterone, antiglucocorticoids, TNFα inhibitors, α-glucosidase inhibitors, pramlintide, amylin, insulin, angiotensin II antagonists, angiotensin converting enzyme inhibitors, platelet aggregation inhibitors, fibrinogen receptor antagonists, LXR α agonists, partial agonists or antagonists, LXR β agonists, partial agonists or antagonists, phenylpropanolamine, phentermine, diethylpropion, mazindol, fenfluramine, dexfenfluramine, phentiramine, β_3 adrenoceptor agonist agents, sibutramine, gastrointestinal lipase inhibitors, neuropeptide Y, enterostatin, cholecytokinin, bombesin, amylin, histamine H_3 receptor agonists or antagonists, dopamine D_2 receptor agonists or antagonists, melanocyte stimulating hormone, corticotrophin releasing factor, leptin, galanin or gamma amino butyric acid (GABA), aspirin or fibric acid derivatives.

17. The use of claim 15, wherein the disease or disorder is selected from hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, dyslipidemia, lipodystrophy, atherosclerosis, atherosclerotic disease, atherosclerotic disease events, atherosclerotic cardiovascular disease, Syndrome X, diabetes mellitus, type II diabetes, insulin insensitivity, hyperglycemia, cholestasis and obesity.

18. The use of claim 17 wherein the medicament further comprises at least one additional active agent selected from phenylpropanolamine, phentermine, diethylpropion, mazindol, fenfluramine, dexfenfluramine, phentiramine, β_3 adrenoceptor agonist agents, sibutramine, gastrointestinal lipase inhibitors, LXR αagonists, partial agonists or antagonists, LXR β agonists, partial agonists or antagonists, neuropeptide Y, enterostatin, cholecytokinin, bombesin, amylin, histamine H_3 receptor agonists or antagonists, dopamine D_2 receptor agonists or antagonists, melanocyte stimulating hormone, corticotrophin releasing factor, leptins, galanin or gamma amino butyric acid (GABA).

19. The use of claim 14, wherein the disease or disorder is selected from the group consisting of hyperlipidemia, hypertriglyceridemia, hypercholesterolemia and dyslipidemia.

20. The use of claim 19 wherein the medicament further comprises at least one additional active agent selected from antihyperlipidemic agents, plasma HDL-raising agents, antihypercholesterolemic agents, cholesterol biosynthesis inhibitors, HMG CoA reductase inhibitors, acyl-coenzyme A:cholesterol acytransferase (ACAT) inhibitors, probucol, raloxifene, nicotinic acid, niacinamide, cholesterol absorption inhibitors, bile acid sequestrants, low density lipoprotein receptor inducers, clofibrate, fenofibrate, benzofibrate, cipofibrate, gemfibrizol, vitamin B_6, vitamin B_{12}, anti-oxidant vitamins, β-blockers, anti-diabetes agents, angiotensin II antagonists, angiotensin converting enzyme inhibitors, platelet aggregation inhibitors, fibrinogen receptor antagonists, aspirin, LXR αagonists, partial agonists or antagonists, LXR β agonists, partial agonists or antagonists, or fibric acid derivatives.

21. The use of claim 14, wherein the disease or disorder is selected from the group consisting of atherosclerosis, atherosclerotic disease, atherosclerotic disease events and atherosclerotic cardiovascular disease.

22. The use of claim 22, wherein the disease or disorder is selected from the group consisting of Syndrome X, diabetes mellitus, type II diabetes, insulin insensitivity and hyperglycemia.

23. The use of 22, wherein the medicament further comprises at least one additional active agent selected from sulfonylureas, biguanides, thiazolidinediones; activators of PPARα PPARβ and PPARγ; agonists, LXR α agonists, partial agonists or antagonists, LXR β agonists, partial agonists or antagonists, dehydroepiandrosterone; antiglucocorticoids; TNF αinhibitors; α-glucosidase inhibitors, pramlintide, amylin, insulin.

24. Use of a compound according to anyone of claims 1-11 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for reducing plasma cholesterol levels, in a subject in need thereof.

25. Use of the compound according to anyone of claims 1-11 or a pharmaceutically acceptable derivative thereof, for the manufacture of a medicament for reducing plasma triglyceride levels in a subject in need thereof.

26. Use of the compound according to anyone of claims 1-11 or a pharmaceutically acceptable derivative thereof, for the manufacture of the medicament for treating, preventing, or ameliorating one or more symptoms of a disease or disorder which is affected by abnormal cholesterol, triglyceride, or bile acid levels.

27. Use of the compound according to anyone of claims 1-11 or a pharmaceutically acceptable derivative thereof for the manufacture of a medicament for modulating cholesterol metabolism, catabolism, synthesis, absorption, re-absorption, secretion or excretion in a mammal.

28. A method for modulating farnesoid X receptor activity comprising contacting a cell *in vitro* with the compound of any one of claims 1-11 or a pharmaceutically acceptable derivative thereof.