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Title: HETERO CYCLIC ACETOPH ENONE POTENTIATORS OF METABOTROPIC GLUTAMATE RECEPTORS

Abstract: The present invention is directed to compounds which are potentiat o rs of metabotropic glutamate receptors, including the mGlur2 receptor, and which are useful in the treatment or prevention of neurological and psychiatric disorders associated with glutamate dysfunction and diseases in which metabotropic glutamate receptors are involved. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which metabotropic glutamate receptors are involved.
TITLE OF THE INVENTION
HETEROCYCLIC ACETOPHENONE POTENTIATORS OF METABOTROPIC
GLUTAMATE RECEPTORS

BACKGROUND OF THE INVENTION

The excitatory amino acid L-glutamate (sometimes referred to herein simply
as glutamate) through its many receptors mediates most of the excitatory neurotransmission
within the mammalian central nervous system (CNS). The excitatory amino acids, including
glutamate, are of great physiological importance, playing a role in a variety of physiological
processes, such as long-term potentiation (learning and memory), the development of
synaptic plasticity, motor control, respiration, cardiovascular regulation, and sensory
perception.

Glutamate acts via at least two distinct classes of receptors. One class is
composed of the ionotropic glutamate (iGlu) receptors that act as ligand-gated ionic channels.

Via activation of the iGlu receptors, glutamate is thought to regulate fast neuronal
transmission within the synapse of two connecting neurons in the CNS. The second general
type of receptor is the G-protein or second messenger-linked "metabotropic" glutamate
(mGluR) receptor. Both types of receptors appear not only to mediate normal synaptic
transmission along excitatory pathways, but also participate in the modification of synaptic
connections during development and throughout life. Schoepf, Bockaert, and Sladeczek,
Trends in Pharmacol. Sci., 11, 508 (1990); McDonald and Johnson, Brain Research Reviews,

The present invention relates to potentiators of mGlu receptors, in particular
mGluR2 receptors. The mGluR receptors belong to the Type III G- protein coupled receptor
(GPCR) superfamily. This superfamily of GPCR'sf including the calcium-sensing receptors,
GABAB receptors and pheromone receptors, which are unique in that they are activated by
binding of effectors to the amino-terminus portion of the receptor protein. The mGlu
receptors are thought to mediate glutamate's demonstrated ability to modulate intracellular
signal transduction pathways. Ozawa, Kamiya and Tsuzuki, Prog. Neurobio., 54, 581
(1998). They have been demonstrated to be localized both pre- and post-synaptically where
they can regulate neurotransmitter release, either glutamate or other neurotransmitters, or
modify the post-synaptic response of neurotransmitters, respectively.

At present, there are eight distinct mGlu receptors that have been positively
identified, cloned, and their sequences reported. These are further subdivided based on their
amino acid sequence homology, their ability to effect certain signal transduction
mechanisms, and their known pharmacological properties. Ozawa, Kamiya and Tsuzuki, Prog. Neurobio., 54, 581 (1998). For instance, the Group I mGluR receptors, which include the mGluR1 and mGlu5R, are known to activate phospholipase C (PLC) via Gaq-proteins thereby resulting in the increased hydrolysis of phosphoinositides and intracellular calcium mobilization. There are several compounds that are reported to activate the Group I mGlu receptors including DHPG, (R/S)-3,5-dihydroxyphenylglycine. Schoepp, Goldworthy, Johnson, Salhoff and Baker, J. Neurochem., 63, 769 (1994); Ito, et al., neurorep., 3, 1013 (1992). The Group II mGlu receptors consist of the two distinct receptors, mGluR2 and mGluR3 receptors. Both have been found to be negatively coupled to adenylate cyclase via activation of Gai-protein. These receptors can be activated by a selective compound such as 1S,2S,SR,6S-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate. Monn, et al., J. Med. Chem., 40, 528 (1997); Schoepp, et al., Neuropharmacol., 36, 1 (1997). Similarly, the Group III mGlu receptors, including mGluR4, mGluR6, mGluR7 and mGluR8, are negatively coupled to adenylate cyclase via Gai and are potently activated by L-AP4 (L- (+) -2-amino-4-phosphonobutyric acid). Schoepp, Neurochem. Int., 24, 439 (1994).

It has become increasingly clear that there is a link between modulation of excitatory amino acid receptors, including the glutamatergic system, through changes in glutamate release or alteration in postsynaptic receptor activation, and a variety of neurological and psychiatric disorders. e.g. Monaghan, Bridges and Cotman, Ann. Rev. Pharmacol. Toxicol., 29, 365-402 (1989); Schoepp and Sacan, Neurobio. Aging, 15, 261-263 (1994); Meldrum and Garthwaite, Tr. Pharmacol. Sci., 11, 379-387 (1990). The medical consequences of such glutamate dysfunction makes the abatement of these neurological processes an important therapeutic goal.

SUMMARY OF THE INVENTION

The present invention is directed to compounds which are potentiatior of metabotropic glutamate receptors, including the mGluR2 receptor, and which are useful in the treatment or prevention of neurological and psychiatric disorders associated with glutamate dysfunction and diseases in which metabotropic glutamate receptors are involved.

The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which metabotropic glutamate receptors are involved.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to compounds of the formula I:
wherein:

A is selected from the group consisting of phenyl, naphthyl, azetidinyl, benzoxazolyl,
benzofuranyl, benzimidazolyl, chromenyl, dihydroindeny, dihydroisoquinolyl,
isoquinolyl, imidazolyl, imidazopyridinyl, indanyl, indazolyl, indolyl, oxadiazolyl,
purinyl, pyridyl, pyrimidinyl, quinolinyl, tetrahydroisoquinolyl, and tetrazolyl,
which is unsubstituted or substituted with oxo;

X is selected from the group consisting of:
(1) a bond;
(2) -O-,
(3) -S-,
(4) -SO₂-,
(5) -NH-, 
(6) -N(C₁₋₃alkyl)-,
(7) -O-phenyl-,
(8) -S-phenyl-,
(9) -S-C₁₋₃alkyl-phenyl-,
(10) -phenyl-,
(11) -piperazinyl-;

Y is selected from the group consisting of:
(1) -O-, 
(2) -NH(CO)-, and
(3) a bond;

R₁ is selected from the group consisting of:
(1) hydrogen,
(2) C₁₋₆alkyl, which is unsubstituted or substituted with a substituent selected from:
(a) halogen,
(b) hydroxyl, and
(c) phenyl, wherein the phenyl is unsubstituted or substituted with 1-5 substituents independently selected from halogen, cyano, CF3, hydroxyl, C1-alkyl, and OC1-alkyl,

(3) C3-7cycloalkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl, and

(4) phenyl, wherein the phenyl is unsubstituted or substituted with 1-5 substituents independently selected from halogen, hydroxyl, cyano, CF3, C1-alkyl, and OC1-alkyl, wherein the C1-alkyl and OC1-alkyl are linear or branched and optionally substituted with 1-5 halogen;

R2 is selected from the group consisting of:

(1) halogen,
(2) hydroxyl,
(3) -OC1-alkyl, and
(4) C1-alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl;

R3 is selected from the group consisting of:

(1) halogen, and
(2) C1-alkyl, which is unsubstituted or substituted with halogen, hydroxyl or phenyl;

R4 may include multiple substituents and is independently selected from the group consisting of:

(1) hydrogen,
(2) halogen,
(3) C1-alkyl, unsubstituted or substituted with halogen, -CN, -COC1-alkyl or -CO2C1-alkyl,
(4) -O-C1-alkyl,
(5) phenyl,
(6) pyridyl,
(7) thiazoly1,
(8) -CN, and

- 4 -
(9) hydroxyl,
or R² may be joined to the phenyl ring at an adjacent carbon to form a
dihydrofuranyl ring;
m is an integer selected from 0, 1, 2 and 3;
n is an integer selected from 0, 1, 2, 3, 4, 5 and 6;
and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

An embodiment of the present invention includes compounds wherein
A is phenyl.

An embodiment of the present invention includes compounds wherein
A is pyridyl.

An embodiment of the present invention includes compounds wherein
X is -O-.

An embodiment of the present invention includes compounds wherein
X is -S-.

An embodiment of the present invention includes compounds wherein
Y is -O-.

An embodiment of the present invention includes compounds wherein
A is pyridyl and X is -S-.

An embodiment of the present invention includes compounds wherein
X is a bond and Y is -O-.

An embodiment of the present invention includes compounds wherein
X is a bond.

An embodiment of the present invention includes compounds wherein
X is -O-phenyl-.

An embodiment of the present invention includes compounds wherein
X is -O-1,3-phenyl-.

An embodiment of the present invention includes compounds wherein
X is -phenyl-.

An embodiment of the present invention includes compounds wherein
X is -1,3-phenyl-.

An embodiment of the present invention includes compounds wherein
R¹ is C₁₋₆alkyl.

An embodiment of the present invention includes compounds wherein
R¹ is CH₃.
An embodiment of the present invention includes compounds wherein
R\(^1\) is CH\(_2\)CH\(_2\)CH\(_3\).

An embodiment of the present invention includes compounds wherein
R\(^1\) is CH\(_2\)CH(CH\(_3\))\(_2\).

An embodiment of the present invention includes compounds wherein
R\(^1\) is CH\(_2\)C(CH\(_3\))\(_3\).

An embodiment of the present invention includes compounds wherein
R\(^1\) is CH\(_2\)CH\(_2\)CH\(_2\)CH\(_3\).

An embodiment of the present invention includes compounds wherein
R\(^2\) is hydroxyl.

An embodiment of the present invention includes compounds wherein
R\(^3\) is methyl.

An embodiment of the present invention includes compounds wherein
R\(^2\) is hydroxyl and R\(^3\) is methyl.

An embodiment of the present invention includes compounds wherein
R\(^4\) is hydrogen or halogen.

An embodiment of the present invention includes compounds wherein
R\(^4\) is hydrogen.

An embodiment of the present invention includes compounds wherein
m is 0.

An embodiment of the present invention includes compounds wherein
m is 1.

An embodiment of the present invention includes compounds wherein
n is 0.

An embodiment of the present invention includes compounds wherein
n is 1.

An embodiment of the present invention includes compounds wherein
n is 2.

An embodiment of the present invention includes compounds wherein
n is 3.

An embodiment of the present invention includes compounds wherein
n is 4.

Specific embodiments of the present invention include a compound which is
selected from the group consisting of:
6,7-Dichloro-2-cyclopentyl-2-methyl-5-[3-(4-(2H-tetrazol-5-yl)-phenoxy)-propoxy]-indan-1-one;
6,7-Dichloro-2-cyclopentyl-2-methyl-5-[2-(4-(2H-tetrazol-5-yl)-phenoxy)-ethoxy]-indan-1-one;
5
6,7-Dichloro-2-cyclopentyl-2-methyl-5-[4-(2H-tetrazol-5-yl)-benzyl]oxy]-indan-1-one;
6,7-Dichloro-2-cyclopentyl-2-methyl-5-[5-(2H-tetrazol-5-yl)-pentyloxy]-indan-1-one;
6,7-Dichloro-2-cyclopentyl-5-[4-(2H-tetrazol-5-yl)-benzyl]oxy]-indan-1-one;
6,7-Dichloro-2-propyl-5-[4-(2H-tetrazol-5-yl)-benzyl]oxy]-indan-1-one;
6,7-Dichloro-2-cyclopentyl-2-methyl-5-[4-(2H-tetrazol-5-yl)-butoxy]-indan-1-one;
6,7-Dichloro-2-cyclopentyl-2-methyl-5-[4-(2H-tetrazol-5-yl)-butoxy]-indan-1-one;
6,7-Dichloro-2-cyclopentyl-2-methyl-5-[4-(2H-tetrazol-5-yl)-benzyl]oxy]-indan-1-one;
6,7-Dichloro-2-cyclopentyl-2-methyl-5-[4-(2H-tetrazol-5-yl)-benzyl]oxy]-indan-1-one;
6,7-Dichloro-2-cyclopentyl-2-methyl-5-[4-(2H-tetrazol-5-yl)-phenylethynyl]-indan-1-one;
6,7-Dichloro-2-cyclopentyl-2-methyl-5-[2-(4-(2H-tetrazol-5-yl)-phenoxy)-ethoxy]-indan-1-one;
6,7-Dichloro-2,2-dimethyl-5-[4-(2H-tetrazol-5-yl)-benzyl]oxy]-indan-1-one;
2-(6,7-Dichloro-2-cyclopentyl-2-methyl-1-oxo-5-yl-oxy)-N-[4-(1H-tetrazol-5-yl)-phenyl]-acetamide;
6,7-Dichloro-2-cyclopentyl-2-methyl-5-[4-(1H-tetrazol-5-yl)-benzyl]oxy]-indan-1-one;
6,7-Dichloro-2-cyclopentyl-2-methyl-5-[3-(1H-tetrazol-5-yl)-benzyl]oxy]-indan-1-one;
6,7-Dichloro-2-cyclopentyl-2-methyl-5-[3-(1H-tetrazol-5-yl)-propoxy]-indan-1-one;
4-(6,7-Dichloro-2-cyclopentyl-2-methyl-1-oxo-5-yl-oxymethyl)-benzoic acid;
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6,7-Dichloro-2-methyl-2-phenyl-5-[4-(1H-tetrazol-5-yl)-benzyl]oxy]-indan-1-one;
2-Butyl-6,7-dichloro-2-cyclopentyl-5-[4-(1H-tetrazol-5-yl)-benzyl]oxy]-indan-1-one;
N-[4-(6,7-Dichloro-2-cyclopentyl-2-methyl-1-oxo-5-yl-oxymethyl)-benzoyl]-methanesulfonamide;
N-[4-(6,7-Dichloro-2-cyclopentyl-2-methyl-1-oxo-5-yl-oxymethyl)-benzoyl]-4-methylbenzenesulfonamide;
6,7-Dichloro-2-cyclopentyl-2-methyl-5-[4-(1H-tetrazol-5-yl)-phenyl]-indan-1-one;
3,5-dibromo-4-[[6,7-dichloro-2-cyclopentyl-2-methyl-1-oxo-2,3-dihydro-1H-inden-5-yl]oxy]methyl]-N-(methylsulfonyl)benzamide;
N-acetyl-4-[[6,7-dichloro-2-cyclopentyl-2-methyl-1-oxo-2,3-dihydro-1H-inden-5-yl]oxy]methyl]benzamide;
6,7-dichloro-2-cyclopentyl-2-methyl-5-[5-(1H-tetrazol-5-yl)pyridin-2-yl]methoxy]-indan-1-one;
6,7-dichloro-2-cyclopentyl-2-methyl-5-[4-(4-(2H-tetrazol-5-yl)phenoxy)butoxy]-indan-1-one;
6,7-dichloro-2-cyclopentyl-2-methyl-5-[4-(3-(2H-tetrazol-5-yl)phenoxy)butoxy]-indan-1-one;
3'-[(2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy)methyl] biphenyl-3-carboxylic acid;
5-(3-[(2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy)methyl]phenyl)nicotinic acid
2-Cyclopentyl-6,7-dimethyl-5-[[3-[5-(1H-tetrazol-5-yl)pyridin-3-yl]benzyl]oxy]indan-1-one;
6,7-dichloro-2-cyclopentyl-2-methyl-5-[[3-[4-(2H-tetrazol-5-yl)phenoxy]benzyl]oxy]indan-1-one
2-cyclopentyl-6,7-dimethyl-5-[[3'-[(2H-tetrazol-5-yl)biphenyl-3-yl]methoxy]indan-1-one;
3'-[(2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy)methyl]biphenyl-4-carboxylic acid;
3'-[[6,7-Dichloro-2-cyclopentyl-2-methyl-1-oxo-2,3-dihydro-1H-inden-5-yl]oxy)methyl]biphenyl-3-carboxylic acid;
3'-[[2-cyclopentyl-2,6,7-trimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl]oxy)methyl]biphenyl-4-carboxylic acid;
3'-[[2-cyclopentyl-2,6,7-trimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl]oxy)methyl]biphenyl-3-carboxylic acid;
2-cyclopentyl-6,7-dimethyl-5-[[4'-[(2H-tetrazol-5-yl)biphenyl-3-yl]methoxy]indan-1-one;
3-(4-[[6,7-dichloro-2-cyclopentyl-2-methyl-1-oxo-2,3-dihydro-1H-inden-5-yl]oxy]butoxy]phenyl)propanoic acid;
3'-[[6,7-Dichloro-2-cyclopentyl-2-methyl-1-oxo-2,3-dihydro-1H-inden-5-yl]oxy)methyl]biphenyl-4-carboxylic acid;
5-(3-[[2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl]oxy]methyl)pyridine-2-carboxylic acid;
4-(3-[[2-cyclopentyl-2,6,7-trimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl]oxy)methyl]phenoxy)benzoic acid;
3'-[[2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl]oxy)methyl]-N-(methylsulfonyl)biphenyl-3-carboxamide;
3'-[[2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl]oxy)methyl]-2-methylbiphenyl-3-carboxylic acid;
3'-[[2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl]oxy)methyl]-3-methylbiphenyl-4-carboxylic acid;
3'-[[2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl]oxy)methyl]-2-methylbiphenyl-4-carboxylic acid;
4-Chloro-3'-([(2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)biphenyl-3-carboxylic acid;
3'-([(2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)6-methylbiphenyl-3-carboxylic acid;
3'-([(6,7-Dichloro-2-cyclopentyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)biphenyl-4-carboxylic acid;
3'-([(6,7-Dichloro-2-isopropyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)biphenyl-4-carboxylic acid;
3'-([(6,7-Dichloro-1-oxo-2-propyl-2,3-dihydro-1H-inden-5-yl)oxy]methyl)biphenyl-4-carboxylic acid;
5-((2-chloro-5-[4-(2H-tetrazol-5-yl)phenoxy]benzyl)oxy)-2-cyclopentyl-6,7-dimethylindan-1-one;
4-(3-[(2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)phenoxy)benzoic acid;
4-3-[(6,7-Dichloro-2-cyclopentyl-2-methyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)phenoxy)benzoic acid;
3'-([(6,7-Dichloro-2,2-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)biphenyl-4-carboxylic acid;
3'-([(6,7-Dichloro-2-methyl-1-oxo-2-phenyl-2,3-dihydro-1H-inden-5-yl)oxy]methyl)biphenyl-4-carboxylic acid;
3'-([(2-Butyl-6,7-dichloro-2-cyclopentyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)biphenyl-4-carboxylic acid;
3'-([(6,7-Dichloro-2-(cyclopentylmethyl)-2-methyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)biphenyl-4-carboxylic acid;
3'-([(7-Chloro-2-cyclopentyl-6-methyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)biphenyl-4-carboxylic acid;
3'-([(2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)-6-fluorobiphenyl-3-carboxylic acid
3'-([(2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)-2-fluorobiphenyl-4-carboxylic acid;
3'-([(2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)-6-methoxybiphenyl-3-carboxylic acid;
3'-([(2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl)-2,6-dimethoxybiphenyl-4-carboxylic acid;
3-Chloro-3'-[(2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl]biphenyl-4-carboxylic acid;
4-Chloro-3'-[(6,7-dichloro-2-cyclopentyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl]biphenyl-3-carboxylic acid;
4-Chloro-3'-[(6,7-dichloro-2-cyclopentyl-2-methyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl]biphenyl-3-carboxylic acid;
3'-[(2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl]biphenyl-3-carboxylic acid;
3'-[(6,7-Dichloro-2-cyclopentyl-2-methyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl]biphenyl-3-carboxylic acid;
3'-[(2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl]biphenyl-3-carboxylic acid;
3'-[(2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl]biphenyl-3-carboxylic acid;
5-(3-[(2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl) phenyl)-2,3-dihydro-1-benzofuran-7-carboxylic acid;
3'-[(7-Chloro-2-cyclopentyl-6-methyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl]biphenyl-3-carboxylic acid;
3'-[(7-Chloro-2-cyclopentyl-6-methyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl]biphenyl-3-carboxylic acid;
4-Chloro-3'-[(7-chloro-2-cyclopentyl-6-methyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl]biphenyl-3-carboxylic acid;
3'-[(2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl]biphenyl-3-carboxylic acid;
3'-[(2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl]biphenyl-3-carboxylic acid;
3'-[(2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)oxy]methyl]biphenyl-3-carboxylic acid;
6,7-Dichloro-2-cyclopentyl-2-methyl-5-[(3'-(2H-tetrazol-5-yl)biphenyl-3-yl)methoxy] indan-1-one;
and pharmaceutically acceptable salts thereof.

The compounds of the present invention are potentiators of metabotropic glutamate (mGluR) receptor function, in particular they are potentiators of mGluR2 receptors. That is, the compounds of the present invention do not appear to bind at the glutamate recognition site on the mGluR receptor, but in the presence of glutamate or a glutamate agonist, the compounds of the present invention increase mGluR receptor response. The present potentiators are expected to have their effect at mGluR receptors by
virtue of their ability to increase the response of such receptors to glutamate or glutamate agonists, enhancing the function of the receptors. It is recognized that the compounds of the present invention would be expected to increase the effectiveness of glutamate and glutamate agonists of the mGluR2 receptor. Thus, the potentiators of the present invention are expected to be useful in the treatment of various neurological and psychiatric disorders associated with glutamate dysfunction described to be treated herein and others that can be treated by such potentiators as are appreciated by those skilled in the art.

The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds. Formula I shows the structure of the class of compounds without preferred stereochemistry.

The independent syntheses of these diastereomers or their chromatographic separations may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

If desired, racemic mixtures of the compounds may be separated so that the individual enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well known in the art.
As appreciated by those of skill in the art, halo or halogen as used herein are intended to include fluoro, chloro, bromo and iodo. Similarly, C_1-6_, as in C_1-galkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6 carbons in a linear or branched arrangement, such that C_1-galkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, and hexyl. A group which is designated as being independently substituted with substituents may be independently substituted with multiple numbers of such substituents.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids including inorganic or organic bases and inorganic or organic acids. Salts derived from inorganic bases include aluminum, ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic salts, manganous, potassium, sodium, zinc, and the like. Particularly preferred are the ammonium, calcium, magnesium, potassium, and sodium salts. Salts in the solid form may exist in more than one crystal structure, and may also be in the form of hydrates. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, and basic ion exchange resins, such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylene-diamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethyl-morpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrazamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine, and the like.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothentic, phosphoric, succinic, sulfuric, tartaric, p-toluensulfonic acid, and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids. It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein. Specific compounds within the present invention include a compound which selected from the group consisting of the compounds disclosed in the following Examples and pharmaceutically acceptable salts thereof and individual diastereomers thereof.
The subject compounds are useful in a method of potentiating metabotropic glutamate receptor activity in a patient such as a mammal in need of such inhibition comprising the administration of an effective amount of the compound. The present invention is directed to the use of the compounds disclosed herein as potentiators of metabotropic glutamate receptor activity. In addition to primates, especially humans, a variety of other mammals can be treated according to the method of the present invention.

The present invention is further directed to a method for the manufacture of a medicament for potentiating metabotropic glutamate receptor activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The subject treated in the present methods is generally a mammal, preferably a human being, male or female, in whom potentiation of metabotropic glutamate receptor activity is desired. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. It is recognized that one skilled in the art may affect the neurological and psychiatric disorders by treating a patient presently afflicted with the disorders or by prophylactically treating a patient afflicted with the disorders with an effective amount of the compound of the present invention. As used herein, the terms "treatment" and "treating" refer to all processes wherein there may be a slowing, interrupting, arresting, controlling, or stopping of the progression of the neurological and psychiatric disorders described herein, but does not necessarily indicate a total elimination of all disorder symptoms, as well as the prophylactic therapy of the mentioned conditions, particularly in a patient who is predisposed to such disease or disorder.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the
carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

The utility of the compounds in accordance with the present invention as inhibitors of metabotropic glutamate receptor activity, in particular mGluR2 activity, may be demonstrated by methodology known in the art. Inhibition constants are determined as follows. The compounds of the present invention were tested in a $^{35}$S-GTPγS assay. The stimulation of $^{35}$S-GTPγS binding is a common functional assay to monitor Gζi-coupled receptor in native and recombinant receptor membrane preparation. Membrane from cells stably expressing hmGlu2 CHO-K1 (50µg) were incubated in a 96 well plate for 1 hour in the presence of GTPγS$^{35}$ (0.05nM), GDP (5µM) and compounds. The reaction was stopped by rapid filtration over Unifilter GF/B plate (Packard, Bioscience, Meriden CT) using a 96-well cell harvester (Brandel Gaithersburg, MD). The filter plates were counted using Topcount counter (Packard, Bioscience, Meriden CT, USA). When compounds were evaluated as potentiator they were tested in the presence of glutamate (1µM). The activation (agonist) or the potentiation of glutamate (potentiator) curves were fitted with a four parameters logistic equation giving EC$_{50}$ and Hill coefficient using the iterative non linear curve fitting software GraphPad (San Diego CA, USA).

In particular, the compounds of the following examples had activity in potentiating the mGluR2 receptor in the aforementioned assays, generally with an EC$_{50}$ of less than about 10 µM. Preferred compounds within the present invention had activity in potentiating the mGluR2 receptor in the aforementioned assays with an EC$_{50}$ of less than about 1 µM. Such a result is indicative of the intrinsic activity of the compounds in use as potentiators of mGluR2 receptor activity.

Metabotropic glutamate receptors including the mGluR2 receptor have been implicated in a wide range of biological functions. This has suggested a potential role for these receptors in a variety of disease processes in humans or other species.

The compounds of the present invention have utility in treating, preventing, ameliorating, controlling or reducing the risk of a variety of neurological and psychiatric disorders associated with glutamate dysfunction, including one or more of the following conditions or diseases: acute neurological and psychiatric disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage,
dementia (including AIDS-induced dementia), Alzheimer’s disease, Huntington’s Chorea, amyotrophic lateral sclerosis, ocular damage, retinopathy, cognitive disorders, idiopathic and drug-induced Parkinson’s disease, muscular spasms and disorders associated with muscular spasticity including tremors, epilepsy, convulsions, migraine (including migraine headache), urinary incontinence, substance tolerance, substance withdrawal (including, substances such as opiates, nicotine, tobacco products, alcohol, benzodiazepines, cocaine, sedatives, hypnotics, etc.), psychosis, schizophrenia, anxiety (including generalized anxiety disorder, panic disorder, and obsessive compulsive disorder), mood disorders (including depression, mania, bipolar disorders), trigeminal neuralgia, hearing loss, tinnitus, macular degeneration of the eye, emesis, brain edema, pain (including acute and chronic pain states, severe pain, intractable pain, neuropathic pain, and post-traumatic pain), tardive dyskinesia, sleep disorders (including narcolepsy), attention deficit/hyperactivity disorder, and conduct disorder.

Of the disorders above, the treatment of migraine, anxiety, schizophrenia, and epilepsy are of particular importance. In a preferred embodiment the present invention provides a method for treating migraine, comprising: administering to a patient in need thereof an effective amount of a compound of formula I. In another preferred embodiment the present invention provides a method for preventing or treating anxiety, comprising: administering to a patient in need thereof an effective amount of a compound of formula I. Particularly preferred anxiety disorders are generalized anxiety disorder, panic disorder, and obsessive compulsive disorder. In another preferred embodiment the present invention provides a method for treating schizophrenia, comprising: administering to a patient in need thereof an effective amount of a compound of formula I. In yet another preferred embodiment the present invention provides a method for treating epilepsy, comprising: administering to a patient in need thereof an effective amount of a compound of formula I.

Of the neurological and psychiatric disorders associated with glutamate dysfunction which are treated according to the present invention, the treatment of migraine, anxiety, schizophrenia, and epilepsy are particularly preferred. Particularly preferred anxiety disorders are generalized anxiety disorder, panic disorder, and obsessive compulsive disorder.

Thus, in a preferred embodiment the present invention provides a method for treating migraine, comprising: administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutical composition thereof. In one of the available sources of diagnostic tools, Dorland’s Medical Dictionary (23’d Ed., 1982, W. B. Saunders
Company, Philadelphia, PA), migraine is defined as a symptom complex of periodic headaches, usually temporal and unilateral, often with irritability, nausea, vomiting, constipation or diarrhea, and photophobia. As used herein the term "migraine" includes these periodic headaches, both temporal and unilateral, the associated irritability, nausea, vomiting, constipation or diarrhea, photophobia, and other associated symptoms. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for neurological and psychiatric disorders, including migraine, and that these systems evolve with medical scientific progress.

In another preferred embodiment the present invention provides a method for treating anxiety, comprising: administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutical composition thereof. At present, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1994, American Psychiatric Association, Washington, D.C.), provides a diagnostic tool including anxiety and related disorders. These include: panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, post-traumatic stress disorder, acute stress disorder, generalized anxiety disorder, anxiety disorder due to a general medical condition, substance-induced anxiety disorder and anxiety disorder not otherwise specified. As used herein the term "anxiety" includes treatment of those anxiety disorders and related disorder as described in the DSM-IV. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for neurological and psychiatric disorders, and particular anxiety, and that these systems evolve with medical scientific progress. Thus, the term "anxiety" is intended to include like disorders that are described in other diagnostic sources.

In another preferred embodiment the present invention provides a method for treating depression, comprising: administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutical composition thereof. At present, the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1994, American Psychiatric Association, Washington, D.C.), provides a diagnostic tool including depression and related disorders. Depressive disorders include, for example, single episodic or recurrent major depressive disorders, and dysthymic disorders, depressive neurosis, and neurotic depression; melancholic depression including anorexia, weight loss, insomnia and early morning waking, and psychomotor retardation; atypical depression (or reactive depression) including increased appetite, hypsomnia, psychomotor agitation or irritability, anxiety and phobias; seasonal affective disorder; or bipolar disorders or manic depression, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder. As
used herein the term "depression" includes treatment of those depression disorders and related disorder as described in the DSM-IV.

In another preferred embodiment the present invention provides a method for treating epilepsy, comprising: administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutical composition thereof. At present, there are several types and subtypes of seizures associated with epilepsy, including idiopathic, symptomatic, and cryptogenic. These epileptic seizures can be focal (partial) or generalized. They can also be simple or complex. Epilepsy is described in the art, such as Epilepsy: A comprehensive textbook. Ed. by Jerome Engel, Jr. and Timothy A. Pedley. (Lippincott-Raven, Philadelphia, 1997). At present, the International Classification of Diseases, Ninth Revision, (ICD-9) provides a diagnostic tool including epilepsy and related disorders. These include: generalized nonconvulsive epilepsy, generalized convulsive epilepsy, petit mal status epilepticus, grand mal status epilepticus, partial epilepsy with impairment of consciousness, partial epilepsy without impairment of consciousness, infantile spasms, epilepsy partialis continua, other forms of epilepsy, epilepsy, unspecified, NOS. As used herein the term "epilepsy" includes these all types and subtypes. The skilled artisan will recognize that there are alternative nomenclatures, nosologies, and classification systems for neurological and psychiatric disorders, including epilepsy, and that these systems evolve with medical scientific progress.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the aforementioned diseases, disorders and conditions in combination with other agents, including an mGluR agonist.

The term "potentiated amount" refers to an amount of an mGluR agonist, that is, the dosage of agonist which is effective in treating the neurological and psychiatric disorders described herein when administered in combination with an effective amount of a compound of the present invention. A potentiated amount is expected to be less than the amount that is required to provided the same effect when the mGluR agonist is administered without an effective amount of a compound of the present invention.

A potentiated amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining a potentiated amount, the dose of an mGluR agonist to be administered in combination with a compound
of formula I, a number of factors are considered by the attending diagnostian, including, but not limited to: the mGluR agonist selected to be administered, including its potency and selectivity; the compound of formula I to be coadministered; the species of mammal; its size, age, and general health; the specific disorder involved; the degree of involvement or the severity of the disorder; the response of the individual patient; the modes of administration; the bioavailability characteristics of the preparations administered; the dose regimens selected; the use of other concomitant medication; and other relevant circumstances.

A potentiated amount of an mGluR agonist to be administered in combination with an effective amount of a compound of formula I is expected to vary from about 0.1 milligram per kilogram of body weight per day (mg/kg/day) to about 100 mg/kg/day and is expected to be less than the amount that is required to provided the same effect when administered without an effective amount of a compound of formula I. Preferred amounts of a co-administered mGlu agonist are able to be determined by one skilled in the art.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or conditions for which compounds of Formula I or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of Formula I is preferred. However, the combination therapy may also includes therapies in which the compound of Formula I and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula I.

The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds.

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

The weight ratio of the compound of the compound of the present invention to the second active ingredient may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, preferably about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s).

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each route of administration. In addition to the treatment of warm-blooded animals such as mice, rats, horses, cattle, sheep, dogs, cats, monkeys, etc., the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the
desired formulation. In the pharmaceutical composition the active object compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Pharmaceutical compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. Compositions for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Oily suspensions may be formulated by suspending the active ingredient in a suitable oil. Oil-in-water emulsions may also be employed. Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives.

Pharmaceutical compositions of the present compounds may be in the form of a sterile injectable aqueous or oleagenous suspension. The compounds of the present invention may also be administered in the form of suppositories for rectal administration. For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention may be employed. The compounds of the present invention may also be formulated for administered by inhalation. The compounds of the

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present invention may also be administered by a transdermal patch by methods known in the
art.

The pharmaceutical composition and method of the present invention may
further comprise other therapeutically active compounds as noted herein which are usually
applied in the treatment of the above mentioned pathological conditions.

In the treatment, prevention, control, amelioration, or reduction of risk of
conditions which require potentiation of metabotropic glutamate receptor activity an
appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight
per day which can be administered in single or multiple doses. Preferably, the dosage level
will be about 0.1 to about 250 mg/kg per day; more preferably about 0.5 to about 100 mg/kg
per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100
mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05
to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are
preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active
ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0,
300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active
ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The
compounds may be administered on a regimen of 1 to 4 times per day, preferably once or
twice per day.

When treating, preventing, controlling, ameliorating, or reducing the risk of
neurological and psychiatric disorders associated with glutamate dysfunction or other
diseases for which compounds of the present invention are indicated, generally satisfactory
results are obtained when the compounds of the present invention are administered at a daily
dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body
weight, preferably given as a single daily dose or in divided doses two to six times a day, or
in sustained release form. For most large mammals, the total daily dosage is from about 1.0
milligrams to about 1000 milligrams, preferably from about 1 milligrams to about 50
milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from
about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide
the optimal therapeutic response.

It will be understood, however, that the specific dose level and frequency of
dosage for any particular patient may be varied and will depend upon a variety of factors
including the activity of the specific compound employed, the metabolic stability and length
of action of that compound, the age, body weight, general health, sex, diet, mode and time of
administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art or as illustrated herein. The compounds of the present invention can be prepared in a variety of fashions.

**SCHEME 1**

The compounds of the present invention can be prepared from an appropriately substituted acetophenone precursor as illustrated in Scheme 1. A substituted acetophenone (either purchased commercially or prepared using techniques well known in the art) is alkylated with variously substituted aryl compounds. These aryl compounds contain alkyl or benzyl linkers with a suitable leaving group (halide, triflate, tosylate, mesylate and the like) and are reacted in the presence of a base (potassium carbonate, sodium hydroxide, and the like) in a suitable solvent (acetone, tetrahydrofuran, dimethoxyethane, etc.). The reaction is generally run at ambient temperature to 45 °C for a period of 4 to 24 hours. The product from the reaction can be isolated and purified employing standard techniques such as solvent extraction, chromatography, crystallization, distillation and the like.

**SCHEME 2**
The compounds of the present invention can also be prepared as outlined in Scheme 2. A substituted acetophenone (either purchased commercially or prepared using techniques well known in the art) is alkylated with a linker containing two suitable leaving groups (halide, triflate, tosylate, mesylate and the like). This reaction is run in the presence of a base (potassium carbonate, sodium hydroxide, and the like) in a suitable solvent (acetone, tetrahydrofuran, dimethoxyethane, etc.). The reaction is generally run at ambient temperature to 45 °C for a period of 4 to 24 hours. The product from the reaction can be isolated and purified employing standard techniques such as solvent extraction, chromatography, crystallization, distillation and the like. The product of this reaction is then reacted with an appropriately substituted phenol in the presence of a base (potassium carbonate, sodium hydroxide, and the like) in a suitable solvent (acetone, tetrahydrofuran, dimethoxyethane, etc.). The reaction is generally run at ambient temperature to 45 °C for a period of 4 to 24 hours. The product from the reaction can be isolated and purified employing standard techniques such as solvent extraction, chromatography, crystallization, distillation and the like.

SCHEME 3

![Chemical structure](image)

The compounds of the present invention can also be prepared as outlined in Scheme 3. A substituted acetophenone (either purchased commercially or prepared using techniques well known in the art) is alkylated with a compound containing a benzylic alcohol. This reaction is run in the presence of a compound such as diethylazodicarboxylate (DEAD), diisopropylazodicarboxylate (DIAD) or di-tertbutylazodicarboxylate (DTAD) and a triarylphosphine in a suitable solvent (tetrahydrofuran, dimethoxyethane, ether etc.). The reaction is generally run at ambient temperature for a period of 4 to 24 hours. The product from the reaction can be isolated and purified employing standard techniques such as solvent extraction, chromatography, crystallization, distillation and the like.

In some cases the final product may be further modified, for example, by manipulation of substituents. These manipulations may include, but are not limited to,
reduction, oxidation, alkylation, acylation, and hydrolysis reactions which are commonly known to those skilled in the art.

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

EXAMPLE 1

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\]

7-\{4-[3-hydroxy-2-methyl-4-(3-methyl-butyryl)-phenoxy]-butoxy\}-chromen-2-one

Potassium carbonate (2.39 g, 17.3 mmol) was added to a stirred solution of 1-(2,4-Dihydroxy-3-methyl-phenyl)-3-methyl-butan-1-one (150 mg, 0.68 mmol) and 1,4-dibromobutane (6.22 g, 28.8 mmol) in acetone (100 mL) at 45 °C. The reaction mixture was stirred for 16 hr, then the acetone was removed \textit{in vacuo}. The residue was then mixed with dichloromethane (100 mL) and water (100 mL). The organic layer was separated, dried over MgSO\textsubscript{4} and then concentrated \textit{in vacuo} to give a residue that was purified via column chromatography on silica gel (eluting 0-60% ethyl acetate/hexanes) to give 3.26 g (98%) of 1-[4-(4-Bromo-butoxy)-2-hydroxy-3-methyl-phenyl]-3-methyl-butan-1-one as a white solid. Then, potassium carbonate (161 mg, 1.16 mmol) was added to a stirred solution of 1-[4-(4-Bromo-butoxy)-2-hydroxy-3-methyl-phenyl]-3-methyl-butan-1-one (200 mg, 0.58 mmol) and 7-hydroxycoumarin (141 mg, 0.87 mmol) in acetone (10 mL) at 45 °C. The reaction mixture was stirred for 16 hr, then the acetone was removed \textit{in vacuo}. The residue was then mixed with dichloromethane (25 mL) and water (25 mL). The organic layer was separated, dried over MgSO\textsubscript{4} and then concentrated \textit{in vacuo} to give a residue that was purified via column chromatography on silica gel (eluting 0-60% ethyl acetate/hexanes) to give 155 mg (63%) of 7-[4-[3-Hydroxy-2-methyl-4-(3-methyl-butyryl)-phenoxy]-butoxy]-chromen-2-one as a white solid. \textsuperscript{1}H NMR(CDCl\textsubscript{3}, 500MHz), δ 13.03 (s, 1H), 7.66-7.62 (m, 2H), 7.39 (d, 1H), 6.86-6.83 (m, 2H), 6.45 (d, 1H), 6.27 (d, 1H), 4.16-4.12 (m, 4H), 2.79 (d, 2H), 2.30-2.27 (m, 1H), 2.12 (s, 3H), 2.09-2.05 (m, 4H), 1.02 (d, 6H). MS (ESI): 425 (M + H\textsuperscript{+}).
EXAMPLE 2

1-[2-hydroxy-3-methyl-4-(4-phenoxy-butoxy)-phenyl]-3-methyl-butan-1-one

Potassium carbonate (398 mg, 12.88 mmol) was added to a stirred solution of 1-(2,4-Dihydroxy-3-methyl-phenyl)-3-methyl-butan-1-one (300 mg, 1.44 mmol) and (4-Bromo-butoxy)-benzene (396 mg, 1.73 mmol) in acetone (20 mL) at 45 °C. The reaction mixture was stirred for 16 hr, then the acetone was removed in vacuo. The residue was then mixed with dichloromethane (50 mL) and water (50 mL). The organic layer was separated, dried over MgSO₄ and then concentrated in vacuo to give a residue that was purified via column chromatography on silica gel (eluting 0-60% ethyl acetate/hexanes) to give 381 mg (74%) of 1-[2-Hydroxy-3-methyl-4-(4-phenoxy-butoxy)-phenyl]-3-methyl-butan-1-one as a colorless oil. ¹H NMR(CDCl₃, 500MHz), δ 13.04 (s, 1H), 7.62 (d, 1H), 7.32-7.28 (m, 2H), 6.98-6.91 (m, 3H), 6.45 (d, 1H), 4.16-4.07 (m, 4H), 2.79 (d, 2H), 2.30-2.28 (m, 1H), 2.10 (s, 3H), 2.07-2.03 (m, 4H), 1.02 (d, 6H). MS (ESI): 358 (M + H)⁺.

EXAMPLE 3

1-[3-bromo-2-hydroxy-4-(4-phenoxy-butoxy)-phenyl]-3-methyl-butan-1-one

A similar procedure as outlined in example 2 was followed using 1-(3-Bromo-2,4-dihydroxy-phenyl)-3-methyl-butan-1-one. ¹H NMR(CDCl₃, 500MHz), δ 13.57 (s, 1H), 7.23 (d, 1H), 7.31-7.28 (m, 2H), 6.97-6.91 (m, 3H), 6.50 (d, 1H), 4.22 (t, 2H), 4.09 (t, 2H), 2.80 (d, 2H), 2.31-2.28 (m, 1H), 2.11-2.05 (m, 4H), 1.02 (d, 6H). MS (ESI): 421 (M + H)⁺.

EXAMPLE 4
1-(2-hydroxy-3-methyl-4-[4-(pyridin-3-yl)-butoxy]-phenyl)-3-methyl-butan-1-one

A similar procedure as outlined in example 1 was followed using 3-hydroxypyridine. $^1$H NMR(CDC$_3$, 500MHz), δ 13.00 (s, 1H), 8.35 (brs, 1H), 8.27-8.26 (m, 1H), 7.65 (d, 1H), 7.31 (brs, 1H), 7.31-7.28 (1H), 6.45 (d, 1H), 4.18-4.10 (m, 4H), 2.80 (d, 2H), 2.33-2.27 (m, 1H), 2.10 (s, 3H), 2.07-2.00 (m, 4H), 1.09 (d, 6H). MS (ESI): 358 (M + H)$^+$. 

EXAMPLE 5

1-(2-hydroxy-3-methyl-4-[4-(pyridin-2-yl)-butoxy]-phenyl)-3-methyl-butan-1-one

A similar procedure as outlined in example 1 was followed using 2-hydroxypyridine. $^1$H NMR(CDC$_3$, 500MHz), δ 13.02 (s, 1H), 8.17-8.12 (m, 1H), 7.53-7.56 (m, 2H), 6.89-6.86 (m, 1H), 6.74-6.72 (m, 1H), 6.44 (d, 1H), 4.40-4.38 (m, 2H), 4.16-4.12 (m, 2H), 2.78 (d, 2H), 2.29-2.27 (m, 1H), 2.11 (s, 3H), 2.07-2.01 (m, 4H), 1.02 (d, 6H). MS (ESI): 358 (M + H)$^+$. 

EXAMPLE 6

1-(2-hydroxy-3-methyl-4-[4-(pyridin-4-yl)-butoxy]-phenyl)-3-methyl-butan-1-one
A similar procedure as outlined in example 1 was followed using 4-hydroxypyridine. $^1$H NMR(CDCl$_3$, 500MHz), δ 13.04 (s, 1H), 8.44 (d, 2H), 7.62 (d, 1H), 6.83 (d, 2H), 6.45 (d, 1H), 4.15-4.11 (m, 4H), 2.78 (d, 2H), 2.37-2.26 (m, 1H), 2.12 (s, 3H), 2.06-2.04 (m, 4H), 1.01 (d, 6H). MS (ESI): 358 (M + H)$^+$.  

**EXAMPLE 7**

![Chemical Structure](image)

1-{[2-hydroxy-3-methyl-4-[3-(pyridin-3-yloxy)-propoxy]-phenyl]-3-methyl-butan-1-one

A similar procedure as outlined in example 1 was followed using 1,3-dibromobutane and 3-hydroxypyridine. $^1$H NMR(CDCl$_3$, 500MHz), δ 13.02 (s, 1H), 8.35-8.34 (m, 1H), 8.25-8.24 (m, 1H), 7.62 (d, 1H), 7.27-7.26 (m, 2H), 6.47 (d, 1H), 4.28-4.24 (m, 4H), 2.78 (d, 2H), 2.38-2.28 (m, 3H), 2.11 (s, 3H), 1.01 (d, 6H). MS (ESI): 344 (M + H)$^+$.  

**EXAMPLE 8**

![Chemical Structure](image)

1-{[2-hydroxy-4-[4-(2-methoxy-phenoxy)-butoxy]-3-methyl-phenyl]-3-methyl-butan-1-one

A similar procedure as outlined in example 1 was followed using 2-methoxyphenol. $^1$H NMR(CDCl$_3$, 500MHz), δ 13.01 (s, 1H), 7.63 (d, 1H), 6.95-6.87 (m, 4H), 6.44 (d, 1H), 4.16-4.06 (m, 4H), 3.87 (s, 3H), 2.78 (d, 2H), 2.31-2.26 (m, 1H), 2.12 (s, 3H), 2.08-2.05 (m, 4H), 1.02 (d, 6H). MS (ESI): 387 (M + H)$^+$.  

**EXAMPLE 9**

![Chemical Structure](image)

7-{[2-bromo-3-hydroxy-4-(3-methyl-butyryl)-phenoxy]-butoxy]-chromen-2-one
A similar procedure as outlined in example 1 was followed using 1-(3-
Bromo-2,4-dihydroxy-phenyl)-3-methyl-butan-1-one. \(^1\)H NMR(DMSO-d6, 500MHz), \(\delta\) 13.43 (s, 1H), 8.00 (d, 1H), 7.96 (d, 1H), 7.59 (d, 1H), 9.97-6.91 (m, 2H), 6.75 (d, 1H), 6.25 (d, 1H), 4.26-4.25 (m, 2H), 4.16-4.15 (m, 2H), 2.89 (d, 2H), 2.16-2.11 (m, 1H), 1.97-1.92 (m, 4H), 0.94 (d, 6H). MS (ESI): 490 (M + H)^+.

EXAMPLE 10

![Chemical Structure](image)

1-[3-bromo-2-hydroxy-4-[4-(pyridin-3-yloxy)-butoxy]-phenyl]-3-methyl-butan-1-one

A similar procedure as outlined in example 1 was followed using 1-(3-
Bromo-2,4-dihydroxy-phenyl)-3-methyl-butan-1-one and 3-hydroxy-pyridine. \(^1\)H NMR(DMSO-d6, 500MHz), \(\delta\) 13.46 (s, 1H), 8.48-8.47 (m, 1H), 8.33 (d, 1H), 8.03 (d, 1H), 7.76-7.74 (m, 1H), 7.63-7.61 (m, 1H), 6.78 (d, 1H), 4.28-4.22 (m, 4H), 2.92 (d, 2H), 2.18-2.13 (m, 1H), 1.96-1.95 (m, 4H), 0.95 (d, 6H). MS (ESI): 423 (M + H)^+.

EXAMPLE 11

![Chemical Structure](image)

1-[2-hydroxy-3-methyl-4-[5-(pyridin-3-yloxy)-pentyloxy]-phenyl]-3-methyl-butan-1-one

A similar procedure as outlined in example 2 was followed using 3-(5-
Bromo-pentyloxy)-pyridine. \(^1\)H NMR (CDCl\textsubscript{3}, 500 MHz) \(\delta\) 13.07 (s, 1H), 8.33 (s, 1H), 8.23 (d, 1H), 7.62 (d, 1H), 7.26-7.21 (m, 2H), 6.43 (d, 1H), 4.11-4.06 (m, 4H), 2.77(d, 2H), 2.31-2.25 (m, 1H), 2.13 (s, 3H), 1.96-1.89 (m, 4H), 1.74-1.69(m, 2H), 1.02-1.01 (d, 6H). ESI: 371 M^+.

EXAMPLE 12
1-{4-[4-(5-chloro-pyridin-3-yloxy)-butoxy]-2-hydroxy-3-methyl-phenyl}-3-methyl-butan-1-one

A similar procedure as outlined in example 1 was followed using 3-chloro-5-hydroxy pyridine. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.04 (s, 1H), 8.22 (m, 2H), 7.63 (d, 1H), 7.23-7.22 (m, 1H), 6.45 (d, 1H), 4.16-4.12 (m, 4H), 2.79 (d, 2H), 2.30-2.26 (m, 1H), 2.08 (s, 3H), 2.06-2.02 (m, 4H), 1.03 (d, 6H). MS (ESI): 392 (M + H)$^+$. 

EXAMPLE 13

1-{4-[4-(3-fluoro-phenoxy)-butoxy]-2-hydroxy-3-methyl-phenyl}-3-methyl-butan-1-one

A similar procedure as outlined in example 1 was followed using 3-fluorophenol. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.04 (s, 1H), 7.63 (d, 1H), 7.28-7.23 (m, 1H), 6.71-6.62 (m, 3H), 6.45 (d, 1H), 4.16-4.13 (m, 2H), 4.07-4.04 (m, 2H), 2.79 (d, 2H), 2.32-2.27 (m, 1H), 2.13 (s, 3H), 2.05-2.00 (m, 4H), 1.02 (d, 6H). MS (ESI): 375 (M + H)$^+$. 

EXAMPLE 14

1-{2-hydroxy-3-methyl-4-[4-(3-trifluoromethyl-phenoxy)-butoxy]-phenyl}-3-methyl-butan-1-one

A similar procedure as outlined in example 1 was followed using 3-(trifluoromethyl)phenol. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.05 (s, 1H), 7.63 (d, 1H), 7.41 (t, 1H), 7.23-7.08 (m, 3H), 6.45 (d, 1H), 4.17-4.10 (m, 4H), 2.79 (d, 2H), 2.32-2.27 (m, 1H), 2.13 (s, 3H), 2.08-2.04 (m, 4H), 1.02 (d, 6H). MS (ESI): 425 (M + H)$^+$. 

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EXAMPLE 15

1-{2-hydroxy-4-[4-(4-methoxy-phenoxo)-butoxy]-3-methyl-phenyl}-3-methyl-butan-1-one

A similar procedure as outlined in example 1 was followed using 4-methoxyphenol. 
$^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 13.11 (s, 1H), 7.62 (d, 1H), 6.86 (m, 4H), 6.44 (d, 1H), 4.14 (m, 2H), 4.04 (m, 2H), 3.80 (s, 3H), 2.78 (d, 2H), 2.31-2.28 (m, 1H), 2.13 (s, 3H), 2.06-1.97 (m, 4H), 1.04 (d, 6H). ESI: 387 (M+H)$^+$

EXAMPLE 16

1-{4-[4-(3-chloro-phenoxo)-butoxy]-2-hydroxy-3-methyl-phenyl}-3-methyl-butan-1-one

A similar procedure as outlined in example 1 was followed using 3-chlorophenol. 
$^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.03 (s, 1H), 7.62 (d, 1H), 7.20 (t, 1H), 6.94 (d, 1H), 6.79 (s, 1H), 6.44 (d, 1H), 4.13-1.12 (m, 2H), 4.06-4.04 (m, 2H), 2.78 (d, 2H), 2.31-2.25 (m, 1H), 2.12 (s, 3H), 2.03-1.99 (m, 4H), 1.01 (d, 6H). MS (ESI): 391 (M + H)$^+$.

EXAMPLE 17

1-{2-hydroxy-3-methyl-4-[4-(pyrimidin-2-yloxy)-butoxy]-phenyl}-3-methyl-butan-1-one

A similar procedure as outlined in example 1 was followed using Pyrimidin-2-ol. 
$^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.02 (s, 1H), 8.52 (d, 2H), 7.61 (d, 1H), 6.93 (t, 1H), 6.44 (d, 1H), 4.48-4.45 (m, 2H), 4.14-1.12 (m, 2H), 2.78 (d, 2H), 2.29-2.26 (m, 1H), 2.10 (s, 3H), 2.06-2.04 (m, 4H), 1.01 (d, 6H). MS (ESI): 359 (M + H)$^+$. 

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EXAMPLE 18

1-[4-[4-(2-fluoro-phenoxy)-butoxy]-2-hydroxy-3-methyl-phenyl]-3-methyl-butan-1-one

A similar procedure as outlined in example 1 was followed using 2-fluorophenol. $^1$H NMR (CDCl₃, 500MHz), δ 13.05 (s, 1H), 7.63 (d, 1H), 7.12-6.92 (m, 4H), 6.46 (d, 1H), 4.17-4.14 (m, 4H), 2.79 (d, 2H), 2.32-2.27 (m, 1H), 2.09 (s, 3H), 2.08-2.05 (m, 4H), 1.02 (d, 6H). MS (ESI): 375 (M + H)$^+$. 

EXAMPLE 19

1-[4-[4-(2,3-difluoro-phenoxy)-butoxy]-2-hydroxy-3-methyl-phenyl]-3-methyl-butan-1-one

A similar procedure as outlined in example 1 was followed using 2,3-difluorophenol. $^1$H NMR (CDCl₃, 500MHz), δ 13.04 (s, 1H), 7.63 (d, 1H), 7.00-6.98 (m, 1H), 6.81-6.75 (m, 2H), 6.45 (d, 1H), 4.17-4.12 (m, 4H), 2.79 (d, 2H), 2.32-2.26 (m, 1H), 2.12 (s, 3H), 2.09-2.04 (m, 4H), 1.01 (d, 6H). MS (ESI): 395 (M + H)$^+$. 

EXAMPLE 20

1-[2-hydroxy-4-[2-(isoquinolin-7-yloxy)-ethoxy]-3-methyl-phenyl]-3-methyl-butan-1-one

A similar procedure as outlined in example 2 was followed using 7-(2-Bromo-ethoxy)-isoquinoline. $^1$H NMR (CDCl₃, 500 MHz) δ 12.99 (s, 1H), 9.19 (s, 1H), 8.47 (d, 1H), 7.80 (d, 1H), 7.67-7.61 (m, 2H), 7.45 (dd, 1H), 7.33 (d, 1H), 6.54 (d, 1H), 4.55-4.50 (m, 4H), 2.80 (d, 2H), 2.34-2.27 (m, 1H), 2.18 (s, 3H), 1.01 (d, 6H).
ESI: 380 (M+H)^+

EXAMPLE 21

1-{2-hydroxy-3-methyl-4-[4-(naphthalen-2-yloxy)-butoxy]-phenyl}-3-methyl-butan-1-one

A similar procedure as outlined in example 1 was followed using 2-naphthol.

^1H NMR (CDCl₃, 500MHz), δ 13.05 (s, 1H), 7.80-7.73 (m, 3H), 7.63 (d, 1H), 7.48-7.45 (m, 1H), 7.38-7.34 (m, 1H), 7.18-7.16 (m, 2H), 6.46 (d, 1H), 4.23-4.13 (m, 4H), 2.79 (d, 2H), 2.32-2.21 (m, 1H), 2.13 (s, 3H), 2.11-2.09 (m, 4H), 1.02 (d, 6H). MS (ESI): 407 (M + H)^+.

EXAMPLE 22

1-{4-[4-(2,3-dihydro-1H-inden-5-yloxy)butoxy]-2-hydroxy-3-methylphenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using indan-5-ol.

^1H NMR (CDCl₃, 500MHz), δ 13.04 (s, 1H), 7.62 (d, 1H), 7.12 (d, 1H), 6.81 (s, 1H), 6.73-6.70 (m, 1H), 6.45 (d, 1H), 4.14 (t, 2H), 4.04 (t, 2H), 2.91-2.84 (m, 4H), 2.79 (d, 2H), 2.33-2.27 (m, 1H), 2.11 (s, 3H), 2.09-2.01 (m, 6H), 1.02 (d, 6H). MS (ESI): 397 (M + H)^+.

EXAMPLE 23

6-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoylphenoxy)butoxy]indan-1-one
A similar procedure as outlined in example 1 was followed using 5-hydroxyindan-1-one. $^1$H NMR (CDCl$_3$, 500MHz), δ 13.04 (s, 1H), 7.70 (d, 1H), 7.62 (d, 1H), 6.92-6.90 (m, 2H), 6.45 (d, 1H), 4.17-4.10 (m, 4H), 3.10 (t, 2H), 2.79 (d, 2H), 2.70 (t, 2H), 2.30-2.27 (m, 1H), 2.07 (s, 3H), 2.06-2.02 (m, 4H), 1.02 (d, 6H). MS (ESI): 411 (M + H)$^+$. 

**EXAMPLE 24**

![Chemical structure](image)

1-(3-bromo-2-hydroxy-4-[[3-(pyridin-3-yl oxy)benzyl]oxy]phenyl)-3-methylbutan-1-one

A mixture of 3-fluoropyridine (0.26 ml, 3.0 mmol), 3-hydroxybenzyl alcohol (760 mg, 6.1 mmol), cesium carbonate (1.5 g, 4.6 mmol) and dimethylformamide (18 ml) was heated to 150°C overnight under nitrogen atmosphere. After cooling reaction mixture to room temperature, the mixture was washed with brine and extracted with ethyl acetate. The combined organic extracts were dried over sodium sulfate and filtered. The filtrate was concentrated *in vacuo* to give a brown oil. Flash chromatography of oil on silica gel (0 – 75% ethyl acetate/hexanes) gave [3-(pyridin-3-yl oxy)phenyl]methanol as a oil (118 mg). A mixture of 1-(3-bromo-2,4-dihydroxyphenyl)-3-methylbutan-1-one (477 mg, 1.8 mmol), [3-(pyridin-3-yl oxy)phenyl]methanol (118 mg, 0.6 mmol), triphenylphosphine (456 mg, 1.8 mmol) and tetrahydrofuran (29 ml) was stirred in room temperature and the cooled to 0°C.

Diisopropylazodicarboxylate (0.34 ml, 1.8 mmol) was added dropwise and the mixture allowed to stir overnight at room temperature. Flash chromatography of mixture (0-70% ethyl acetate/hexanes) afforded the desire product as an oil (80 mg, 30%). $^1$H NMR (CDCl$_3$, 300 MHz) □ 13.74 (s, 1H), 8.44 (d, 1H), 8.42 (d, 1H), 7.73 (d, 1H), 7.49 – 7.40 (m, 1H), 7.36-7.25 (m, 4H), 7.16 (s, 1H), 7.02 -7.00 (dd, 1H), 6.52 (d, 1H), 5.23 (s, 2H), 2.80 (d, 2H), 2.33 – 2.25 (m, 1H), 1.02 (d, 6H). MS (ESI) 459, 458 (M$^+$ + H).

**EXAMPLE 25**

![Chemical structure](image)
1-{(2-hydroxy-3-methyl-4-[4-(4-pyridin-2-yl)piperazin-1-yl)butoxy]phenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 1-pyridin-2-ylpiperazine. $^1$H NMR (CDCl$_3$, 500MHz), δ 13.05 (s, 1H), 8.15 (d, 2H), 7.59 (d, 1H), 6.64 (d, 2H), 6.41 (d, 1H), 4.06 (t, 2H), 3.40-3.32 (m, 4H), 2.73 (d, 2H), 2.58-2.54 (m, 4H), 2.46 (t, 2H), 2.26-2.20 (m, 1H), 2.07 (s, 3H), 1.88-1.70 (m, 4H), 0.98 (d, 6H). MS (ESI): 426 (M + H)$^+$. 

EXAMPLE 26

1-{(2-hydroxy-3-methyl-4-[4-(4-pyridin-2-yl)piperazin-1-yl)butoxy]phenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 1-pyridin-2-ylpiperazine. $^1$H NMR (CDCl$_3$, 500MHz), δ 13.04 (s, 1H), 8.21-8.19 (m, 1H), 7.61 (d, 1H), 7.50-7.41 (m, 1H), 6.67-6.62 (m, 2H), 6.44 (d, 1H), 4.11 (t, 2H), 3.58-3.55 (m, 4H), 2.78 (d, 2H), 2.59-2.56 (m, 4H), 2.48 (t, 2H), 2.29-2.25 (m, 1H), 2.13 (s, 3H), 1.91-1.87 (m, 2H), 1.79-1.74 (m, 2H), 1.01 (d, 6H). MS (ESI): 426 (M + H)$^+$. 

EXAMPLE 27

1-{4-[4-(3,4-dihydroisoquinolin-2(1H)-yl)butoxy]-2-hydroxy-3-methylphenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 1,2,3,4-tetrahydroisoquinoline. $^1$H NMR (CDCl$_3$, 500MHz), δ 13.06 (s, 1H), 7.60 (d, 1H), 7.16-7.11 (m, 3H), 7.06-7.04 (m, 1H), 6.46 (d, 1H), 4.12 (t, 2H), 3.67 (s, 2H), 2.94 (t, 2H), 2.80-2.75 (m, 4H), 2.62 (t, 2H), 2.32-2.27 (m, 1H), 2.15 (s, 3H), 1.95-1.91 (m, 2H), 1.85-1.82 (m, 2H), 1.02 (d, 6H). MS (ESI): 396 (M + H)$^+$.
7-(3-[[2-bromo-3-hydroxy-4-(3-methylbutanoyl)phenoxy)methyl]phenoxy]-2H-chromen-2-one

7-Hydroxycoumarin (195 mg, 1.2 mmol) was added to a stirred mixture of potassium tert-butoxide (121 mg, 1.1 mmol), benzene (8 ml) and methanol (2 ml). The reaction was stirred until homogenous, then concentrated in vacuo to give a yellow solid. To the yellow solid, added copper (I) chloride (120 mg, 1.2 mmol), 3-iodobenzyl alcohol and pyridine (8 ml). Heated mixture at reflux conditions overnight. Mixture was cooled and quenched with 1.0 N HCl aqueous solution to pH 1. Organics were extracted with dichloromethane, dried over sodium sulfate and filtered. The filtrate was concentrated in vacuo to give the crude material as an oil. Flash chromatography of oil on silica gel (0-70% ethyl acetate/hexanes) afforded 7-[3-(hydroxymethyl)phenoxy]-2H-chromen-2-one (128 mg). A mixture of 1-(3-bromo-2,4-dihydroxyphenyl)-3-methylbutan-1-one (389 mg, 1.4 mmol), 7-[3-(hydroxymethyl)phenoxy]-2H-chromen-2-one (128 mg, 0.5 mmol), triphenylphosphine (377 mg, 1.4 mmol) and tetrahydrofuran (20 ml) was stirred in room temperature and the cooled to 0°C. Diisopropyl-azodicarboxylate (0.28 ml, 1.4 mmol) was added dropwise and the mixture allowed to stir overnight at room temperature. Flash chromatography on silica gel of mixture (0-40% ethyl acetate/hexanes) afforded the desire product as white solid (51 mg, 20%). $^1$H NMR (CDCl$_3$, 300 MHz) δ 13.58 (s, 1H), 7.74 (d, 1H), 7.69 (d, 1H), 7.48 – 7.44 (m, 2H), 7.33 (d, 1H), 7.23 (m, 1H), 7.08 (dd, 1H), 6.98 (dd, 1H), 6.88 (m, 1H), 6.53 (d, 1H), 6.34 (d, 1H), 5.28 (s, 2H), 2.82 (d, 2H), 2.32 – 2.26 (m, 1H), 1.03-1.01 (d, 6H).

MS (ESI) 546, 547 (M$^+$ + Na), 523, 522 (M$^-$).

EXAMPLE 29
1-{3-bromo-4-[4-(2,3-difluorophenoxy)butoxy]-2-hydroxyphenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 2,3-difluorophenol and 1-(3-bromo-2,4-dihydroxyphenyl)-3-methylbutan-1-one. $^1$H NMR (CDCl$_3$, 500MHz), δ 13.58 (s, 1H), 7.74 (d, 1H), 7.00-6.97 (m, 1H), 6.79-6.72 (m, 2H), 6.51 (d, 1H), 4.24 (t, 2H), 4.18 (t, 2H), 2.81 (d, 2H), 2.32-2.26 (1H), 2.12-2.09 (m, 4H), 0.98 (d, 6H). MS (ESI): 459 (M + H)$^+$. 

EXAMPLE 30

1-{2-hydroxy-3-methyl-4-[4-{methyl[(6-methylpyridin-2-yl)methyl]amino})butoxy]phenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using N-methyl-1-(6-methylpyridin-2-yl)methanamine. $^1$H NMR (CDCl$_3$, 500MHz), δ 13.03 (s, 1H), 7.60 (d, 1H), 7.53 (t, 1H), 7.24 (d, 1H), 7.01 (d, 1H), 6.41 (d, 1H), 4.05 (t, 2H), 3.65 (s, 2H), 2.77 (d, 2H), 2.54 (s, 3H), 2.52 (t, 2H), 2.30-2.25 (m, 4H), 2.10 (s, 3H), 1.89-1.84 (m, 2H), 1.76-1.71 (m, 2H), 1.01 (d, 6H). MS (ESI): 399 (M + H)$^+$. 

EXAMPLE 31

7-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy)butoxy]-4-methyl-2H-chromen-2-one

A similar procedure as outlined in example 1 was followed using 7-hydroxy-4-methyl-2H-chromen-2-one. $^1$H NMR (CDCl$_3$, 500MHz), δ 13.03 (s, 1H), 7.62 (d, 1H), 7.52 (d, 1H), 6.91-6.81 (m, 2H), 6.44 (d, 1H), 6.16-6.13 (m, 1H), 4.16-4.12 (m, 4H), 2.78 (d, 2H), 2.42 (s, 3H), 2.30-2.25 (m, 1H), 2.11 (s, 3H), 2.08-2.05 (m, 4H), 1.01 (d, 6H). MS (ESI): 439 (M + H)$^+$. 

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EXAMPLE 32

7-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butoxy}-4-(trifluoromethyl)-2H-chromen-2-one

A similar procedure as outlined in example 1 was followed using 7-hydroxy-4-(trifluoromethyl)-2H-chromen-2-one. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.04 (s, 1H), 7.665-7.62 (m, 2H), 6.95-6.87 (m, 2H), 6.63 (s, 1H), 6.44 (d, 1H), 4.19-4.12 (m, 4H), 7.78 (d, 2H), 2.31-2.27 (m, 1H), 2.10 (s, 3H), 2.08-2.04 (m, 4H), 1.02 (d, 6H). MS (ESI): 493 (M + H)$^+$.  

EXAMPLE 33

1-{2-hydroxy-3-methyl-4-[4-(2-pyridin-2-yl-1H-benzimidazol-1-yl)butoxy]phenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 2-pyridin-2-yl-1H-benzimidazole. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.04 (s, 1H), 8.61-8.59 (m, 1H), 8.46-8.43 (m, 1H), 7.88-7.84 (m, 2H), 7.59 (d, 1H), 7.47-7.45 (m, 1H), 7.36-7.31 (m, 3H), 6.37 (d, 1H), 4.96 (t, 2H), 4.04 (t, 2H), 2.78 (d, 2H), 2.30-2.25 (m, 1H), 2.18-2.12 (m, 2H), 2.06 (s, 3H), 1.91-1.88 (m, 2H), 1.01 (d, 6H). MS (ESI): 458 (M + H)$^+$.  

EXAMPLE 34
1-[2-hydroxy-4-{4-(1H-imidazo[4,5-b]pyridin-1-yl)butoxy}-3-methylphenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 1H-imidazo[4,5-b]pyridine. \(^1\)H NMR (CDCl\(_3\), 500MHz), \(\delta\) 13.02 (s, 1H), 8.45-8.43 (m, 1H), 8.14-8.10 (m, 2H), 7.60 (d, 1H), 7.30-7.27 (m, 1H), 6.40 (d, 1H), 4.44 (t, 2H), 4.10 (t, 2H), 2.78 (d, 2H), 2.30-2.18 (m, 3H), 2.10 (s, 3H), 1.93-1.88 (m, 2H), 1.01 (d, 6H). MS (ESI): 382 (M + H)^+.

EXAMPLE 35

\[
\begin{align*}
\text{OH} & \\
\text{O} & \\
\text{O} & \\
\text{Cl} & \\
\end{align*}
\]

1-(4-{4-[(2-chloropyridin-3-yl)oxy]butoxy}-2-hydroxy-3-methylphenyl)-3-methylbutan-1-one

A mixture of 2-chloro-3-pyridinol (24 mg, 0.2 mmol), 1-[4-(4-bromobutoxy)-2-hydroxy-3-methylphenyl]-3-methylbutan-1-one (64 mg, 0.2 mmol), cesium carbonate (94 mg, 0.3 mmol) and acetone (2.0 ml) was heated to 45°C overnight. The reaction mixture was cooled to room temperature and concentrated \textit{in vacuo}. The resulting oil was washed with brine and extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered and concentrated \textit{in vacuo}. Flash chromatography of crude oil on silica gel (0-20% ethyl acetate/hexanes) afforded the desired product as a white solid (40 mg, 55%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 13.04 (s, 1H), 8.02 – 8.01 (m, 1H), 7.64 (d, 1H), 6.46 (d, 1H), 4.21 – 4.08 (m, 4H), 2.80 (d, 2H), 2.31 – 2.26 (m, 1H), 2.12 – 2.05 (m, 7H), 1.10 – 0.97 (d, 6H). MS (ESI) 394, 392 (M^+).

EXAMPLE 36

\[
\begin{align*}
\text{OH} & \\
\text{O} & \\
\text{O} & \\
\end{align*}
\]
1-(2-hydroxy-3-methyl-4-[(4-[(2-methylpyridin-3-yl)oxy]butoxy]phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 3-hydroxy-2-methylpyridine to give the desired product as a white solid. \( ^1H \) NMR (CDCl3, 300 MHz) \( \delta \) 13.08 (s, 1H), 8.10 (m, 1H), 7.63 (d, 1H), 7.14 (m, 2H), 6.45 (d, 1H), 4.20 – 4.12 (t, 2H), 4.02 (t, 2H), 2.79 (d, 2H), 2.51 (s, 3H), 2.30 – 2.26 (m, 1H), 2.13 (s, 3H), 2.09 – 2.06 (m, 4H), 1.03 – 0.97 (d, 6H). MS (ESI) 374 (M\(^+\) + 2H), 373 (M\(^+\) + H), 372 (M\(^+\)).

EXAMPLE 37

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\end{align*}
\]

1-4-[4-((2-[dimethylamino)methyl]pyridin-3-yl)oxy]butoxy]-2-hydroxy-3-methylphenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 2-(dimethylaminomethyl)-3-hydroxy pyridine to give the desire product as an oil. \( ^1H \) NMR (CDCl3, 300 MHz) \( \delta \) 13.04 (s, 1H), 8.21 – 8.20 (m, 1H), 7.62 (d, 1H), 7.17 – 7.11 (m,2H), 6.45 (d, 1H), 4.16 (t, 2H), 4.14 (t, 2H), 3.66 (s, 2H), 2.78 (d, 2H), 2.36 (s, 6H), 2.32 – 2.25 (m, 1H), 2.12 (s, 3H), 2.08 – 2.05 (m, 4H), 1.02 – 0.95 (d, 6H). MS (ESI) 417 (M\(^+\) + 2H), 416 (M\(^+\) + H), 415 (M\(^+\)).

EXAMPLE 38

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

6-[4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxylbutoxy]-4-methyl-2H-chromen-2-one

A similar procedure as outlined in example 1 was followed using 6-hydroxy-4-methyl-2H-chromen-2-one. \( ^1H \) NMR (CDCl3, 500MHz), \( \delta \) 13.03 (s, 1H), 7.60 (d, 1H), 7.24 (d, 1H), 7.11-7.08 (m, 1H), 7.01 (d, 1H), 6.44 (d, 1H), 6.27 (s, 1H), 4.15-4.09 (m, 4H), 2.76 - 39 -
(d, 2H), 2.40 (s, 3H), 2.29-2.23 (m, 1H), 2.11 (s, 3H), 2.10-2.05 (m, 4H), 1.00 (d, 6H). MS (ESI): 439 (M + H)⁺.

EXAMPLE 39

7-[4-{3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butoxy}-3,4,8-trimethyl-2H-chromen-2-one

A similar procedure as outlined in example 1 was followed using 7-hydroxy-3,4,8-trimethyl-2H-chromen-2-one. ¹H NMR (CDCl₃, 500 MHz) δ 13.04 (s, 1H), 7.62 (d, 1H), 7.41 (d, 1H), 6.82 (d, 1H), 6.44 (d, 1H), 4.17-4.10 (m, 4H), 2.78 (d, 2H), 2.39 (s, 3H), 2.33 (s, 3H), 2.28-2.24 (m, 1H), 2.21 (s, 3H), 2.10 (s, 3H), 2.09-2.07 (m, 4H), 1.01 (d, 6H). MS (ESI): 467 (M + H)⁺.

EXAMPLE 40

1-(2-hydroxy-3-methyl-4-{4-[6-methylpyridin-3-yl)oxy]butoxy}phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 3-hydroxy-6-methylpyridine to give the desired product as a white solid. ¹H NMR (CDCl₃, 300 MHz) δ 13.11 (s, 1H), 8.21 (d, 1H), 7.63 (d, 1H), 7.17 - 7.14 (dd, 1H), 7.09 - 7.07 (d, 1H), 6.45 (d, 1H), 4.18 - 4.13 (t, 2H), 4.10 - 4.06 (t, 2H), 2.80 (d, 2H), 2.47 (s, 3H), 2.31 - 2.25 (m, 1H), 2.12 (s, 3H), 2.08 - 2.02 (m, 4H), 1.03 - 0.95 (d, 6H). MS (ESI) 373 (M⁺ + 2H), 372 (M⁺ + H).
1-(2-hydroxy-3-methyl-4-[4-[(1,3,4-oxadiazol-2-yl)phenoxy]butoxy]phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 4-(1,3,4-oxadiazol-2-yl)phenol to give the desired product as a white solid. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.00 (s, 1H), 8.44 (s, 1H), 8.05 – 8.00 (m, 2H), 7.63 (d, 1H), 7.05 – 7.00 (m, 2H), 6.50 (d, 1H), 4.20 – 4.10 (m, 4H), 2.80 (d, 2H), 2.32 – 2.26 (m, 1H), 1.15 (s, 3H), 2.08 – 2.05 (m, 4H), 1.03 – 0.89 (d, 6H). MS (ESI) 447 (M$^+$ + Na), 425 (M$^+$ + H).

**EXAMPLE 42**

2,3-difluoro-4-[4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butoxy]benzonitrile

A similar procedure as outlined in example 1 was followed with 2,3-difluoro-4-hydroxy-benzonitrile to give the desired product as a white solid. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.05 (s, 1H), 7.63 (d, 1H), 7.37 – 7.34 (m, 1H), 6.85 – 6.81 (m, 1H), 6.45 (d, 1H), 4.24 – 4.22 (t, 2H), 4.18 – 4.14 (t, 2H), 2.80 -2.79 (d, 2H), 2.30 – 2.28 (m, 1H), 2.13 – 2.06 (m, 7H), 1.03 – 0.98 (d, 6H). MS (ESI) 418 (M$^+$ + H).

**EXAMPLE 43**

1-(2-hydroxy-3-methyl-4-[4-(pentafluorophenoxy)butoxy]phenyl)-3-methylbutan-1-one
A similar procedure as outlined in example 1 was followed using pentafluorophenol. $^1$H NMR (CDCl$_3$, 500 MHz), $\delta$ 13.03 (s, 1H), 7.63 (d, 1H), 6.45 (d, 1H), 4.27 (t, 2H), 4.13 (t, 2H), 2.78 (d, 2H), 2.31-2.27 (m, 1H), 2.09 (s, 3H), 2.06-2.02 (m, 4H), 1.00 (d, 6H). MS (ESI): 447 (M + H)$^+$.  

**EXAMPLE 44**

![Chemical Structure](image)

1-(2-hydroxy-3-methyl-4-[4-(2,3,5,6-tetrafluorophenoxy)butoxy]phenyl)-3-methylbutan-1-one  

A similar procedure as outlined in example 1 was followed using 2,3,5,6-tetrafluorophenol. $^1$H NMR (CDCl$_3$, 500 MHz), $\delta$ 13.04 (s, 1H), 7.63 (d, 1H), 6.82-6.77 (m, 1H), 6.45 (d, 1H), 4.34 (t, 2H), 4.15 (t, 2H), 2.79 (d, 2H), 2.31-2.29 (m, 1H), 2.10 (s, 3H), 2.07-1.99 (m, 4H), 1.03 (d, 6H). MS (ESI): 429 (M + H)$^+$.  

**EXAMPLE 45**

![Chemical Structure](image)

1-(2-hydroxy-3-methyl-4-[4-[(5-methylpyridin-3-yl)oxy]butoxy]phenyl)-3-methylbutan-1-one  

A similar procedure as outlined in example 3 was followed with 5-methylpyridin-3-ol to give the desired product as a white solid. $^1$H NMR (CDCl$_3$, 300 MHz), $\delta$ 13.08 (s, 1H), 8.17 (s, 1H), 8.11 (s, 1H), 7.63 (d, 1H), 7.02 (s, 1H), 6.45 (d, 1H), 4.18 – 4.15 (t, 2H), 4.14 – 4.09 (t, 2H), 2.80 (d, 2H), 2.33 (s, 3H), 2.31 – 2.25 (m, 1H), 2.12 (s, 3H), 2.05 – 1.99 (m, 4H), 1.03 – 1.01 (d, 6H). MS (ESI) 374 (M$^+$ + 2H), 373 (M$^+$ + H), 372 (M$^+$).  

**EXAMPLE 46**
1-\{(2-hydroxy-3-methyl-4-[4-(2,3,4-trifluorophenoxy)butoxy]phenyl)-3-methylbutan-1-one\}

A similar procedure as outlined in example 1 was followed using 2,3,4-trifluorophenol. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.04 (s, 1H), 7.63 (d, 1H), 6.89-6.85 (m, 1H), 6.70-6.65 (m, 1H), 6.45 (d, 1H), 4.16-4.11 (m, 4H), 2.78 (d, 2H), 2.31-2.26 (m, 1H), 2.11 (s, 3H), 2.07-2.04 (m, 4H), 1.02 (d, 6H). MS (ESI): 411 (M + H)$^+$.  

EXAMPLE 47

1-\{(2-hydroxy-3-methyl-4-[4-(2,3,6-trifluorophenoxy)butoxy]phenyl)-3-methylbutan-1-one\}

A similar procedure as outlined in example 1 was followed using 2,3,6-trifluorophenol. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.03 (s, 1H), 7.62 (d, 1H), 6.86-6.83 (m, 2H), 6.45 (d, 1H), 4.28 (t, 2H), 4.15 (t, 2H), 2.78 (d, 2H), 2.31-2.26 (m, 1H), 2.11 (s, 3H), 2.09-2.01 (m, 4H), 1.02 (d, 6H). MS (ESI): 411 (M + H)$^+$.  

EXAMPLE 48

1-\{(2-hydroxy-4-[4-\{(2-iodopyridin-3-yl)oxy\}butoxy]-3-methylphenyl)-3-methylbutan-1-one\}

A similar procedure as outlined in example 1 was followed with 2-iodo-3-hydroxypyridine to give the desired product as a beige solid. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.07 (s, 1H), 8.02 (dd, 1H), 7.63 (d, 1H), 7.22 – 7.17 (dd, 1H), 7.03 – 6.98 (dd, 1H), 6.49 (d, 1H), 4.21 – 4.18 (t, 2H), 4.16 – 4.13 (t, 2H), 2.48 (d, 2H), 2.32 – 2.26 (m, 1H), 2.16 – 2.13 (m, 4H), 1.03 – 1.01 (d, 6H). MS (ESI) 484 (M$^+$ + H).
EXAMPLE 49

1-{2-hydroxy-3-methyl-4-[4-(5,6,7,8-tetrahydroquinolin-3-yl)oxy]butoxy}phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 5,6,7,8-tetrahydroquinolin-3-ol to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.14 (s, 1H), 8.08 (d, 1H), 7.63 – 7.61 (d, 1H), 6.91 (d, 1H), 6.46 – 6.44 (d, 1H), 4.17 (t, 2H), 4.09 (t, 2H), 2.89 – 2.86 (t, 2H), 2.80 – 2.74 (m, 4H), 2.30 – 2.27 (m, 1H), 2.05 (s, 3H), 2.50 – 2.02 (m, 4H), 1.90 – 1.87 (m, 2H), 1.82 – 1.79 (m, 2H), 1.03 – 1.02 (d, 6H).

MS (ESI) 414 (M$^+$ + 2H), 413 (M$^+$ + H), 412 (M$^+$).

EXAMPLE 50

7-{3-[2-bromo-3-hydroxy-4-(3-methylbutanoyl)phenoxy]propoxy}-2H-chromen-2-one

A similar procedure as outlined in example 1 was followed using 7-hydroxy-2H-chromen-2-one and 1-(3-bromo-2,4-dihydroxyphenyl)-3-methylbutan-1-one. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.57 (s, 1H), 7.74 (d, 1H), 7.65 (d, 1H), 7.38 (d, 1H), 6.91-6.85 (m, 2H), 6.53 (d, 1H), 6.26 (d, 1H), 4.39-4.30 (m, 4H), 2.78 (d, 2H), 2.40-2.21 (m, 3H), 1.02 (d, 6H). MS (ESI): 476 (M + H)$^+$. 

EXAMPLE 51

1-{3-bromo-2-hydroxy-4-[4-(2-pyridin-2-yl-1H-benzimidazol-1-yl)butoxy]phenyl}-3-methylbutan-1-one
A similar procedure as outlined in example 1 was followed using 2-pyridin-2-yl-1H-benzimidazole and 1-(3-bromo-2,4-dihydroxyphenyl)-3-methylbutan-1-one.

$^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.56 (s, 1H), 8.64 (d, 1H), 8.42-8.41 (m, 1H), 7.86-7.82 (m, 2H), 7.50 (m, 1H), 7.38-7.30 (m, 3H), 6.74 (d, 1H), 6.41 (d, 1H), 4.99 (t, 2H), 4.13 (t, 2H), 2.79 (d, 2H), 2.28-2.17 (m, 3H), 1.96-1.90 (m, 2H), 1.00 (d, 6H). MS (ESI): 523 (M + H$^+$).

EXAMPLE 52

![Example 52](image)

1-(4-{4-[(2,6-dimethylpyridin-3-yl)oxy]butoxy}-2-hydroxy-3-methylphenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 2,6-dimethylpyridin-3-ol to give the desired product as a white solid. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.04 (s, 1H), 7.64 -7.62 (d, 1H), 7.02 - 7.00 (d, 1H), 6.95 - 6.93 (d, 1H), 6.46 - 6.44 (d, 1H), 4.16 (t, 2H), 4.04 (t, 2H), 2.79 (d, 2H), 2.49 (s, 3H), 2.47 (s, 3H), 2.31 - 2.27 (m, 1H), 2.12 (s, 3H), 2.07 - 2.06 (m, 4H), 1.03 - 1.02 (d, 6H).

MS (ESI) 388 (M$^+$ + 2H), 387 (M$^+$ + H), 386 (M$^+$).

EXAMPLE 53

![Example 53](image)

1-{2-hydroxy-3-methyl-4-[4-(pyridin-4-ylthio)butoxy]phenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 4-mercaptopyridine. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.04 (s, 1H), 8.40 (d, 2H), 7.61 (d, 1H), 7.12 (d, 2H), 6.42 (d, 1H), 4.09 (t, 2H), 3.08 (t, 2H), 2.77 (d, 2H), 2.29-2.26 (m, 1H), 2.10 (s, 3H), 2.05-1.94 (m, 4H), 1.01 (d, 6H). MS (ESI): 374 (M + H$^+$).

EXAMPLE 54
1-(2-hydroxy-3-methyl-4-[4-(4-pyrimidin-2-yl)piperazin-1-yl)butoxy]phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 2-piperazin-1-ylpyrimidine. $^1$H NMR (CDCl$_3$, 500MHz) $\delta$ 13.04 (s, 1H), 8.31 (d, 2H), 7.61 (d, 1H), 6.50 (t, 1H), 6.44 (d, 1H), 4.10 (t, 2H), 3.86-3.84 (m, 4H), 2.77 (d, 2H), 2.54-2.52 (m, 4H), 2.47 (t, 2H), 2.29-2.25 (m, 1H), 2.12 (s, 3H), 1.91-1.87 (m, 2H), 1.78-1.74 (m, 2H), 1.01 (d, 6H). MS (ESI): 427 (M + H$^+$).

EXAMPLE 55

1-[4-{4-(2,3-dichlorophenoxy)butoxy]-2-hydroxy-3-methylphenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-(4-bromobutoxy)-2,3-dichlorobenzene and 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one to give the desired product as a white solid. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.04 (s, 1H), 7.64 (d, 1H), 7.17-7.14 (m, 1H), 7.10-7.07 (m, 1H), 6.86-6.84 (dd, 1H), 6.47-6.45 (d, 1H), 4.19-4.17 (m, 2H), 4.167-4.14 (m, 2H), 2.79 (d, 2H), 2.32-2.26 (m, 1H), 2.12 (s, 3H), 2.11-2.09 (m, 4H), 1.02 (d, 6H). MS (ESI) 427, 425 (M$^+$).

EXAMPLE 56

1-[3-bromo-2-hydroxy-4-[4-(5,6,7,8-tetrahydroquinolin-3-yloxy)butoxy]phenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-[3-bromo-4-(4-bromobutoxy)-2-hydroxyphenyl]-3-methylbutan-1-one and 5,6,7,8-tetrahydroquinolin-3-
of to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) δ 13.58 (s, 1H), 8.08 (d, 1H), 7.75 (d, 1H), 6.94 (d, 1H), 6.50 (d, 1H), 4.23 - 4.21 (t, 2H), 4.12 - 4.10 (t, 2H), 2.90 - 2.88 (t, 2H), 2.82 (d, 2H), 2.78 - 2.75 (t, 2H), 2.13 - 2.28 (m, 1H), 2.09 - 2.05 (m, 4H), 1.91-1.88 (m, 2H), 1.83 - 1.79 (m, 2H), 1.03 (d, 6H). MS (ESI) 479, 478 (M$^+$ + H).

EXAMPLE 57

![Diagram of molecule](image)

1-(2-hydroxy-3-methyl-4-{4-[2,3,5,6-tetrafluorophenyl]thio}butoxy)phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 2,3,5,6-pentafluorothiophenol. $^1$H NMR (CDCl$_3$, 500MHz), δ 13.03 (s, 1H), 7.61 (d, 1H), 7.07-7.03 (m, 1H), 6.41 (d, 1H), 4.08 (t, 2H), 3.05 (t, 2H), 2.78 (d, 2H), 2.30-2.27 (m, 1H), 2.06 (s, 3H), 2.00-1.96 (m, 2H), 1.84-1.77 (m, 2H), 1.01 (d, 6H). MS (ESI): 445 (M + H)$^+$. 

EXAMPLE 58

![Diagram of molecule](image)

1-(4-{4-[(5-bromopyridin-3-yl)oxy]butoxy}-2-hydroxy-3-methylphenyl)-3-methylbutan-1-one

1-(4-{4-{(5-bromopyridin-3-yl)oxy}butoxy}-2-hydroxy-3-methylphenyl)-3-methylbutan-1-one was synthesized by alkylation according to example 1 using 3-bromo-5-(4-bromobutoxy)pyridine and 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one as starting materials. $^1$H NMR (CDCl$_3$, 500 MHz) δ 13.01 (s, 1H), 8.27 (s, 1H), 8.23 (d, 1H), 7.60 (s, 1H), 7.35 (s, 1H), 6.42 (d, 1H), 4.14-4.02 (m, 4H), 2.74 (d, 2H), 2.25 (m, 1H), 2.10 (s, 3H), 2.02 (m, 4H), 1.00 (s, 3H), 0.99 (s, 3H). MS (ESI$^+$) 436 (M$^+$).
1-(2-hydroxy-3-methyl-4-[4-(3-pyridin-2-ylphenoxo)butoxy]phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 3-pyridin-2-ylphenol to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) δ 13.07 (s, 1H), 8.7 (d, 1H), 7.78 - 7.73 (m, 2H), 7.63 - 7.61 (m, 2H), 7.56 (d, 1H), 7.41 - 7.38 (t, 1H), 7.26 - 7.24 (t, 1H), 6.99 (dd, 1H), 6.46 - 6.44 (d, 1H), 4.19 - 4.11 (m, 4H), 2.78 (d, 2H), 2.32 - 2.24 (m, 1H), 2.13 (s, 3H), 2.10 - 2.00 (m, 4H), 1.02 (d, 6H). MS (ESI) 435 (M$^+$ + H), 434 (M$^+$).

EXAMPLE 60

methyl-3-(2-hydroxy-4-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxo]butoxy}-phenyl)propanoate

A similar procedure as outlined in example 1 was followed using methyl 3-(2,4-dihydroxyphenyl)propanoate. $^1$H NMR (CDCl$_3$, 500 MHz), δ 13.03 (s, 1H), 7.61 (d, 1H), 7.33 (s, 1H), 6.97 (d, 1H), 6.50-6.40 (m, 3H), 4.12 (t, 2H), 4.01 (t, 2H), 3.71 (s, 3H), 2.85 (t, 2H), 2.79 (d, 2H), 2.70 (t, 2H), 2.30-2.27 (m, 1H), 2.12 (s, 3H), 2.10-1.99 (m, 4H), 1.01 (d, 6H). MS (ESI): 459 (M + H)$^+$. 

EXAMPLE 61

1-(2-hydroxy-3-methyl-4-[4-{2-(1,3-thiazol-4-yl)-1H-benzimidazol-1-yl]butoxy}phenyl)-3-methylbutan-1-one
A similar procedure as outlined in example 1 was followed using 2-(1,3-thiazol-4-yl)-1H-benzimidazole. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.04 (s, 1H), 8.83 (d, 1H), 8.36-8.34 (m, 1H), 7.83-7.81 (m, 1H), 7.59 (d, 1H), 7.46-7.43 (m, 1H), 7.34-7.31 (m, 2H), 6.37 (d, 1H), 4.88 (t, 2H), 4.04 (t, 2H), 2.77 (d, 2H), 2.29-2.26 (m, 1H), 2.16-2.09 (m, 2H), 2.05 (s, 3H), 1.91-1.88 (m, 2H), 1.01 (d, 6H). MS (ESI$^+$): 464 (M + H)$^+$. 

**EXAMPLE 62**

![Chemical structure](image)

1-(4-[(4-(3-fluorophenyl)thio)butoxy]-2-hydroxy-3-methylphenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 3-fluorothiophenol. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.03 (s, 1H), 7.61 (d, 1H), 7.26-7.23 (m, 1H), 7.11-7.03 (m, 2H), 6.89-6.88 (m, 1H), 6.25 (d, 1H), 4.08 (t, 2H), 3.04 (t, 2H), 2.78 (d, 2H), 2.32-2.27 (m, 1H), 2.01 (s, 3H), 2.00-1.88 (m, 4H), 1.01 (d, 6H). MS (ESI$^+$): 391 (M + H)$^+$. 

**EXAMPLE 63**

![Chemical structure](image)

5-{3-[(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]phenoxy}pyridine-2-carbonitrile

5-{3-[(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]phenoxy}pyridine-2-carbonitrile was synthesized by alkylation according to example 1 using 5-{3-(bromomethyl)phenoxy}pyridine-2-carbonitrile and 1-(2,4-dihydroxy-3-propylphenyl)ethanone as starting materials. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 12.75 (s, 1H), 8.45 (s, 1H), 7.63 (d, 1H), 7.56 (d, 1H), 7.48 (t, 1H), 7.32 (d, 1H), 7.28 (m, 1H), 7.16 (s, 1H), 7.06 (d, 1H), 6.46 (d, 1H), 5.17 (s, 2H), 2.67 (t, 2H), 2.56 (s, 3H), 1.49 (m, 2H), 0.88 (t, 3H). MS (ESI$^+$) 403 (M$^+$+1).
EXAMPLE 64

1-{2-hydroxy-3-methyl-4-[4-(4-pyridin-2-ylphenoxy)butoxy]phenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 3 was followed with 4-pyridin-2-ylphenol to give the desired product as a white solid. $^1$H NMR (CDCl$_3$, 300 MHz) δ 13.11 (s, 1H), 8.70 (m, 1H), 7.97 - 7.95 (d, 2H), 7.76 - 7.68 (m, 2H), 7.62 (d, 1H), 7.21 - 7.18 (m,1H), 7.02 - 7.00 (d, 2H), 6.45 (d, 1H), 4.19 - 4.06 (m,4H), 2.79 (d, 2H), 2.33 - 2.29 (m, 1H), 2.13 (s, 3H), 2.07 - 2.04 (m, 4H), 1.01 (d, 6H). MS (ESI) 436 (M$^+$ + 2H), 435 (M$^+$ + H), 434 (M$^+$).

EXAMPLE 65

1-{4-[4-(1H-benzimidazol-1-yl)butoxy]-2-hydroxy-3-methylphenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 1H-benzimidazole. $^1$H NMR (CDCl$_3$, 500MHz), δ 13.03 (s, 1H), 7.97 (brs, 1H), 7.84 (d, 1H), 7.60 (d, 1H), 7.44-7.42 (m, 1H), 7.35-7.29 (m, 2H), 6.38 (d, 1H), 4.31 (d, 2H), 4.06 (d, 2H), 2.77 (d, 2H), 2.29-2.26 (m, 1H), 2.19-2.12 (m, 2H), 2.10 (s, 3H), 1.90-1.85 (m, 2H), 1.02 (d, 6H). MS (ESI): 381 (M + H)$^+$. 

EXAMPLE 66

(1-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butyl}-1H-benzimidazol-2-yl)acetonitrile
A similar procedure as outlined in example 1 was followed using 1H-benzimidazol-2-ylacetonitrile. \(^1\)H NMR (CDCl\(_3\), 500MHz), \(\delta\) 13.04 (s, 1H), 7.81 (d, 1H), 7.62 (d, 1H), 7.44-7.33 (m, 3H), 6.40 (d, 1H), 4.35 (t, 2H), 4.10 (t, 2H), 2.78 (d, 2H), 2.36 (s, 2H), 2.28-2.25 (m, 1H), 2.19-2.12 (m, 2H), 2.10 (s, 3H), 1.90-1.85 (m, 2H), 1.01 (d, 6H). MS (ESI): 420 (M + H)^+. 

**EXAMPLE 67**

![Chemical Structure](image)

1-(2-hydroxy-3-methyl-4-{4-[2-(trifluoromethyl)-1H-benzimidazol-1-yl]butoxy}phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 2-(trifluoromethyl)-1H-benzimidazole. \(^1\)H NMR (CDCl\(_3\), 500MHz), \(\delta\) 13.04 (s, 1H), 7.91 (d, 1H), 7.62 (d, 1H), 7.48-7.40 (m, 3H), 6.40 (d, 1H), 4.46 (t, 2H), 4.11 (t, 2H), 2.78 (d, 2H), 2.28-2.25 (m, 1H), 2.19-2.12 (m, 2H), 2.10 (s, 3H), 1.90-1.85 (m, 2H), 1.01 (d, 6H). MS (ESI): 449 (M + H)^+. 

**EXAMPLE 68**

![Chemical Structure](image)

1-{3-[4-acetyl-3-hydroxy-2-propylphenoxy)methyl]benzyl}azetidine-3-carbonitrile

A mixture of 3-(bromomethyl)benzaldehyde (2 g, 10.0 mmol), 1-(2,4-dihydroxy-3-propylphenyl)ethanone (2.3 g, 12 mmol), and potassium carbonate (2.7 g, 20 mmol) in acetone (25 mL) was stirred at rt for 18 h. The mixture was filtered and concentrated. The crude residue was purified by chromatography on silica gel (EtOAc/hexanes) to give 3-{4-acetyl-3-hydroxy-2-propylphenoxy)methyl]benzaldehyde as a colorless solid. A solution of tert-butyl 3-cyanoazetidine-1-carboxylate (0.4g, 2.2 mmol) and TFA (3mL) was aged in CH\(_2\)Cl\(_2\) (5mL) for 4h and then concentrated. To a
solution of this crude residue in dichloroethane (10mL) was added 3-{[4-acetyl-3-hydroxy-2-propylphenoxy)methyl]benzaldehyde and NaBH(OAc)₃ (0.47 g, 2.2 mmol) and HOAc (0.1mL). The mixture was stirred at rt for 12h, diluted with EtOAc and brine, and the layers were separated. The organic layer was washed with brine, dried (MgSO₄) and concentrated. The crude residue was purified chromatography on silica gel (EtOAc/hexanes) to give the title compound as a pale yellow oil. MS (ESI⁺) 379.4 (M⁺+1).

**EXAMPLE 69**

![](image)

1-{4-{4-(1,3-benzothiazol-2-ylthio)butoxy}-2-hydroxy-3-methylphenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 1,3-benzothiazole-2-thiol. ¹H NMR (CDCl₃, 500MHz), δ 13.04 (s, 1H), 7.87 (d, 1H), 7.77 (d, 1H), 7.61 (d, 1H), 7.45-7.31 (m, 2H), 6.44 (d, 1H), 4.15 (t, 2H), 3.48 (t, 2H), 2.78 (d, 2H), 2.28-2.25 (m, 1H), 2.07 (s, 3H), 2.06-2.03 (m, 4H), 1.02 (d, 6H). MS (ESI⁺): 430 (M + H)⁺.

**EXAMPLE 70**

![](image)

1-{4-{4-{(6-chloro-1,3-benzoxazol-2-ylthio)butoxy}-2-hydroxy-3-methylphenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 6-chloro-1,3-benzoxazole-2-thiol. ¹H NMR (CDCl₃, 500MHz), δ 13.04 (s, 1H), 7.62 (d, 1H), 7.51-7.45 (m, 2H), 7.30-7.27 (m, 1H), 6.43 (d, 1H), 4.13 (t, 2H), 3.41 (t, 2H), 2.78 (d, 2H), 2.31-2.27 (m, 1H), 2.12 (s, 3H), 2.10-2.03 (m, 4H), 1.02 (d, 6H). MS (ESI⁺): 448 (M + H)⁺.
1-[(2-hydroxy-3-methyl-4-[4-(2-phenyl-1H-imidazol-1-yl)butoxy]phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-(4-bromobutyl)-2-phenyl-1H-imidazole and 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one to give the desired product as an oil. 1H NMR (CDCl3, 300 MHz) δ 13.01 (s, 1H), 7.59 – 7.55 (m, 3H), 7.47 – 7.38 (m, 3H), 7.16 (d, 1H), 7.05 (d, 1H), 6.31 (d, 1H), 4.12 (t, 2H), 3.94 (t, 2H), 2.77 – 2.75 (d, 2H), 2.29 – 2.17 (m, 1H), 2.04 (s, 3H), 1.99 – 1.93 (m, 2H), 1.82 – 1.72 (m, 4H), 1.00 – 0.98 (d, 6H). MS (ESI) 409 (M\(^+\) + 2H), 408 (M\(^+\) + H), 407 (M\(^+\)).

EXAMPLE 72

1-[(2-hydroxy-3-methyl-4-[4-(2-phenyl-1H-benzimidazol-1-yl)butoxy]phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one and 1-(4-bromobutyl)-2-phenyl-1H-benzimidazole to give the desired product as an oil. 1H NMR (CDCl3, 300 MHz) δ 13.03 (s, 1H), 7.87 – 7.85 (m, 1H), 7.73 – 7.72 (m, 2H), 7.60 – 7.58 (d, 1H), 7.51 – 7.44 (m, 3H), 7.44 (m, 1H), 7.34 – 7.33 (m, 2H), 6.32 – 6.30 (d, 1H), 4.38 (t, 2H), 3.93 (t, 2H), 2.77 (d, 2H), 2.31 – 2.27 (m, 1H), 2.08 – 2.05 (m, 2H), 2.05 (s, 3H), 1.79 – 1.73 (m, 2H), 1.02 (d, 6H). MS (ESI) 456 (M\(^+\)).

EXAMPLE 73
1-(2-hydroxy-3-methyl-4-[4-[(1-methyl-1H-tetrazol-5-yl)thio]butoxy]phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 1-methyl-1H-tetrazole-5-thiol. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.01 (s, 1H), 7.61 (d, 1H), 6.41 (d, 1H), 4.09 (t, 2H), 3.92 (s, 3H), 3.45 (t, 2H), 2.77 (d, 2H), 2.29-2.24 (m, 1H), 2.09 (s, 3H), 2.05-1.99 (m, 4H), 1.00 (d, 6H). MS (ESI): 379 (M + H)$^+$. 

EXAMPLE 74

1-[2-hydroxy-3-methyl-4-[4-(quinolin-3-yloxy)butoxy]phenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with quinolin-3-ol to give the desired product as a solid. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.12 (s, 1H), 8.70 (d, 1H), 8.09 – 8.06 (d, 1H), 7.74 – 7.72 (m, 1H), 7.64 – 7.62 (d, 1H), 7.64 – 7.52 (m, 2H), 7.40 (d, 1H), 6.47 – 6.46 (d, 1H), 4.23 – 4.17 (m, 4H), 2.80 – 2.78 (d, 2H), 2.30 – 2.26 (m, 1H), 2.14 (s, 3H), 2.14 – 2.12 (m, 4H), 1.02 (d, 6H). MS (ESI) 409 (M$^+$ + H$^+$), 408 (M$^+$)

EXAMPLE 75

1-[4-[4-(1,3-benzoxazol-2-ylthio)butoxy]-2-hydroxy-3-methylphenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 1,3-benzoxazole-2-thiol. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.04 (s, 1H), 7.62-7.59 (m, 2H), 7.45 (d, 1H), 7.730-7.24 (m, 2H), 6.42 (d, 1H), 4.11 (t, 2H), 3.40 (t, 2H), 2.78 (d, 2H), 2.30-2.27 (m, 1H), 2.10 (s, 3H), 1.90-1.85 (m, 4H), 1.01 (d, 6H). MS (ESI): 414 (M + H)$^+$. 

EXAMPLE 76
1-(4-{4-[5-chloro-1,3-benzoxazol-2-yl]thio}butoxy)-2-hydroxy-3-methylphenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 5-chloro-1,3-benzoxazole-2-thiol. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.04 (s, 1H), 7.62 (d, 1H), 7.49-7.46 (m, 1H), 7.25-7.21 (m, 2H), 6.42 (d, 1H), 4.13 (t, 2H), 3.41 (t, 2H), 2.78 (d, 2H), 2.29-2.25 (m, 1H), 2.11 (s, 3H), 1.90-1.85 (m, 4H), 1.01 (d, 6H). MS (ESI): 448 (M + H)$^+$.  

EXAMPLE 77

1-[2-hydroxy-4-[4-(1H-indol-1-yl)butoxy]-3-methylphenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-(4-bromobutyl)-1H-indole and 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.06 (s, 1H), 7.68 – 7.66 (m, 1H), 7.62 – 7.60 (d, 1H), 7.39 – 7.38 (d, 1H), 7.28 – 7.23 (m, 1H), 7.16 – 7.15 (m, 2H), 6.55 – 6.54 (d, 1H), 6.39 – 6.37 (d, 1H), 4.26 (t, 2H), 4.03 (t, 2H), 2.80 (d, 2H), 2.31 – 2.28 (m, 1H), 2.19 (s, 3H), 2.14 – 2.06 (m, 2H), 1.87 – 1.83 (m, 2H), 1.04 – 1.02 (d, 6H). MS (ESI) 380 (M+).

EXAMPLE 78

1-[2-hydroxy-3-methyl-4-[4-(7H-purin-6-ylthio)butoxy]phenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 7H-purine-6-thiol. $^1$H NMR (DMSO-d$_6$, 500MHz), $\delta$ 13.48 (brs, 1H), 13.01 (s, 1H), 8.66 (brs, 1H), 8.43 - 55 -
(b.r.s, 1H), 7.83 (d, 1H), 6.63 (d, 1H), 4.17-4.15 (m, 2H), 3.43-3.37 (m, 2H), 2.85 (d, 2H), 2.18-2.10 (m, 1H), 1.94 (s, 3H), 1.87-1.81 (m, 4H), 0.92 (d, 6H). MS (ESI): 415 (M + H)^+.

**EXAMPLE 79**

1-{2-hydroxy-3-methyl-4-[4-(2-phenyl-1H-indol-1-yl)butoxy]phenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-(4-bromobutyl)-2-phenyl-1H-indole and 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one to give the desired product as an oil. ^1^H NMR (CDCl₃, 300 MHz) δ 13.00 (s, 1H), 7.64 (d, 1H), 7.54 (d, 1H), 7.48 - 7.46 (m, 2H), 7.43 - 7.37 (m, 4H), 7.24 - 7.22 (m, 1H), 7.15 - 7.13 (m, 1H), 6.49 (s, 1H), 6.24 (d, 1H), 4.26 (t, 2H), 3.81 (t, 2H), 2.75 (d, 2H), 2.28 - 2.21 (m, 1H), 2.01 (s, 3H), 1.95 - 1.86 (m, 2H), 1.65 - 1.59 (m, 2H), 0.98 (d, 6H). MS (ESI) 457 (M^+ + H), 456 (M^+).

**EXAMPLE 80**

1-{2-hydroxy-3-methyl-4-[4-(pyridin-4-ylsulfonyl)butoxy]phenyl}-3-methylbutan-1-one

Tetrapropylammonium perruthenate (3 mg, 0.007 mmol) was added to a solution of 1-{2-hydroxy-3-methyl-4-[4-(pyridin-4-ylthio)butoxy]phenyl}-3-methylbutan-1-one (25 mg, 0.0669 mmol), N-methylmorpholine-N-oxide (47 mg, 0.4 mmol) and 4Å molecular sieves (50 mg) in acetonitrile (5 mL) at 0 °C. The reaction was stirred for 4 hours, filtered through celite and concentrated in vacuo to give a residue that was purified via column chromatography on silica gel (eluting 0-60% ethyl acetate/hexanes) to give 12 mg (40%) of 1-{2-hydroxy-3-methyl-4-[4-(pyridin-4-ylsulfonyl)butoxy]phenyl}-3-methylbutan-1-one as a colorless oil. ^1^H NMR (CDCl₃, 500MHz), δ 13.01 (s, 1H), 8.93 (d, 2H), 7.77 (d,
2H), 7.60 (d, 1H), 6.37 (d, 1H), 4.04 (t, 2H), 3.23 (t, 2H), 2.76 (d, 2H), 2.28-2.25 (m, 1H), 2.08 (s, 3H), 1.90-1.85 (m, 4H), 1.00 (d, 6H). MS (ESI): 406 (M + H)⁺.

EXAMPLE 81

1-(2-hydroxy-3-methyl-4-[4-(pyridin-3-ylthio)butoxy]phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with pyridine-3-thiol sodium salt and dimethylformamide as solvent to give the desired product as an oil.

¹H NMR (CDCl₃, 300 MHz) δ 13.04 (s, 1H), 8.60 (d, 1H), 8.45 (m, 1H), 7.67 (m, 1H), 7.62 (d, 1H), 7.23 (dd, 1H), 6.42 (d, 1H), 4.08 (t, 2H), 3.03 (t, 2H), 2.78 (d, 1H), 2.32 – 2.25 (m, 1H), 2.08 (s, 3H), 2.02 – 1.97 (m, 2H), 1.91 – 1.85 (m, 2H), 1.01 (d, 6H). MS (ESI) 375 (M⁺ + H), 374 (M⁺⁻).

EXAMPLE 82

3'-(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]biphenyl-2-carbonitrile

1-[4-[(3-Bromobenzyl)oxy]-2-hydroxy-3-propylphenyl]ethanone was synthesized by alkylation according to example 1 using 1-bromo-3-(bromomethyl)benzene and 1-(2,4-dihydroxy-3-propylphenyl)ethanone as starting materials. A mixture of 1-(2,4-dihydroxy-3-propylphenyl)ethanone (200 mg, 0.55 mmol), (2-cyanophenyl)boronic acid (122 mg, 0.83 mmol), PdCl₂(PPh₃)₂ (19 mg, 0.03 mmol), and potassium carbonate (152 mg, 1.1 mmol) in DME/Water (5:1, 5 mL) was heated in the microwave at 150 °C for 15 min. The resulting black mixture was cooled to room temperature, filtered through celite, and poured into a EtOAc/brine mixture. The two layers were separated and the aqueous was extracted with EtOAc (3×). The organics were combined, dried over sodium sulfate, filtered, and evaporated to dryness. The residue was purified by flash chromatography on silica gel
eluting with a mixture of EtOAc/Hexane to yield 119 mg of 3'-[(4-Acetyl-3-hydroxy-2-
propylphenoxy)methyl]bibenzen-2-carbonitrile. ¹H NMR (CDCl₃, 500 MHz) δ 12.76 (bs, 
1H), 7.77 (d, 1H), 7.66 (t, 1H), 7.60 (d, 1H), 7.53 (m, 5H), 7.45 (t, 1H), 6.51 (d, 1H), 5.24 (s, 
2H), 2.72 (t, 2H), 2.55 (s, 3H), 1.60 (m, 2H), 0.95 (t, 3H). MS (ESI⁺) 386 (M⁺+1).

EXAMPLE 83

[Chemical structure image]

1-hydroxy-3-[(3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy)butoxy]pyridinium

A similar procedure as outlined in example 1 was followed with 3-hydroxy pyridine-N-oxide to give the desired product as an oil. ¹H NMR (CDCl₃, 300 MHz) δ 13.04 
(s, 1H), 7.99 (m, 1H), 7.91 (d, 1H), 7.63 (d, 1H), 7.19 – 7.14 (m, 1H), 6.88 (dd, 1H), 6.43 (d, 
1H), 4.14 – 4.08 (m, 4H), 2.79 (d, 2H), 2.27 (m, 1H), 2.12 (s, 3H), 2.05 – 2.04 (m, 4H), 1.02 
– 0.97 (d, 6H). MS (ESI) 374 (M⁺).

EXAMPLE 84

[Chemical structure image]

1-[(2-hydroxy-3-methyl-4-[(4-methyl-2-phenyl-1H-imidazol-1-yl)butoxy]phenyl]-3-
methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-(4-
bromobutyl)-4-methyl-2-phenyl-1H-imidazole and 1-(2,4-dihydroxy-3-methylphenyl)-3-
methylbutan-1-one to give the desired product as an oil. ¹H NMR (CDCl₃, 300 MHz) δ 13.05 
(s, 1H), 7.59 – 7.55 (d, 1H), 7.54 – 7.53 (m, 2H), 7.41 – 7.36 (m, 3H), 6.74 (m, 1H), 6.31 – 
6.26 (d, 1H), 4.01 (t, 2H), 3.91 (t, 2H), 2.75 (d, 2H), 2.29 – 2.22 (m, 4H), 2.04 (s, 3H), 1.98 – 
1.91 (m, 2H), 1.79 – 1.71 (m, 2H), 1.00 – 0.99 (d, 6H). MS (ESI) 422 (M⁺ + H), 421 (M⁺).

EXAMPLE 85
1-(2-hydroxy-3-methyl-4-{4-[2-(methylthio)-1H-benzimidazol-1-yl]butoxy}phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-(4-bromobutyl)-2-(methylthio)-1H-benzimidazole and 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) □

13.05 (s, 1H), 7.68 (m, 1H), 7.59 – 7.58 (d, 1H), 7.23 (m, 1H), 7.21 – 7.19 (m, 2H), 6.33 (d, 1H), 4.17 (t, 2H), 4.03 (t, 2H), 2.79 (s, 3H), 2.75 (d, 2H), 2.27 – 2.17 (m, 1H), 2.08 (s, 3H), 2.08 – 2.03 (m, 2H), 1.90 – 1.86 (m, 2H), 1.00 – 0.98 (d, 6H). MS (ESI) 429 (M$^+$ + 2H), 428 (M$^+$ + H), 427 (M$^+$).

EXAMPLE 86

1-(3-bromo-4-{4-[(6-chloro-1,3-benzoxazol-2-yl)thio]butoxy}-2-hydroxyphenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 6-chloro-1,3-benzoxazole-2-thiol and 1-(3-bromo-2,4-dihydroxyphenyl)-3-methylbutan-1-one. $^1$H NMR (CDCl$_3$, 500MHz), δ 13.58 (s, 1H), 7.73 (d, 1H), 7.51-7.45 (m, 2H), 7.29-7.26 (m, 1H), 6.42 (d, 1H), 4.20 (t, 2H), 3.44 (t, 2H), 2.78 (d, 2H), 2.28-2.25 (m, 1H), 2.19-2.08 (m, 4H), 1.02 (d, 6H). MS (ESI): 513 (M + H)$^+$. 

EXAMPLE 87

- 59 -
1-{2-hydroxy-3-methyl-4-[4-(4-phenyl-1H-imidazol-1-yl)butoxy]phenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-(4-bromobutyl)-4-phenyl-1H-imidazole and 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.05 (s, 1H), 7.76 (m, 2H), 7.56 (d, 1H)7.53 (m, 1H), 7.36 (m, 2H), 7.25 – 7.20 (m, 2H), 6.38 (d, 1H), 4.11 – 4.04 (m, 4H), 2.76 (d, 2H), 2.28 – 2.23 (m, 1H), 2.11 (s, 3H), 2.08 – 2.03 (m, 2H), 1.88 – 1.83 (m, 2H), 1.00 – 0.95 (d, 6H). MS (ESI) 408 (M$^+$ + H), 407 (M$^+$).

**EXAMPLE 88**

1-{2-hydroxy-3-methyl-4-[4-(pyridin-2-ylthio)butoxy]phenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 2-mercaptopyridine. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.01 (s, 1H), 8.40-8.38 (m, 1H), 7.58 (d, 1H), 7.47-7.44 (m, 1H), 7.16 (d, 1H), 6.97-6.94 (m, 1H), 6.40 (d, 1H), 4.07 (t, 2H), 3.25 (t, 2H), 2.75 (d, 2H), 2.27-2.23 (m, 1H), 2.07 (s, 3H), 1.90-1.85 (m, 4H), 1.01 (d, 6H). MS (ESI): 374 (M + H$^+$).

**EXAMPLE 89**

1-{4-[(4-{2-(2-chlorophenyl)-1H-benzimidazol-1-yl)butoxy]-2-hydroxy-3-methylphenyl)-3-methylbutan-1-one

- 60 -
A similar procedure as outlined in example 1 was followed with 1-(4-bromobutyl)-2-(2-chlorophenyl)-1H-benzipimidazole and 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.06 (s, 1H), 7.88 - 7.85 (m, 1H), 7.58 - 7.51 (m, 3H), 7.47 - 7.45 (m, 2H), 7.41 - 7.39 (m, 1H), 7.36 - 7.33 (m, 2H), 6.25 (d, 1H), 4.17 (t, 2H), 3.89 (t, 2H), 2.76 (d, 2H), 2.30 - 2.24 (m, 1H), 2.02 (s, 3H), 1.96 (m, 2H), 1.70 - 1.67 (m, 2H), 1.01 (d, 6H). MS (ESI): 493, 491 (M$^+$).

EXAMPLE 90

![Chemical Structure](image)

1-(2-hydroxy-3-methyl-4-[(4-oxidoypyridin-2-yl)thiobutoxy]phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 2-mercaptopryidine-N-oxide. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.03 (s, 1H), 8.25 (d, 1H), 7.61 (d, 1H), 7.25-7.04 (m, 3H), 6.42 (d, 1H), 4.11 (t, 2H), 3.01 (t, 2H), 2.77 (d, 2H), 2.27-2.25 (m, 1H), 2.09 (s, 3H), 2.05-2.01 (m, 4H), 1.00 (d, 6H). MS (ESI): 390 (M + H)$^+$.  

EXAMPLE 91

![Chemical Structure](image)

1-(2-hydroxy-3-methyl-4-[(5-(2-phenyl-1H-benzimidazol-1-yl)pentyl]oxy]phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one and 1-(5-bromopentyl)-2-phenyl-1H-benzimidazole to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.12 (s, 1H), 7.87 - 7.85 (m, 1H), 7.73 - 7.71 (m, 2H), 7.61 (d, 1H), 7.54 - 7.52 (m, 3H), 7.45 - 7.43 (m, 1H), 7.34 - 7.32 (m, 2H), 6.36 (d, 1H), 4.31 (t, 2H), 3.96 (t, 2H), 2.78 (d, 2H), 2.31 - 2.26 (m, 1H), 2.06 (s, 3H), 1.94 - 1.91 (m, 2H), 1.78 - 1.72 (m, 2H), 1.47 - 1.43 (m, 2H), 1.01 (d, 6H). MS (ESI) 473 (M$^+$ + 2H), 472 (M$^+$ + H), 471 (M$^+$).
EXAMPLE 92

7-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butoxy}chroman-2-one

A 2.0 N solution of aqueous sodium hydroxide (0.6 ml, 1.2 mmol) was added
to a mixture of ethyl 3-[4-(4-bromobutoxy)-2-hydroxyphenyl]propanoate (200 mg, 0.6 mmol)
in tetrahydrofuran (3.0 ml) and stirred at room temperature until no starting material was
observed by tlc. The mixture was quenched with 1.0 N HCl aqueous solution and extracted
with ethyl acetate. The combined organic extracts were dried over sodium sulfate, filtered
and concentrated in vacuo to give 3-[4-(4-bromobutoxy)-2-hydroxyphenyl]propanoic acid as
a tan solid which needed no further purification (180 mg). A mixture of 3-[4-(4-
bromobutoxy)-2-hydroxyphenyl]propanoic acid (189 mg, 0.6 mmol) and 1-(2,4-dihydroxy-3-
methylphenyl)-3-methylbutan-1-one (161 mg, 0.8 mmol), cesium carbonate (627 mg, 1.9
mmol) and acetone (7.7 ml) was heated overnight at 40°C. The reaction mixture was cooled
and concentrated in vacuo. The resulting oil was acidified to pH 1 with 1.0 N HCl aqueous
solution and extracted with ethyl acetate. The combined organic extracts were dried over
sodium sulfate, filtered and concentrated. The crude material was purified by flash
chromatography on silica gel (0-100% ethyl acetate/hexanes) to give 3-(2-hydroxy-4-[4-[3-
hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butoxy]phenyl)propanoic acid as a tan solid
(98 mg). A mixture of 3-(2-hydroxy-4-[4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)
phenoxy]butoxy]phenyl)propanoic acid (25 mg, 0.06 mmol), benzene (1.0 ml) and p-
toluenesulfonic acid (20 mg, 0.1 mmol) was refluxed for two hours. Reaction mixture was
cooled, washed with saturated sodium bicarbonate and extracted with dichloromethane.
The organic extracts were combined, dried over sodium sulfate, filtered and concentrated in
vacuo. Flash chromatography of crude material on silica gel (0-100% ethyl acetate/hexanes)
gave the desired product as a oil (15 mg, 65%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.00 (s, 1H),
7.60 (d, 1H), 7.06 (d, 1H), 6.63 (d, 1H), 6.60 (d, 1H), 6.42 (d, 1H), 4.11 (t, 2H), 4.02 (t,
2H), 2.93 (t, 2H), 2.78 – 2.75 (m, 4H), 2.29 – 2.25 (m, 1H), 2.09 (s, 3H), 2.03 – 1.98 (m, 4H),
1.00 – 0.99 (d, 6H). MS (ESI) 449 (M$^+$ + Na), 427 (M$^+$).
EXAMPLE 93

1-(2-hydroxy-3-methyl-4-{4-[4-(3-oxobutyl)phenoxy]butoxy}phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 4-hydroxybenzylacetone to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) δ 13.03 (s, 1H), 7.62 (d, 1H), 7.11 (m, 2H), 6.83 (m, 2H), 6.44 (d, 1H), 4.13 (t, 2H), 4.04 (t, 2H), 2.87 - 2.84 (m, 2H), 2.79 (d, 2H), 2.76 - 2.73 (2H), 2.30 - 2.27 (m, 1H), 2.15 (s, 3H), 2.12 (s, 3H), 2.05 - 1.99 (m, 4H), 1.03 - 1.01 (d, 6H). MS (ESI): 449 (M$^+$ + Na), 427 (M$^+$).

EXAMPLE 94

1-(2-hydroxy-3-methyl-4-{[3-(pyridin-4-ylthio)benzyl]oxy}phenyl)-3-methylbutan-1-one

Ditertbutylazodicarboxylate (478 mg, 2.08 mmol) was added to a stirred solution of 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one (323 mg, 1.55 mmol), [3-(pyridin-4-ylthio)phenyl]methanol (225 mg, 1.04 mmol) and triphenylphosphine (545 mg, 2.08 mmol) in tetrahydrofuran (10 mL) at rt. The reaction mixture was stirred for 16 hr, then the solvent was removed in vacuo. The residue was purified via column chromatography on silica gel (eluting 0-95% ethyl acetate/hexanes) to give 164 mg (39%) of 1-(2-hydroxy-3-methyl-4-{[3-(pyridin-4-ylthio)benzyl]oxy}phenyl)-3-methylbutan-1-one as a colorless oil.

$^1$H NMR (CDCl$_3$, 500MHz), δ 13.04 (s, 1H), 8.38 (d, 2H), 7.64-7.62 (m, 2H), 7.56-7.50 (m, 3H), 6.98 (d, 2H), 6.48 (d, 1H), 5.20 (s, 2H), 2.79 (d, 2H), 2.30-2.28 (m, 1H), 2.11 (s, 3H), 1.01 (d, 6H). MS (ESI): 408 (M + H)$^+$. 

EXAMPLE 95
1-[4-(4-[[2-(2-fluorophenyl)-1H-benzimidazol-1-yl]oxy]butoxy)-2-hydroxy-3-methylphenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-(4-bromobutyl)-2-(2-fluorophenyl)-1H-benzimidazole and 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.01 (s, 1H), 7.88 - 7.86 (m, 1H), 7.67 (m, 1H), 7.58 (d, 1H), 7.48 - 7.46 (m, 2H), 7.36 - 7.30 (m, 3H), 7.22 - 7.20 (m, 1H), 6.29 (d, 1H), 4.25 (t, 2H), 3.91 (t, 2H), 2.78 (d, 2H), 2.32 - 2.27 (m, 1H), 2.05 - 1.99 (m, 2H), 2.00 (s, 3H), 1.73 - 1.68 (m, 2H), 1.03 - 1.01 (d, 6H). MS (ESI) 497 ($M^+$ + Na) 476 ($M^+$ + H).

EXAMPLE 96

1-[4-(4-[[2-(4-fluorophenyl)-1H-benzimidazol-1-yl]oxy]butoxy)-2-hydroxy-3-methylphenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-(4-bromobutyl)-2-(4-fluorophenyl)-1H-benzimidazole and 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.05 (s, 1H), 7.85 (m, 1H), 7.73 - 7.70 (M, 2H), 7.60 (d, 1H), 7.45 - 7.43 (m, 1H), 7.35 - 7.33 (m, 2H), 7.20 - 7.17 (m, 2H), 6.31 (d, 1H), 4.36 (t, 2H), 3.95 (t, 2H), 2.79 (d, 2H), 2.40 (m, 1H), 2.06 (m, 2H), 2.05 (s, 3H), 1.77 - 1.63 (m, 2H), 1.03 (d, 6H). MS (ESI) 477 ($M^+$ + 2H), 476 ($M^+$ + H), 475 ($M^+$).
1-(4-[[4-[[2-(2,4-dichlorophenyl)-1H-imidazol-1-yl)butoxy]-2-hydroxy-3-methylphenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one and 1-(4-bromobutyl)-2-(2,4-dichlorophenyl)-1H-imidazole to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) δ 13.03 (s, 1H), 7.62 (d, 1H), 7.50 (d, 1H), 7.39 (d, 1H), 7.34 (dd, 1H), 7.21 (m, 1H), 7.09 (m, 1H), 6.31 (d, 1H), 3.94 – 3.89 (m, 4H), 2.78 (d, 2H), 2.32 – 2.26 (m, 1H), 2.06 (s, 3H), 1.93 – 1.88 (m, 2H), 1.75 – 1.69 (m, 2H), 0.99 (d, 6H). MS (ESI) 479, 477 (M$^+$ + 2H), 475 (M$^+$).

EXAMPLE 98

1-[4-[[4-[[2-(3-chlorophenyl)-1H-benzimidazol-1-yl]oxy]butoxy]-2-hydroxy-3-methylphenyl]-3-methylbutan-1-one

A similar procedure as outline in example 1 was followed with 1-(4-bromobutyl)-2-(3-chlorophenyl)-1H-benzimidazole and 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) δ 13.00 (s, 1H), 7.85 (m, 1H), 7.76 (m, 1H), 7.62 – 7.59 (m, 2H), 7.49 – 7.41 (m, 3H), 7.36 – 3.34 (m, 2H), 6.32 (d, 2H), 4.37 (t, 2H), 3.96 (t, 2H), 2.78 (d, 2H), 2.33 – 2.26 (m, 1H), 2.11 – 2.05 (m, 2H), 2.06 (s, 3H), 1.81 – 1.75 (m, 2H), 1.01 – 0.99 (d, 6H). MS (ESI) 493, 491 (M$^+$).
7-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butoxy}-2,3-dihydro-4H-chromen-4-one

Trifluoromethanesulfonic acid (5.0 g, 33.3 mmol) was added in one portion to a mixture of resorcinol (1.0 g, 9.0 mmol) and 3-chloropropionic acid (1.0 g, 9.3 mmol) at room temperature under nitrogen atmosphere. The mixture was heated to 80°C for 30 minutes and cooled to room temperature. To the orange oily reaction mixture was added chloroform (35 ml) and then water (40 ml). The layers were separated and the organic layer dried over sodium sulfate, filtered and concentrated in vacuo. Flash chromatography of crude oil on silica gel (0-50% ethyl acetate/hexanes) gave 3-chloro-1-(2,4-dihydroxyphenyl)propan-1-one as a yellow solid (1.1 g). A cooled solution of 2.0 N sodium hydroxide (46 ml) at 5°C was added in one portion to 3-chloro-1-(2,4-dihydroxyphenyl)propan-1-one and stirred slowly, warming to room temperature. The reaction was stirred until no starting material was observed by tlc and then cooled to 0°C. The mixture was acidified to pH2 with 6.0 N aqueous sulfuric acid. The mixture was extracted with ethyl acetate and washed with brine. The organic extracts were combined, dried over sodium sulfate, filtered and concentrated in vacuo. Flash chromatography of crude oil on silica gel (0-50% ethyl acetate/hexanes) afforded 7-hydroxy-2,3-dihydro-4H-chromen-4-one as a white solid (780 mg). A mixture of 7-hydroxy-2,3-dihydro-4H-chromen-4-one (100 mg, 0.61 mmol), dibromobutane (0.3 ml, 2.5 mmol), cesium carbonate (500 mg, 1.5 mmol) and acetone (6.5 ml) was stirred at 40°C overnight. The reaction mixture was cooled to room temperature and filtered, washing with acetone. The filtrate was concentrated in vacuo to give an oil which was purified by flash chromatography on silica gel (0-50% ethyl acetate/hexanes) to give 7-(4-bromobutoxy)-2,3-dihydro-4H-chromen-4-one as an oil (76 mg). A mixture of 7-(4-bromobutoxy)-2,3-dihydro-4H-chromen-4-one (76 mg, 0.25 mmol) and 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one (69 mg, 0.33 mol), cesium carbonate (163 mg, 0.5 mmol) and acetone (2.5 ml) was heated to 40°C overnight. The reaction mixture was cooled and filtered. The collected filtrate was concentrated to give a crude oil which was purified by flash chromatography on silica gel (0-50% ethyl acetate/hexanes) to give the desired product as an
oil (22 mg, 20%). 1H NMR (CDCl₃, 300 MHz) δ 13.00 (s, 1H), 7.82 (d, 1H), 7.61 (d, 1H), 6.58 – 6.55 (dd, 1H), 6.42 (d, 1H), 6.38 (d, 1H), 4.51 (t, 2H), 4.14 – 4.08 (m, 4H), 2.77 – 2.73 (m, 4H), 2.30 – 2.24 (m, 1H), 2.12 (s, 3H), 2.04 – 1.99 (m, 4H), 0.99 (d, 6H).
MS (ESI) 450 (M⁺ + Na), 427 (M⁺)

EXAMPLE 100

![Chemical structure]

1-(2-hydroxy-4-{[4-(3-hydroxypropyl)phenoxy]butoxy}-3-methylphenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one and 3-[4-(4-bromobutoxy)phenyl]propan-1-ol to give the desired product as a solid. 1H NMR (CDCl₃, 300 MHz) δ 13.12 (s, 1H), 7.67 (d, 1H), 7.13 – 7.12 (m, 2H), 6.85 – 6.83 (m, 2H), 6.45 (d, 1H), 4.14 (t, 2H), 4.06 (t, 2H), 3.69 – 3.68 (m, 2H), 2.78 (d, 2H), 2.67 (t, 2H), 2.30 – 2.27 (m, 1H), 2.12 (s, 3H), 2.05 – 2.00 (m, 4H), 1.91 – 1.86 (m, 2H), 1.26 (s, 1H), 1.03 – 1.01 (d, 6H). MS (ESI) 437 (M⁺ + Na), 415 (M⁺ + H).

EXAMPLE 101

![Chemical structure]

methyl 3-[4-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butoxy}phenyl]-propanoate

A similar procedure as outlined in example 1 was followed with 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one and methyl 3-[4-(4-bromobutoxy)phenyl]-propanoate to give the desired product as an oil. 1H NMR (CDCl₃, 300 MHz) δ 13.03 (s, 1H), 7.62 (d, 1H), 7.13 – 7.11 (m, 2H), 6.85 – 6.82 (m, 2H), 6.44 (d, 1H), 4.15 (t, 2H), 4.05 (t, 2H), 3.68 (s, 3H), 2.91 (t, 2H), 2.78 (t, 2H), 2.62 (t, 2H), 2.30 – 2.27 (m, 1H), 2.12 (s, 3H), 2.05 – 1.99 (m, 4H), 1.03 – 1.01 (d, 6H). MS (ESI) 465 (M⁺ + Na), 443 (M⁺)
EXAMPLE 102

1-(2-hydroxy-4-[2-(6-hydroxy-1-benzofuran-3-yl)ethoxy]-3-methylphenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 3-(2-bromoethyl)-1-benzofuran-6-ol. $^1$H NMR (DMSO, 500MHz), δ 13.00 (s, 1H), 9.48 (s, 1H), 7.83 (d, 1H), 7.67 (s, 1H), 7.47 (d, 1H), 6.87 (d, 1H), 6.74 (dd, 1H), 6.67 (d, 1H), 4.35 (t, 2H), 3.10 (t, 2H), 2.85 (d, 2H), 2.17–2.11 (m, 1H), 1.96 (s, 3H), 0.93 (d, 6H). MS (ESI): 369.0 (M + H$^+$).

EXAMPLE 103

methyl 2-hydroxy-4-[4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butoxy]benzoate

A similar procedure as outlined in example 1 was followed with 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one and methyl 4-(4-bromobutoxy)-2-hydroxybenzoate to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) δ 13.28 (s, 1H), 11.02 (s, 1H), 7.77 (d, 1H), 7.63 (d, 1H), 6.46 – 6.43 (m, 2H), 4.18 – 4.08 (m, 4H), 3.93 (s, 3H), 2.79 (d, 2H), 2.31 – 2.26 (m, 1H), 2.12 (s, 3H), 2.04 – 2.01 (m, 4H), 1.03 – 1.01 (d, 6H). MS (ESI) 453 (M$^+$ + Na).

EXAMPLE 104
ethyl 7-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butoxy}chromane-2-carboxylate

A similar procedure as outlined in example 1 was followed with 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one and ethyl 7-(4-bromobutoxy)chromane-2-carboxylate to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.07 (s, 1H), 7.62 (d, 1H), 6.93 (d, 1H), 6.52 (m, 1H), 6.48 (dd, 1H), 6.43 (d, 1H), 4.72 (m, 1H), 4.28 (q, 2H), 4.13 (t, 2H), 4.02 (t, 2H), 2.78 (d, 2H), 2.28 (m, 1H), 2.20 (m, 1H), 2.08 – 2.02 (m, 2H), 2.12 (s, 3H), 2.02 – 1.98 (m, 4H), 1.31 (t, 3H), 1.03 – 1.01 (d, 6H). MS (ESI) 508 ($M^+$ + Na), 485 ($M^+$).

**EXAMPLE 105**

1-{3-chloro-2,4-bis[4-(pyridin-4-ylthio)butoxy]phenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 4-[(4-bromobutyl)thio]pyridine and 1-(2,4-dihydroxy-3-chlorophenyl)-3-methylbutan-1-one. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 8.58-8.54 (m, 4H), 7.65 (d, 2H), 7.59 (d, 2H), 7.54 (d, 1H), 6.77 (d, 1H), 4.19-4.15 (m, 2H), 4.06 (t, 2H), 3.33-3.30 (m, 4H), 2.79 (d, 2H), 2.22-2.18 (m, 1H), 2.18-2.03 (m, 8H), 0.96 (d, 6H). MS (ESI): 559 (M + H$^+$).

**EXAMPLE 106**

1-{3-bromo-2-hydroxy-4-[4-(pyridin-4-ylthio)butoxy]phenyl}-3-methylbutan-1-one
A similar procedure as outlined in example 1 was followed using 4-mercaptopyridine and -(2,4-dihydroxy-3-bromophenyl)-3-methylbutan-1-one. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.57 (s, 1H), 8.39 (d, 2H), 7.73 (d, 1H), 7.13 (d, 2H), 6.48 (d, 1H), 4.17 (t, 2H), 3.13 (t, 2H), 2.80 (d, 2H), 2.31-2.25 (m, 1H), 2.08-1.98 (m, 4H), 1.01 (d, 6H). MS (ESI): 438 (M + H)$^+$. 

EXAMPLE 107

![Structure](image)

1-(2-hydroxy-3-methyl-4-[4-(pyridin-4-ylthio)butoxy]phenyl)-3,3-dimethylbutan-1-one

A similar procedure as outlined in example 1 was followed using 4-mercaptopyridine and 1-(2,4-dihydroxy-3-methylphenyl)-3,3-dimethylbutan-1-one. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.23 (s, 1H), 8.37 (d, 2H), 7.61 (d, 1H), 7.11 (d, 2H), 6.39 (d, 1H), 4.08 (t, 2H), 3.07 (t, 2H), 2.77 (s, 2H), 2.08 (s, 3H), 2.02-1.93 (m, 4H), 1.06 (s, 9H). MS (ESI): 388 (M + H)$^+$. 

EXAMPLE 108

![Structure](image)

1-[2-hydroxy-3-methyl-4-([3-[(pyridin-4-ylthio)methyl]benzyl]oxy)phenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 94 was followed using {3-[(pyridin-4-ylthio)methyl]phenyl}methanol. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.05 (s, 1H), 8.39 (d, 2H), 7.60 (d, 1H), 7.49 (s, 1H), 7.40-7.35 (m, 3H), 7.12 (d, 2H), 6.47 (d, 1H), 5.16 (s, 2H), 4.25 (s, 2H), 2.78 (d, 2H), 2.31-2.26 (m, 1H), 2.18 (s, 3H), 1.01 (d, 6H). MS (ESI): 423 (M + H)$^+$. 

EXAMPLE 109
1-(2-hydroxy-3-methyl-4-{4-[(2-phenyl-1H-benzimidazol-1-yl)oxy]butoxy}phenyl)-3,3-dimethylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-(4-bromobutyl)-2-phenyl-1H-benzimidazole and 1-(2,4-dihydroxy-3-methylphenyl)-3,3-dimethylbutan-1-one to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.28 (s, 1H), 7.85 (m, 1H), 7.73 - 7.71 (m, 2H), 7.60 (d, 1H), 7.50 - 7.48 (m, 3H), 7.45 (m, 1H), 7.34 - 7.32 (m, 2H), 6.30 (d, 1H), 4.37 (t, 2H), 3.93 (t, 2H), 2.79 (s, 2H), 2.10 - 2.03 (m, 2H), 2.01 (s, 3H), 1.80 - 1.73 (m, 2H), 1.08 (s, 9H). MS (ESI) 494 (M$^+$ + Na), 473 (M$^+$ + 2H), 472 (M$^+$ + H).

**EXAMPLE 110**

1-(2-hydroxy-3-methyl-4-{[4-(pyridin-4-ylthio)benzyl]oxy}phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 94 was followed using [4-(pyridin-4-ylthio)phenyl]methanol. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.06 (s, 1H), 8.38 (d, 2H), 7.64 (d, 1H), 7.60 (d, 2H), 7.54 (d, 2H), 6.98 (d, 2H), 6.50 (d, 1H), 5.23 (s, 2H), 2.80 (d, 2H), 2.32-2.26 (m, 1H), 2.12 (s, 3H), 1.00 (d, 6H). MS (ESI): 409 (M + H$^+$).

**EXAMPLE 111**

1-(2-hydroxy-4-{4-(3-hydroxyphenoxo)butoxy}-3-methylphenyl)-3-methylbutan-1-one
A similar procedure as outlined in example 1 was followed with resorcinol to give the desired product as an oil. $^1$H NMR (CDCl$_3$, 300MHz) $\delta$ 13.01 (s, 1H), 7.60 (d, 1H), 7.12 (t, 1H), 6.49 – 6.47 (m, 1H), 6.43 – 6.39 (m, 2H), 4.75 (s, 1H), 4.11 (t, 2H), 4.01 (t, 2H), 2.76 (d, 2H), 2.29 – 2.24 (m, 1H), 2.10 (s, 3H), 2.04 – 1.98 (m, 4H), 1.00 – 0.99 (d, 6H).

MS (ESI) 373 (M$^+$).

EXAMPLE 112

![Chemical Structure](image)

1-(4-[4-(3,4-dihydro-2H-chroman-7-yloxy)butoxy]-2-hydroxy-3-methylphenyl)-3-methylbutan-1-one

A mixture of 7-hydroxy-2,3-dihydro-4H-chromen-4-one (200 mg, 1.2 mmol), 10% palladium on carbon (20 mg) and ethyl acetate (12 ml) was placed under hydrogen atmosphere at room temperature at 1.0 atmosphere overnight. Nitrogen was bubbled through the mixture, then filtered through celite. The collected filtrate was concentrated to give a crude solid which was purified by flash chromatography on silica gel (0-50% ethyl acetate/hexanes) to afford chroman-7-ol as a white solid (130 mg). A mixture of chroman-7-ol (130 mg, 0.8 mmol), 1,4-dibromobutane (0.41 ml, 3.5 mmol), cesium carbonate (700 mg, 2.1 mmol) and acetone (8.6 ml) was stirred overnight at 40°C. The mixture was cooled and filtered. The filtrate was concentrated to give an oil which was purified by flash chromatography on silica gel (0-20% ethyl acetate/hexanes) to give 7-(4-bromobutoxy)-chromane as an oil (128 mg). A mixture of 7-(4-bromobutoxy)chromane (65 mg, 0.2 mmol), 1-(2,4-dihydroxy-3-methylphenyl)-3-methylbutan-1-one (47 mg, 0.2 mmol), potassium carbonate (77 mg, 0.6 mmol) and acetone (2.2 ml) was stirred at 45°C overnight. The reaction mixture was cooled and filtered. The collected filtrate was concentrated in vacuo to give a crude oil which was purified by flash chromatography on silica gel (0-20% ethyl acetate/hexanes) to give the desired product as an oil (42 mg, 46%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 13.07 (s, 1H), 7.59 (d, 1H), 6.91 (d, 1H), 6.43 – 6.38 (m, 2H), 6.34 (d, 1H), 4.18 (t, 2H), 4.11 (t, 2H), 4.00 (t, 2H), 2.72 (d, 2H), 2.71 (t, 2H), 2.29 – 2.22 (m, 1H), 2.09 (s, 3H), 2.01 – 1.93 (m, 4H), 1.03 – 1.01 (d, 6H). MS (ESI) 413 (M$^+$).
EXAMPLE 113

![Chemical Structure]

1-(2-hydroxy-3-methyl-4-d-[4-(pyridin-4-ylthio)benzyl]oxy phenyl)-3,3-dimethylbutan-1-one

A similar procedure as outlined in example 94 was followed using [4-(pyridin-4-ylthio)phenyl]methanol and 1-(2,4-dihydroxy-3-methylphenyl)-3,3-dimethylbutan-1-one. $^1$H NMR (CDCl$_3$, 500MHz), δ 13.28 (s, 1H), 8.38 (d, 2H), 7.66 (d, 1H), 7.59 (d, 2H), 7.53 (d, 2H), 6.98 (d, 2H), 6.50 (d, 1H), 5.23 (s, 2H), 2.81 (s, 2H), 2.22 (s, 3H), 1.09 (s, 9H). MS (ESI): 422 (M + H)$^+$.  

EXAMPLE 114

![Chemical Structure]

1-(3-bromo-2-hydroxy-4-d-[4-(pyridin-4-ylthio)benzyl]oxy phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 94 was followed using [4-(pyridin-4-ylthio)phenyl]methanol and 1-(3-bromo-2,4-dihydroxyphenyl)-3-methylbutan-1-one. $^1$H NMR (CDCl$_3$, 500MHz), δ 13.57 (s, 1H), 8.35 (d, 2H), 7.73 (d, 1H), 7.60-7.56 (m, 4H), 6.97 (d, 2H), 6.54 (d, 1H), 5.30 (s, 2H), 2.80 (d, 2H), 2.31-2.25 (m, 1H), 1.01 (d, 6H). MS (ESI): 473 (M + H)$^+$.  

EXAMPLE 115

![Chemical Structure]

1-(2-hydroxy-3-methyl-4-d-[3-(pyridin-4-ylthio)benzyl]oxy phenyl)-3,3-dimethylbutan-1-one

A similar procedure as outlined in example 94 was followed using [3-(pyridin-4-ylthio)phenyl]methanol and 1-(2,4-dihydroxy-3-methylphenyl)-3,3-dimethylbutan-1-one. $^1$H NMR (CDCl$_3$, 500MHz), δ 13.24 (s, 1H), 8.35 (d, 2H), 7.63-7.60 (m, 2H), 7.53-
7.47 (m, 3H), 6.95 (d, 2H), 6.45 (d, 1H), 5.17 (s, 2H), 2.78 (s, 2H), 2.15 (s, 3H), 1.06 (s, 9H).
MS (ESI): 422 (M+H)+.

EXAMPLE 116

3'-[(4-(3,3-dimethylbutanoyl)-3-hydroxy-2-methylphenoxy)methyl]biphenyl-3-carboxamide

A mixture of 3-bromobenzamide (3 g, 15.1 mmol), 3-(hydroxymethyl)-phenyl]boronic acid (3 g, 19.6 mmol), PdCl2(PPh3)2 (0.46 g, 0.66 mmol), and potassium carbonate (3.6 g, 26.2 mmol) in Toluene/MeOH (10:1, 40 mL) was stirred at 80 °C for 18 h. The resulting black mixture was cooled to room temperature, filtered through celite, and poured into a EtOAc/brine mixture. The two layers were separated and the aqueous was extracted with EtOAc (3x). The organics were combined, dried over sodium sulfate, filtered, and evaporated to dryness. The residue was purified by flash chromatography on silica gel eluting with a mixture of EtOAc/Hexane to give 3'-[(hydroxymethyl)biphenyl-3-carboxamide as a solid. A mixture of this solid (0.68 g, 3 mmol) and triphenyl phosphine (1.0 g, 3.9 mmol) in CH2Cl2 (20 mL) was cooled to 0 °C. Carbon tetrabromide (1.3 g, 3.9 mmol) was then added and the resulting orange mixture was stirred at room temperature for 48 h. The solvent was removed and the residue was purified by flash chromatography on silica gel (EtOAc/Hexane) to give 3'-[bromomethyl]biphenyl-3-carboxamide as a yellow solid. A mixture of this yellow solid (260 mg, 0.9 mmol), 1-(2,4-dihydroxy-3-methylphenyl)-3,3-dimethylbutan-1-one (183 mg, 0.75 mmol), and potassium carbonate (249 mg, 1.8 mmol) in acetone (5 mL) was stirred at 50 °C for 18 h. The mixture was cooled to room temperature, filtered and concentrated. The crude residue was purified by reverse-phase preparative HPLC chromatography to give the title compound as a colorless solid. 1H NMR (CDCl3, 500 MHz) δ 13.28 (s, 1H), 8.10 (s, 1H), 7.76-7.80 (m, 2H), 7.68 (s, 1H), 7.65 (d, 1H), 7.45-7.62 (m, 4H), 6.52 (d, 1H), 6.20-6.40 (br s, 2H), 5.19 (s, 2H), 2.79 (s, 2H), 2.24 (s, 3H), 1.08 (s, 9H). MS (ESI+) 432.06 (M+1).
1-(3-bromo-2-hydroxy-4-{4-[(2-phenyl-1H-benzimidazol-1-yl)oxy]butoxy}phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed with 1-(3-bromo-2,4-dihydroxyphenyl)-3-methylbutan-1-one and 1-(4-bromobutyl)-2-phenyl-1H-benzimidazole to give the desired product as an oil. \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 13.53 (s, 1H), 7.83 (m, 1H), 7.72 (m, 2H), 7.67 (d, 1H), 7.48 – 7.44 (m, 4H), 7.32 – 7.30 (m, 2H), 6.33 (d, 1H), 4.39 (t, 2H), 3.96 (t, 2H), 2.77 (d, 2H), 2.33 – 2.24 (m, 1H), 2.12 – 2.06 (m, 2H), 1.80 – 1.74 (m, 2H), 1.01 – 0.99 (d, 6H). MS (ESI) 523, 521 (M\(^+\) + H).

EXAMPLE 118

\[
\begin{align*}
\text{S} & \quad \text{N} \\
\text{O} & \quad \text{H}
\end{align*}
\]

1-[2-hydroxy-3-methyl-4-((4-[(pyridin-4-ylthio)methyl]benzyl)oxy)phenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 94 was followed using \{4-[(pyridin-4-ylthio)methyl]phenyl\}methanol. \(^1\)H NMR (CDCl\(_3\), 500MHz), \(\delta\) 13.01 (s, 1H), 8.38 (d, 2H), 7.59 (d, 1H), 7.43-7.38 (m, 4H), 7.12 (d, 2H), 6.46 (d, 1H), 5.14 (s, 2H), 4.22 (s, 2H), 2.75 (d, 2H), 2.29-2.23 (m, 1H), 2.16 (s, 3H), 1.00 (d, 6H). MS (ESI): 422 (M + H\(^+\)).

EXAMPLE 119

\[
\begin{align*}
\text{S} & \quad \text{N} \\
\text{O} & \quad \text{H}
\end{align*}
\]
1-[2-hydroxy-4-[(3-methoxy-4-[(pyridin-4-ylthio)methyl]benzyl]oxy]-3-methylphenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 94 was followed using {3-methoxy-4-{(pyridin-4-ylthio)methyl]phenyl}methanol. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.03 (s, 1H), 8.37 (d, 2H), 7.59 (d, 1H), 7.35 (d, 1H), 7.14 (d, 2H), 6.98-6.95 (m, 2H), 6.46 (d, 1H), 5.13 (s, 2H), 4.23 (s, 2H), 3.88 (s, 3H), 2.75 (d, 2H), 2.29-2.23 (m, 1H), 2.17 (s, 3H), 0.99 (d, 6H). MS (ESI): 452 (M + H)$^+$.  

EXAMPLE 120

\[ 
\text{\begin{center}
\includegraphics[width=0.3\textwidth]{example120}
\end{center}} \]

1-(2-hydroxy-3-methyl-4-{[2-(pyridin-4-ylthio)benzyl]oxy}phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 94 was followed using [2-(pyridin-4-ylthio)phenyl]methanol. $^1$H NMR (CDCl$_3$, 500MHz), $\delta$ 13.00 (s, 1H), 8.35 (d, 2H), 7.71 (d, 1H), 7.63 (d, 1H), 7.56-7.52 (m, 2H), 7.45-7.43 (m, 1H), 6.89 (d, 2H), 6.35 (d, 1H), 5.24 (s, 2H), 2.73 (d, 2H), 2.27-2.21 (m, 1H), 2.13 (s, 3H), 0.98 (d, 6H). MS (ESI): 408 (M + H)$^+$.  

EXAMPLE 121

\[ 
\text{\begin{center}
\includegraphics[width=0.3\textwidth]{example121}
\end{center}} \]

1-(2-hydroxy-3-methyl-4-{[4-(2-methylpyridin-4-yl)thio]butoxy}phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 4-chloro-2-methylpyridine. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 13.01 (s, 1H), 8.29-8.28 (d, 1H), 8.24 (s, 1H),
7.61-7.60 (d, 1H), 7.03-7.02 (d, 1H), 6.42-6.40 (d, 1H), 4.11-4.09 (t, 2H), 3.08-3.06 (t, 2H), 2.78-2.76 (d, 2H), 2.25(s, 3H), 2.10 (s, 3H), 2.02-1.906 (m, 5H) 1.00-0.99 (d, 6H).

EXAMPLE 122

\[ \text{1-(2-hydroxy-3-methyl-4-[(3-(pyridin-3-ylamino)benzyl)oxy]phenyl)-3-methylbutan-1-one} \]

A solution of pyridin-3-amine (198mg, 1.2mmol), 1-[2-hydroxy-4-[(3-iodobenzyl)oxy]-3-methylphenyl]-3-methylbutan-1-one (424mg, 1.0mmol), Tris(dibenzylideneacetone)dipalladium(0) (40mg, 0.043mmol), bipheny1-2-yl(dicyclohexyl)phosphine (68mg, 0.194mmol), sodium tert-butoxide (115mg, 1.2mmol) in 5ml toluene was heated to 70°C for 24 hours. The reaction mixture was directly loaded chromatographed on silica gel using an ISCO single channel system (Hexane/EtOAc = 10/0 to 5/5) to afford 1-(2-hydroxy-3-methyl-4-[(3-(pyridin-3-ylamino)benzyl)oxy]phenyl)-3-methylbutan-1-one as a pale oil.

\[ ^1H \text{ NMR (MeOD, 500 MHz)} \delta 8.32 (s, 1H), 8.12-8.11 (d, 1H), 8.02-7.99 (m, 1H), 7.77-7.74 (m, 2H), 7.46-7.43 (m, 1H), 7.35 (s, 1H), 7.27-7.23 (m, 2H), 6.66-6.65 (d, 1H), 5.24 (s, 2H), 2.82-2.81 (d, 2H), 2.27-2.20 (m, 1H), 2.12 (s, 3H), 1.00-0.98 (d, 6H). \text{ MS (ESI) 391.27 (M}^+{H}).\]

EXAMPLE 123

\[ \text{1-[2-hydroxy-3-methyl-4-[(3-[pyridin-4-ylthio)methyl]benzyl]oxy]phenyl]-3,3-dimethylbutan-1-one} \]

A similar procedure as outlined in example 94 was followed using [3-[pyridin-4-ylthio)methyl]phenyl]methanol and 1-(2,4-dihydroxy-3-methylphenyl)-3,3-dimethylbutan-1-one. \[ ^1H \text{ NMR (CDCl}_3, 500MHz) \delta 13.27 (s, 1H), 8.39 (d, 2H), 7.62 (d, 1H), \]
7.49 (s, 1H), 7.40-7.36 (m, 3H), 7.12 (d, 2H), 6.46 (d, 1H), 5.16 (s, 2H), 4.25 (s, 2H), 2.80 (s, 2H), 2.18 (s, 3H), 1.04 (s, 9H). MS (ESI): 437 (M + H)^+.

**EXAMPLE 124**

1-(2-hydroxy-3-methyl-4-[(3-(pyridin-2-ylamino)benzyl]oxy)phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 122 was followed using pyridin-2-amine, the free base treated with 1.0 equivalent 1N HCl in THF give its salt form. ^1H NMR (MeOD, 500 MHz) δ 8.07-8.03 (m, 1H), 7.88-7.86 (d, 1H), 7.78-7.76 (d, 1H), 7.61-7.49 (m, 3H), 7.39-7.37 (d, 1H), 7.22-7.20 (d, 1H), 7.08-7.05 (m, 1H), 6.68-6.66 (d, 1H), 5.29 (s, 2H), 2.82-2.81 (d, 2H), 2.25-2.20 (m, 1H), 2.11 (s, 3H), 1.00-0.99 (d, 6H). MS (ESI) 391.34 (M^+H).

**EXAMPLE 125**

1-(2-hydroxy-3-methyl-4-[(3-(pyridin-4-ylamino)benzyl]oxy)phenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 122 was followed using pyridin-4-amine, the free base treated with 1.0 equivalent 1N HCl in THF give its salt form. ^1H NMR (CDCl3, 500 MHz) δ 13.02 (s, 1H), 9.95 (s, 1H), 7.99-7.97 (d, 2H), 7.61-7.59 (d, 1H), 7.46-7.43 (m, 1H), 7.36-7.34 (m, 2H), 7.24-7.22 (d, 1H), 7.09-7.08 (d, 2H), 6.46-6.44 (d, 1H), 5.14 (s, 2H), 2.76-2.74 (d, 2H), 2.29-2.20 (m, 1H), 2.13 (s, 3H), 1.00-0.99 (d, 6H). MS (ESI) 391.30 (M^+H).

**EXAMPLE 126**
1-{2-hydroxy-4-[4-(1H-indazol-5-yloxy)butoxy]-3-methylphenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 1H-indazol-5-ol. 1H NMR (DMSO, 500MHz), δ 13.02 (s, 1H), 7.92 (s, 1H), 7.84 (d, 1H), 7.43 (d, 1H), 7.17 (d, 1H), 6.99 (dd, 1H), 6.65 (d, 1H), 4.20–4.15 (m, 2H), 4.09–4.03 (m, 2H), 2.85 (d, 2H), 2.18–2.12 (m, 1H), 1.99 (s, 3H), 1.96–1.91 (m, 4H), 0.94 (d, 6H). MS (ESI): 397.0 (M + H)+.

EXAMPLE 127

1-{2-hydroxy-4-[4-(1H-indazol-6-yloxy)butoxy]-3-methylphenyl}-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 1H-indazol-6-ol. 1H NMR (DMSO, 500MHz), δ 13.02 (s, 1H), 12.78 (s, 1H), 7.92 (s, 1H), 7.84 (d, 1H), 7.60 (d, 1H), 6.92 (s, 1H), 6.74 (dd, 1H), 6.65 (d, 1H), 4.21–4.16 (m, 2H), 4.12–4.07 (m, 2H), 2.85 (d, 2H), 2.19–2.11 (m, 1H), 2.00 (s, 3H), 1.97–1.91 (m, 4H), 0.94 (d, 6H). MS (ESI): 397.0 (M + H)+

EXAMPLE 128

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1-(2-hydroxy-4-[4-(1H-indol-4-yloxy)butoxy]-3-methylphenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 1H-indol-4-ol. 1H NMR (DMSO, 500MHz), δ 13.02 (s, 1H), 11.03 (s, 1H), 7.83 (d, 1H), 7.18 (t, 1H), 6.99–6.93 (m, 2H), 6.65 (d, 1H), 6.48 (dd, 1H), 6.39 (t, 1H), 4.22–4.18 (m, 2H), 4.17–4.13 (m, 2H), 2.85 (d, 2H), 2.18–2.12 (m, 1H), 2.00 (s, 3H), 2.00–1.95 (m, 4H), 0.94 (d, 6H). MS (ESI): 396.0 (M + H)+.

EXAMPLE 129

1-(2-hydroxy-4-[4-(1H-indol-5-yloxy)butoxy]-3-methylphenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 1H-indol-5-ol. 1H NMR (DMSO, 500MHz), δ 13.02 (s, 1H), 10.88 (s, 1H), 7.84 (d, 1H), 7.28–7.23 (m, 2H), 7.03 (s, 1H), 6.72 (d, 1H), 6.65 (d, 1H), 6.30 (t, 1H), 4.21–4.15 (m, 2H), 4.05–3.99 (m, 2H), 2.85 (d, 2H), 2.18–2.12 (m, 1H), 2.00 (s, 3H), 1.99–1.90 (m, 4H), 0.94 (d, 6H). MS (ESI): 396.1 (M + H)+.

EXAMPLE 130

1-(2-hydroxy-4-[4-(1H-indol-6-yloxy)butoxy]-3-methylphenyl)-3-methylbutan-1-one

A similar procedure as outlined in example 1 was followed using 1H-indol-6-ol. 1H NMR (DMSO, 500MHz), δ 13.02 (s, 1H), 10.83 (s, 1H), 7.84 (d, 1H), 7.38 (d, 1H), 7.17 (s, 1H), 6.89 (s, 1H), 6.67–6.62 (m, 2H), 6.32 (t, 1H), 4.19–4.15 (m, 2H), 4.07–4.02 (m, 2H), 2.85 (d, 2H), 2.18–2.12 (m, 1H), 2.00 (s, 3H), 1.99–1.90 (m, 4H), 0.94 (d, 6H). MS (ESI): 396.0 (M + H)+.

EXAMPLE 131
Ethyl 5-[(3-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]methyl)phenyl)amino]-2-methoxybenzoate

To 0°C solution of ethyl salicylate (1.66g, 10mmol) in 20ml THF was added NaH (60% 0.4g, 10mmol) in several potion, then iodomethane (1.42g, 10mmol) was added. The solution was allowed warm up and stirred for over night. The reaction mixture was quenched with saturated aqueous NH₄Cl (40mL), extracted with dimethyl ether (3 x 25mL) and washed with brine. The organic phase was dried over Na₂SO₄, concentrated in vacuo and chromatographed on silica gel using an ISCO single channel system (Hexane/EtOAc = 10/0 to 9/1) to give product ethyl 2-methoxybenzoate as clear oil. ¹H NMR (CDCl₃, 500 MHz) δ 7.79-7.77 (m, 1H), 7.44-7.42 (m, 1H), 6.98-6.95 (m, 2H), 4.37-4.33 (q, 2H), 3.88 (s, 3H), 1.38-1.35 (t, 3H). To 0°C solution of ethyl 2-methoxybenzoate (1.8g, 10mmol) in mixed solvent of 15ml acetic acid and 15ml of acetic anhydride was added fume nitric acid (0.63g, 10mmol) dropwised. The solution was stirred for 1 hour and allowed warm up to room temperature, the increase the temperature to 50°C, stirred for overnight. The reaction mixture was quenched with saturated aqueous NH₄HCO₃ (50mL), extracted with EtOAc (3 x 25mL) and washed with brine. The organic phase was dried over Na₂SO₄, concentrated in vacuo and chromatographed on silica gel using an ISCO single channel system (Hexane/EtOAc = 9/1 to 1/9) to give product ethyl 2-methoxy-5-nitrobenzoate as clear oil. ¹H NMR (CDCl₃, 500 MHz) δ 8.68-8.67 (d, 1H), 8.37-8.35 (dd, 1H), 7.08-7.07 (d, 1H), 4.42-4.38 (q, 2H), 4.03 (s, 3H), 1.43-1.40 (t, 3H). To a solution of ethyl 2-methoxy-5-nitrobenzoate (1.6g) in 20ml EtOAc was added 100mg of palladium on carbon, the resulting solution treated with 1 atmosphere of Hydrogen gas for 4 hour. The reaction mixture was filtrated over celite, concentrated in vacuo and chromatographed on silica gel using an ISCO single channel system (Hexane/EtOAc = 9/1 to 1/9) to give product ethyl 5-amino-2-methoxybenzoate. ¹H NMR (CDCl₃, 500 MHz) δ 8.7.142-7.137 (m, 1H), 6.83-6.79 (m, 2H), 4.36-4.32 (q, 2H), 3.83 (s, 3H), 1.38-1.36 (t, 3H). A similar procedure as outlined in example 122 was followed using ethyl 5-amino-2-methoxybenzoate. ¹H NMR (CDCl₃, 500 MHz) δ 13.01 (s, 1H), 10.61 (s, 1H), 7.63-7.62 (d, 1H), 7.59-7.58 (d, 1H), 7.30-7.28 (dd, 1H), 7.25-7.22 (m, 1H), 6.96-6.95 (d, 1H), 6.91 (s, 1H), 6.89-6.88 (d, 1H), 6.83-6.81 (dd, 1H), 6.47-6.45 (d, 1H), 5.53 (s,
1H), 5.08 (s, 2H), 4.42-4.37 (q, 2H), 2.77-2.75 (d, 2H), 2.29-2.24 (m, 1H), 2.14 (s, 3H), 1.40-1.37 (t, 3H), 1.00-0.97 (d, 6H). MS (ESI) 500.13 (M^+Na).

**EXAMPLE 132**

\[
\text{OH} \quad \text{O} \quad \text{O}
\]

1-[2-hydroxy-4-([3-[(3-methoxyphenyl)amino]benzyl]oxy)-3-methylphenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 122 was followed using (3-methoxyphenyl)amine. \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 13.02 (s, 1H), 7.59-7.57 (d, 1H), 7.28-7.25 (m, 1H), 7.18-7.14 (m, 2H), 7.03-7.02 (m, 1H), 6.96-6.95 (d, 1H), 6.66-6.63 (m, 2H), 6.51-6.49 (dd, 1H), 6.47-6.45 (d, 1H), 5.76 (s, 1H), 5.11 (s, 2H), 3.76 (s, 3H), 2.76-2.75 (d, 2H), 2.28-2.23 (m, 1H), 2.16 (s, 3H), 1.00-0.98 (d, 6H). MS (ESI) 420.54 (M^+H).

**EXAMPLE 133**

\[
\text{OH} \quad \text{O} 
\]

1-[4-([(3-ethoxyphenyl)amino]benzyl)oxy]-2-hydroxy-3-methylphenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 122 was followed using (3-ethoxyphenyl)amine. \(^1\)H NMR (CDCl\(_3\), 500 MHz) \(\delta\) 13.02 (s, 1H), 7.59-7.57 (d, 1H), 7.28-7.25 (m, 1H), 7.16-7.13 (m, 2H), 7.03-7.01 (m, 1H), 6.96-6.94 (d, 1H), 6.64-6.63 (m, 2H), 6.50-6.46 (m, 2H), 6.53 (s, 1H), 5.10 (s, 2H), 4.01-3.96 (q, 2H), 2.76-2.75 (d, 2H), 2.29-2.23 (m, 1H), 2.16 (s, 3H), 1.40-1.37 (t, 3H), 1.00-0.98 (d, 6H). MS (ESI) 434.61 (M^+H).
1-[2-hydroxy-4-[(3-[(3-isopropylphenyl)amino]benzyl)oxy]-3-methylphenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 122 was followed using (3-isopropylphenyl)amine. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 13.02 (s, 1H), 7.59-7.57 (d, 1H), 7.27-7.24 (m, 1H), 7.20-7.17 (m, 1H), 7.11 (s, 1H), 7.00-6.98 (m, 1H), 6.93-6.90 (m, 3H), 6.84-6.82 (d, 1H), 6.47-6.45 (d, 1H), 5.74 (s, 1H), 5.10 (s, 2H), 2.86-2.81 (m, 1H), 2.76-2.74 (d, 2H), 2.28-2.23 (m, 1H), 2.16 (s, 3H), 1.23-1.22 (d, 6H), 1.00-0.99 (d, 6H).

EXAMPLE 135

1-[2-hydroxy-3-methyl-4-[[3-[methyl(pyridin-2-yl)amino]benzyl]oxy]phenyl]-3-methylbutan-1-one

A similar procedure as outlined in example 122 was followed using N-methylpyridin-2-amine. $^1$H NMR (CDCl$_3$, 500 MHz) $\delta$ 13.05 (s, 1H), 8.27-8.25 (m, 1H), 7.64-7.62 (d, 1H), 7.46-7.43 (m, 1H), 7.36-7.32 (m, 2H), 7.32-7.25 (m, 2H), 6.68-6.65 (m, 1H), 6.61-6.60 (m, 1H), 6.52-6.50 (d, 1H), 5.18 (s, 2H), 3.51 (s, 3H), 2.80-2.79 (d, 2H), 2.32-2.27 (m, 1H), 2.18 (s, 3H), 1.03-1.02 (d, 6H). MS (ESI) 405.15 (M$^+$+H).

EXAMPLE 136

1-[2-(benzyl)oxy]-3-methyl-4-[4-(pyridin-4-ylthio)butoxy]phenyl]-3-methylbutan-1-one

- 83 -
Potassium carbonate (91 mg, 0.66 mmol) was added to a stirred solution of 1-[2-(benzyloxy)-4-(4-bromobutoxy)-3-methylphenyl]-3-methylbutan-1-one (95 mg, 0.22 mmol) and 4-mercaptopyridine (61 mg, 0.55 mmol) in acetone (10 mL) at 45 °C. The reaction mixture was stirred for 16 hr, then the acetone was removed in vacuo. The residue was then mixed with dichloromethane (50 mL) and water (50 mL). The organic layer was separated, dried over MgSO₄ and then concentrated in vacuo to give a residue that was purified via column chromatography on silica gel (eluting 0-60% ethyl acetate/hexanes) to give 85 mg (83%) of 1-[2-(benzyloxy)-3-methyl-4-[4-(pyridin-4-ylthio)butoxy]phenyl]-3-methylbutan-1-one as a colorless oil. ¹H NMR (CDCl₃, 500MHz), δ 8.41 (d, 2H), 7.50-7.36 (m, 6H), 7.13 (d, 2H), 6.68 (d, 1H), 4.83 (s, 2H), 4.08 (t, 2H), 3.09 (t, 2H), 2.83 (d, 2H), 2.20-2.16 (m, 4H), 2.04-1.95 (m, 4H), 0.90 (d, 6H). MS (ESI): 464 (M + H)⁺.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention.
WHAT IS CLAIMED IS:

1. A compound of the formula I:

\[
\begin{array}{c}
\text{R}^4 \quad \text{A} \\
\text{X} \\
\text{Y} \\
\text{R}^1 \quad \text{R}^2 \quad \text{O} \\
\end{array}
\]

wherein:
A is selected from the group consisting of phenyl, napthyl, azetidinyl, benzoxazolyl, benzofuranyl, benzimidazolyl, chromenyl, dihydroindenyl, dihydroisoquinolinyl, isoquinolinyl, imidazolyl, imidazopyridinyl, indanyl, indazolyl, indolyl, oxadiazolyl, purinyl, pyridyl, pyrimidinyl, quinolinyl, tetrahydroisoquinolinyl, and tetrazolyl, which is unsubstituted or substituted with oxo;

X is selected from the group consisting of:

1. a bond;
2. \(-\text{O}^{-}\);
3. \(-\text{S}^{-}\);
4. \(-\text{SO}_2^{-}\);
5. \(-\text{NH}^{-}\);
6. \(-\text{N(C}_1\text{-alkyl)}^{-}\);
7. \(-\text{O-phenyl}^{-}\);
8. \(-\text{S-phenyl}^{-}\);
9. \(-\text{S-C}_1\text{-alkyl-phenyl}^{-}\);
10. \(-\text{phenyl}^{-}\), and
11. \(-\text{piperazinyl}^{-}\);

Y is selected from the group consisting of:

1. \(-\text{O}^{-}\);
2. \(-\text{NH(CO)}^{-}\), and
3. a bond;
R1 is selected from the group consisting of:

(1) hydrogen,

(2) C1-alkyl, which is unsubstituted or substituted with a substituent selected from:

(a) halogen,

(b) hydroxy, and

(c) phenyl, wherein the phenyl is unsubstituted or substituted with 1-5 substituents independently selected from halogen, cyano, CF3, hydroxy, C1-alkyl, and OC1-alkyl,

(3) C3-cycloalkyl, which is unsubstituted or substituted with halogen, hydroxy or phenyl, and

(4) phenyl, wherein the phenyl is unsubstituted or substituted with 1-5 substituents independently selected from halogen, hydroxy, cyano, CF3, C1-alkyl, and OC1-alkyl, wherein the C1-alkyl and OC1-alkyl are linear or branched and optionally substituted with 1-5 halogen;

R2 is selected from the group consisting of:

(1) halogen,

(2) hydroxy,

(3) -OC1-alkyl, and

(4) C1-alkyl, which is unsubstituted or substituted with halogen, hydroxy or phenyl;

R3 is selected from the group consisting of:

(1) halogen, and

(2) C1-alkyl, which is unsubstituted or substituted with halogen, hydroxy or phenyl;

R4 may include multiple substituents and is independently selected from the group consisting of:

(1) hydrogen,

(2) halogen,

(3) C1-alkyl, unsubstituted or substituted with halogen, -CN, -COC1-alkyl or -CO2C1-alkyl,
(4) -O-C₃₀galkyl,
(5) phenyl,
(6) pyridyl,
(7) thiazolyl,
(8) -CN, and
(9) hydroxyl,

or R₄ may be joined to the phenyl ring at an adjacent carbon to form a
dihydrofuranyl ring;
m is an integer selected from 0, 1, 2 and 3;
n is an integer selected from 0, 1, 2, 3, 4, 5 and 6;
and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

2. The compound of Claim 1 wherein A is phenyl.

3. The compound of Claim 1 wherein A is pyridyl.

4. The compound of Claim 1 wherein X is -O-.

5. The compound of Claim 1 wherein X is -S-.

6. The compound of Claim 5 wherein A is pyridyl and X is -S-.

7. The compound of Claim 1 wherein X is a bond and Y is -O-.

8. The compound of Claim 1 wherein X is -O-phenyl-.

9. The compound of Claim 1 wherein X is -phenyl-.

10. The compound of Claim 1 wherein R₁ is C₃₀galkyl.

11. The compound of Claim 10 wherein R₁ is CH₂CH(CH₃)₂.

12. The compound of Claim 1 wherein R₂ is hydroxyl.
13. The compound of Claim 1 wherein R³ is methyl.

14. The compound of Claim 1 wherein R⁴ is hydrogen.

15. The compound of Claim 1 wherein m is 0.

16. The compound of Claim 1 wherein n is 1.

17. The compound of Claim 1 wherein n is 2.

18. A compound which is selected from the group consisting of:
   7-[4-{3-hydroxy-2-methyl-4-(3-methyl-butyryl)phenoxyl-butoxy}-chromen-2-one;
   1-[2-hydroxy-3-methyl-4-(4-phenoxy-butoxy)-phenyl]-3-methyl-butan-1-one;
   1-[3-bromo-2-hydroxy-4-(4-phenoxy-butoxy)-phenyl]-3-methyl-butan-1-one;
   1-[2-hydroxy-3-methyl-4-[4-(pyridin-3-yloxy)-butoxy]-phenyl]-3-methyl-butan-1-one;
   1-[2-hydroxy-3-methyl-4-[4-(pyridin-2-yloxy)-butoxy]-phenyl]-3-methyl-butan-1-one;
   1-[2-hydroxy-3-methyl-4-[4-(pyridin-4-yloxy)-butoxy]-phenyl]-3-methyl-butan-1-one;
   1-[2-hydroxy-3-methyl-4-[3-(pyridin-3-yloxy)-propoxy]-phenyl]-3-methyl-butan-1-one;
   1-[2-hydroxy-4-[4-(2-methoxy-phenoxyl)-butoxy]-3-methyl-phenyl]-3-methyl-butan-1-one;
   7-[4-{3-bromo-3-hydroxy-4-(3-methyl-butyryl)phenoxyl-butoxy}-chromen-2-one;
   1-[3-bromo-2-hydroxy-4-(4-pyridin-3-yloxy)-butoxy]-phenyl]-3-methyl-butan-1-one;
   1-[2-hydroxy-3-methyl-4-[5-(pyridin-3-yloxy)-pentyl]-phenyl]-3-methyl-butan-1-one;
   1-[4-{4-(5-chloro-pyridin-3-yloxy)-butoxy]-2-hydroxy-3-methyl-phenyl]-3-methyl-butan-1-one;
1-{4-[4-(3-fluoro-phenoxy)-butoxy]-2-hydroxy-3-methyl-phenyl}-3-methyl-butano-1-one;
1-{2-hydroxy-3-methyl-4-[4-(3-trifluoromethyl-phenoxy)-butoxy]-phenyl}-3-methyl-butano-1-one;
5 1-{2-hydroxy-4-[4-(4-methoxy-phenoxy)-butoxy]-3-methyl-phenyl}-3-methyl-butano-1-one;
1-{4-[4-(3-chloro-phenoxy)-butoxy]-2-hydroxy-3-methyl-phenyl}-3-methyl-butano-1-one;
1-{2-hydroxy-3-methyl-4-[4-(pyrimidin-2-ylxy)-butoxy]-phenyl}-3-methyl-butano-1-one;
10 1-{4-[4-(2-fluoro-phenoxy)-butoxy]-2-hydroxy-3-methyl-phenyl}-3-methyl-butano-1-one;
1-{4-[4-(2,3-difluoro-phenoxy)-butoxy]-2-hydroxy-3-methyl-phenyl}-3-methyl-butano-1-one;
15 1-{2-hydroxy-4-[2-(isoquinolin-7-ylxy)-ethoxy]-3-methyl-phenyl}-3-methyl-butano-1-one;
1-{2-hydroxy-3-methyl-4-[4-(naphthalen-2-ylxy)-butoxy]-phenyl}-3-methyl-butano-1-one;
1-{4-[4-(2,3-dihydro-1H-inden-5-ylxy)butoxy]-2-hydroxy-3-methylphenyl}-3-methyl-butano-1-one;
20 6-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butoxy} indan-1-one;
1-(3-bromo-2-hydroxy-4-{[3-(pyridin-3-ylxy)benzyl]oxy} phenyl)-3-methylbutano-1-one;
25 1-{2-hydroxy-3-methyl-4-[4-(4-pyridin-4-ylpiperazin-1-yl)butoxy]phenyl}-3-methyl-butano-1-one;
1-{2-hydroxy-3-methyl-4-[4-(4-pyridin-2-ylpiperazin-1-yl)butoxy]phenyl}-3-methyl-butano-1-one;
1-{4-[4-(3,4-dihydroisoquinolin-2(1H)-yl)butoxy]-2-hydroxy-3-methyl-phenyl}-3-methyl-butano-1-one;
30 7-3-{[2-bromo-3-hydroxy-4-(3-methylbutanoyl)phenoxy]methyl}phenoxy)-2H-chromen-2-one;
1-{3-bromo-4-[4-(2,3-difluorophenoxy)butoxy]-2-hydroxyphenyl}-3-methyl-butano-1-one;

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1-[2-hydroxy-3-methyl-4-(4-{methyl[(6-methylpyridin-2-yl)methyl]amino}butoxy)phenyl]-3-methylbutan-1-one;
7-[4-{3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy}butoxy]-4-methyl-2H-chromen-2-one;
5
7-[4-{3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy}butoxy]-4-(trifluoromethyl)-2H-chromen-2-one;
1-[2-hydroxy-3-methyl-4-[4-(2-pyridin-2-yl-1H-benzimidazol-1-yl)butoxy]phenyl]-3-methylbutan-1-one;
1-[2-hydroxy-4-[4-(1H-imidazo[4,5-b]pyridin-1-yl)butoxy]-3-methylphenyl]-3-methylbutan-1-one;
1-(4-{4-{[(2-chloropyridin-3-yl)oxy]butoxy}-2-hydroxy-3-methylphenyl)-3-methylbutan-1-one;
1-(2-hydroxy-3-methyl-4-{4-[(2-methylpyridin-3-yl)oxy]butoxy}phenyl)-3-methylbutan-1-one;
1-[4-{4-{[(2-dimethylamino)methyl]pyridin-3-yl}oxy]butoxy]-2-hydroxy-3-methylphenyl]-3-methylbutan-1-one;
6-[4-{3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy}butoxy]-4-methyl-2H-chromen-2-one;
7-[4-{3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy}butoxy]-3,4,8-trimethyl-2H-chromen-2-one;
1-(2-hydroxy-3-methyl-4-{4-[(6-methylpyridin-3-yl)oxy]butoxy}phenyl)-3-methylbutan-1-one;
1-(2-hydroxy-3-methyl-4-{4-{4-(1,3,4-oxadiazol-2-yl)phenoxy}butoxy}phenyl)-3-methylbutan-1-one;
2,3-difluoro-4-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butoxy}benzonitrile;
1-[2-hydroxy-3-methyl-4-{4-{pentfluorophenoxy}butoxy}phenyl]-3-methylbutan-1-one;
1-[2-hydroxy-3-methyl-4-{4-(2,3,5,6-tetrafluorophenoxy)butoxy}phenyl]-3-methylbutan-1-one;
1-(2-hydroxy-3-methyl-4-{4-{[5-methylpyridin-3-yl]oxy}butoxy}phenyl)-3-methylbutan-1-one;
1-(2-hydroxy-3-methyl-4-{4-{(2,3,4-trifluorophenoxy)butoxy}phenyl}-3-methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[4-(2,3,6-trifluorophenoxy)butoxy]phenyl}-3-methylbutan-1-one;
1-{2-hydroxy-4-{4-[(2-iodopyridin-3-yl)oxy]butoxy}-3-methylphenyl}-3-methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-{4-(5,6,7,8-tetrahydroquinolin-3-yloxy)butoxy]phenyl}-3-methylbutan-1-one;
7-{3-[2-bromo-3-hydroxy-4-(3-methylbutanoyl)phenoxy]propoxy}2H-chromen-2-one;
1-{3-bromo-2-hydroxy-4-[4-(2-pyridin-2-yl-1H-benzimidazol-1-yl)butoxy]phenyl}-3-methylbutan-1-one;
1-{4-{4-[(2,6-dimethylpyridin-3-yl)oxy]butoxy}-2-hydroxy-3-methylphenyl}-3-methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[4-(pyridin-4-ythio)butoxy]phenyl}-3-methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[4-(4-pyrimidin-2-yl)piperazin-1-yl)butoxy]phenyl}-3-methylbutan-1-one;
1-{4-[4-(2,3-dichlorophenoxy)butoxy]-2-hydroxy-3-methylphenyl}-3-methylbutan-1-one;
1-{3-bromo-2-hydroxy-4-[4-(5,6,7,8-tetrahydroquinolin-3-yloxy)butoxy]phenyl}-3-methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[4-{3-(pyridin-2-ylphenoxy)butoxy}phenyl}-3-methylbutan-1-one;
methyl-3-({2-hydroxy-4-[4-{3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy)butoxy}phenyl}propanoate;
1-{2-hydroxy-3-methyl-4-[4-2-(1,3-thiazol-4-yl)-1H-benzimidazol-1-yl)butoxy]phenyl}-3-methylbutan-1-one;
1-{4-{4-[3-fluorophenyl]thio)butoxy}-2-hydroxy-3-methylphenyl}-3-methylbutan-1-one;
5-{3-[4-Acetyl-3-hydroxy-2-propylphenoxy)methyl]phenoxy}pyridine-2-carbonitrile;
1-{2-hydroxy-3-methyl-4-[4-(4-pyridin-2-ylphenoxy)butoxy]phenyl}-3-methylbutan-1-one;
1-{4-[4-(1H-benzimidazol-1-yl)butoxy]-2-hydroxy-3-methylphenyl}-3-methylbutan-1-one;
(1-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butyl}-1H-benzimidazol-2-yl)acetonitrile;
1-{2-hydroxy-3-methyl-4-[4-[2-(trifluoromethyl)-1H-benzimidazol-1-yl]butoxy]phenyl}-3-methylbutan-1-one;
1-{3-[(4-acetyl-3-hydroxy-2-propylphenoxy)methyl]benzyl}azetidine-3-carbonitrile;
1-{4-[4-(1,3-benzothiazol-2-ylthio)butoxy]-2-hydroxy-3-methylphenyl}-3-methylbutan-1-one;
1-{4-[6-chloro-1,3-benzoxazol-2-yl]thiobutoxy]-2-hydroxy-3-methylphenyl}-3-methylbutan-1-one;
1-[2-hydroxy-3-methyl-4-[4-(2-phenyl-1H-imidazol-1-yl)butoxy]phenyl]-3-methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[4-(2-phenyl-1H-benzimidazol-1-yl)butoxy]phenyl}-3-methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[4-[1-methyl-1H-tetrazol-5-yl]thiobutoxy]phenyl}-3-methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[4-(quinolin-3-yl)oxy]butoxy]phenyl}-3-methylbutan-1-one;
1-{4-[4-(1,3-benzoxazol-2-ylthio)butoxy]-2-hydroxy-3-methylphenyl}-3-methylbutan-1-one;
1-{4-[4-(5-chloro-1,3-benzoxazol-2-yl)thiobutoxy]-2-hydroxy-3-methylphenyl}-3-methylbutan-1-one;
1-{2-hydroxy-4-[4-(1H-indol-1-yl)butoxy]-3-methylphenyl}-3-methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[4-(7H-purin-6-ylthio)butoxy]phenyl}-3-methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[4-(2-phenyl-1H-indol-1-yl)butoxy]phenyl}-3-methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[4-(5-pyridin-4-ylsulfonyl)butoxy]phenyl}-3-methylbutan-1-one;

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1-{2-hydroxy-3-methyl-4-[4-(pyridin-3-ylthio)butoxy]phenyl}-3-
methylbutan-1-one;
3'-(4-Acetyl-3-hydroxy-2-propylphenoxy)methyl)bisphenyl-2-carbonitrile;
1-hydroxy-3-[4-[3-hydroxy-2-methyl-4-(3-
methylbutanoyl)phenoxy]butoxy]pyridinium;
1-{2-hydroxy-3-methyl-4-[4-(4-methyl-2-phenyl-1H-imidazol-1-
yl)butoxy]phenyl}-3-methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[4-[2-(methylthio)-1H-benzimidazol-1-
yl]butoxy]phenyl}-3-methylbutan-1-one;
1-{3-bromo-4-[4-{(6-chloro-1,3-benoxazol-2-yl)thio]butoxy}-2-
hydroxyphenyl}-3-methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[4-[1-oxidopyridin-2-yl]thio]butoxy]phenyl}-3-
methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[4-(pyridin-2-ylthio)butoxy]phenyl}-3-
methylbutan-1-one;
1-{4-{4-[2-(2-chlorophenyl)-1H-benzimidazol-1-yl]butoxy}-2-hydroxy-3-
methylphenyl}-3-methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[4-{(1-oxidopyridin-2-yl)thio]butoxy}phenyl}-3-
methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[5-{2-phenyl-1H-benzimidazol-1-
yl}pentyloxy]phenyl}-3-methylbutan-1-one;
7-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butoxy}chroman-2-
one;
1-{2-hydroxy-3-methyl-4-[4-[4-(3-oxobutyl)phenoxy]butoxy]phenyl}-3-
methylbutan-1-one;
1-{2-hydroxy-3-methyl-4-[[3-(pyridin-4-ylthio)benzyl]oxy]phenyl}-3-
methylbutan-1-one;
1-{4-{4-{[2-(2-fluorophenyl)-1H-benzimidazol-1-yl]oxy}butoxy}-2-hydroxy-
3-methylphenyl]-3-methylbutan-1-one;
1-{4-{4-[[2-(4-fluorophenyl)-1H-benzimidazol-1-yl]oxy}butoxy}-2-hydroxy-
3-methylphenyl]-3-methylbutan-1-one;
1-{4-{4-[[2-(2,4-dichlorophenyl)-1H-benzimidazol-1-yl]oxy}butoxy}-2-hydroxy-3-
methylphenyl]-3-methylbutan-1-one;
1-{4-{4-{[2-(3-chlorophenyl)-1H-benzimidazol-1-yl]oxy}butoxy}-2-hydroxy-
3-methylphenyl]-3-methylbutan-1-one;
7-{4-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]butoxy}-2,3-
dihydro-4H-chromen-4-one;
1-(2-hydroxy-4-{4-[3-hydroxypropyl]phenoxy}butoxy)-3-methylphenyl-
3-methylbutan-1-one;
5
methyl 3-(4-{4-[3-hydroxy-2-methyl-4-(3-
methylbutanoyl)phenoxy]butoxy}phenyl)-propanoate;
1-(2-hydroxy-4-[2-(6-hydroxy-1-benzofuran-3-yl)ethoxy]-3-methylphenyl)-
3-methylbutan-1-one;
methyl 2-hydroxy-4-{4-[3-hydroxy-2-methyl-4-(3-
methylbutanoyl)phenoxy]butoxy}-benzoate;
ethyl 7-{4-[3-hydroxy-2-methyl-4-(3-
methylbutanoyl)phenoxy]butoxy}chromane-2-carboxylate;
1-[3-chloro-2,4-bis[4-(pyridin-4-ylthio)butoxy]phenyl]-3-methylbutan-1-
one;
1-[3-bromo-2-hydroxy-4-{4-(pyridin-4-ylthio)butoxy]phenyl}-3-
methylbutan-1-one;
1-(2-hydroxy-3-methyl-4-{4-(pyridin-4-ylthio)butoxy]phenyl}-3,3-
dimethylbutan-1-one;
1-[2-hydroxy-3-methyl-4-{3-[4-(pyridin-4-ylthio)methyl]benzyl}oxy]phenyl]-
3-methylbutan-1-one;
1-(2-hydroxy-3-methyl-4-{4-[2-phenyl-1H-benzimidazol-1-
yl]oxy}butoxy]phenyl)-3,3-dimethylbutan-1-one;
1-(2-hydroxy-3-methyl-4-{4-(pyridin-4-ylthio)benzyl}oxy]phenyl)-3-
methylbutan-1-one;
25
1-{2-hydroxy-4-{4-(3-hydroxyphenoxy)butoxy]-3-methylphenyl]-3-
methylbutan-1-one;
1-{4-[4-(3,4-dihydro-2H-chromen-7-yl)oxy]butoxy]-2-hydroxy-3-
methylphenyl]-3-methylbutan-1-one;
1-(2-hydroxy-3-methyl-4-{4-(pyridin-4-ylthio)benzyl}oxy]phenyl)-3,3-
dimethylbutan-1-one;
1-(3-bromo-2-hydroxy-4-{4-(pyridin-4-ylthio)benzyl}oxy]phenyl)-3-
methylbutan-1-one;
1-(2-hydroxy-3-methyl-4-{3-(pyridin-4-ylthio)benzyl}oxy]phenyl)-3,3-
dimethylbutan-1-one;
3’-[4-(3,3-dimethylbutanoyl)-3-hydroxy-2-methylphenoxy]methyl]biphenyl-3-carboxamide;
1-(3-bromo-2-hydroxy-4-[(2-phenyl-1H-benzimidazol-1-yl)oxy]butoxy)phenyl]-3-methylbutan-1-one;
1-[2-hydroxy-3-methyl-4-[(4-[(pyridin-4-ythio)methyl]benzyl]oxy]phenyl]-3-methylbutan-1-one;
1-[2-hydroxy-4-[(3-methoxy-4-[(pyridin-4-ythio)methyl]benzyl]oxy]-3-methylphenyl]-3-methylbutan-1-one;
1-(2-hydroxy-3-methyl-4-[(2-(pyridin-4-ythio)benzyl]oxy)phenyl]-3-methylbutan-1-one;
1-(2-hydroxy-3-methyl-4-[(2-methylpyridin-4-yl)thio]butoxy)phenyl]-3-methylbutan-1-one;
1-(2-hydroxy-3-methyl-4-[(3-(pyridin-3-ylamino)benzyl]oxy)phenyl]-3-methylbutan-1-one;
1-[2-hydroxy-3-methyl-4-[(3-(pyridin-4-ythio)methyl]benzyl]oxy)phenyl]-3,3-dimethylbutan-1-one;
1-(2-hydroxy-3-methyl-4-[(3-(pyridin-2-ylamino)benzyl]oxy)phenyl]-3-methylbutan-1-one;
1-(2-hydroxy-3-methyl-4-[(3-(pyridin-4-ylamino)benzyl]oxy)phenyl]-3-methylbutan-1-one;
1-[2-hydroxy-4-[(4-(1H-indazol-5-yloxy)butoxy]-3-methylphenyl]-3-methylbutan-1-one;
1-[2-hydroxy-4-[(4-(1H-indazol-6-yloxy)butoxy]-3-methylphenyl]-3-methylbutan-1-one;
1-[2-hydroxy-4-[(1H-indol-4-yloxy)butoxy]-3-methylphenyl]-3-methylbutan-1-one;
1-[2-hydroxy-4-[(1H-indol-5-yloxy)butoxy]-3-methylphenyl]-3-methylbutan-1-one;
1-[2-hydroxy-4-[(1H-indol-6-yloxy)butoxy]-3-methylphenyl]-3-methylbutan-1-one;
ethyl 5-[(3-[3-hydroxy-2-methyl-4-(3-methylbutanoyl)phenoxy]methyl]phenyl]amino]-2-methoxybenzoate;
1-[2-hydroxy-4-[(3-[3-methoxyphenyl]amino)benzyl]oxy]-3-methylphenyl]-3-methylbutan-1-one;
1-[4-((3-ethoxyphenyl)amino)benzyl]oxy)-2-hydroxy-3-methylphenyl]-3-methylbutan-1-one;
1-[2-hydroxy-4-((3-isopropylphenyl)amino)benzyl]oxy)-3-methylphenyl]-3-methylbutan-1-one;
1-[2-hydroxy-3-methyl-4-((3-[methyl(pyridin-2-yl)amino]benzyl)oxy)phenyl]-3-methylbutan-1-one;
1-[(benzyl]oxy)-3-methyl-4-[4-(pyridin-4-ylthio)butoxy]phenyl]-3-methylbutan-1-one;
and pharmaceutically acceptable salts thereof.

19. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

20. A method for potentiation of metabotropic glutamate receptor activity in a mammal which comprises the administration of an effective amount of the compound of Claim 1.

21. A method for the manufacture of a medicament for potentiation of metabotropic glutamate receptor activity in a mammal comprising combining the compound of Claim 1 with a pharmaceutical carrier or diluent.

22. A method for treating, controlling, ameliorating or reducing the risk of a neurological and psychiatric disorders associated with glutamate dysfunction in a mammalian patient in need of such which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

23. A method for treating, controlling, ameliorating or reducing the risk of anxiety in a mammalian patient in need of such which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

24. A method for treating, controlling, ameliorating or reducing the risk of depression in a mammalian patient in need of such which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.
25. A method for treating, controlling, ameliorating or reducing the risk of migraine in a mammalian patient in need of such which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

26. A method for treating, controlling, ameliorating or reducing the risk of schizophrenia in a mammalian patient in need of such which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.

27. A method for treating, controlling, ameliorating or reducing the risk of epilepsy in a mammalian patient in need of such which comprises administering to the patient a therapeutically effective amount of a compound of Claim 1.