(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
16 November 2006 (16.11.2006)

PCT

(10) International Publication Number
WO 2006/120125 A1

(51) International Patent Classification:
C07C 243/38 (2006.01) *A61K 31/166* (2006.01)
C07C 255/56 (2006.01) *A61K 31/277* (2006.01)
C07D 333/38 (2006.01) *A61K 31/4409* (2006.01)
C07D 307/68 (2006.01) *A61K 31/341* (2006.01)
C07D 213/56 (2006.01) *A61K 31/381* (2006.01)
A61P 3/00 (2006.01)

(21) International Application Number:
PCT/EP2006/061900

(22) International Filing Date: 27 April 2006 (27.04.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/679,521 10 May 2005 (10.05.2005) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

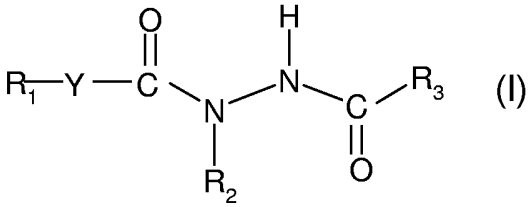
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/120125 A1

(54) Title: DIACYLGLYCEROL ACYLTRANSFERASE INHIBITORS



(I)

(57) Abstract: Provided herein are compounds of the formula (I), as well as pharmaceutically acceptable salts thereof, wherein the substituents are as those disclosed in the specification. These compounds, and the pharmaceutical compositions containing them, are useful for the treatment of diseases such as, for example, obesity, type II diabetes mellitus and metabolic syndrome.

DIACYLGLYCEROL ACYLTRANSFERASE INHIBITORS

The invention relates to inhibitors of diacylglycerol acyltransferase. The inhibitors include, for example, phenyl acrylic and propionic acid derivatives and are useful for the treatment of diseases such as obesity, type II diabetes mellitus and metabolic syndrome.

Triglycerides or triacylglycerols are the major form of energy storage in eukaryotic organisms. In mammals, these compounds are primarily synthesized in three tissues: the small intestine, liver and adipocytes. Triglycerides or triacylglycerols support the major functions of dietary fat absorption, packaging of newly synthesized fatty acids, and storage in fat tissue (see Subauste and Burant, Current Drug Targets – Immune, Endocrine & Metabolic Disorders (2003) 3, 263-270).

Diacylglycerol O-acyltransferase, also known as diglyceride acyltransferase or DGAT, is a key enzyme in triglyceride synthesis. DGAT catalyzes the final and rate-limiting step in triacylglycerol synthesis from 1,2-diacylglycerol (DAG) and long chain fatty acyl CoA as substrates. Thus, DGAT plays an essential role in the metabolism of cellular diacylglycerol and is critically important for triglyceride production and energy storage homeostasis (see Mayorek et al, European Journal of Biochemistry (1989) 182, 395-400).

DGAT has a specificity for sn-1,2 diacylglycerols and will accept a wide variety of fatty acyl chain lengths (see Farese et al, Current Opinions in Lipidology (2000) 11, 229-234). DGAT activity levels increase in fat cells as they differentiate *in vitro* and recent evidence suggests that DGAT may be regulated in adipose tissue post-transcriptionally (see Coleman et al, Journal of Molecular Biology (1978) 253, 7256-7261 and Yu et al, Journal of Molecular Biology (2002) 277, 50876-50884). DGAT activity is primarily expressed in the endoplasmic reticulum (see Colman, Methods in Enzymology (1992) 209, 98-104). In hepatocytes, DGAT activity has been shown to be expressed on both the cytosolic and luminal surfaces of the endoplasmic reticular membrane (see Owen et al, Biochemical Journal (1997) 323 (pt 1), 17-21 and Waterman et al, Journal of Lipid Research (2002) 43, 1555-156). In the liver, the regulation of triglyceride synthesis and partitioning, between retention as cytosolic droplets and secretion, is of primary importance in determining the rate of VLDL production (see Shelness and Sellers,

Current Opinions in Lipidology (2001) 12, 151-157 and Owen et al, Biochemical Journal (1997) 323 (pt 1), 17-21).

Two forms of DGAT were cloned and designated DGAT1 and DGAT2 (see Cases et al, Proceedings of the National Academy of Science, USA (1998) 95, 13018-13023, Lardizabal et al, Journal of Biological Chemistry (2001) 276, 38862-38869 and Cases et al, Journal of Biological Chemistry (2001) 276, 38870-38876). Although both enzymes utilize the same substrates, there is no homology between DGAT1 and DGAT2. Further, although both enzymes are widely expressed, differences exist in the relative abundance of DGAT1 and DGAT2 expression in various tissues.

The gene encoding mouse DGAT1 has been used to create DGAT knock-out mice. These mice, although unable to express a functional DGAT enzyme (*Dgat-/-* mice), are viable and continue to synthesize triglycerides (see Smith et al, Nature Genetics (2000) 25, 87-90). This would suggest that multiple catalytic mechanisms contribute to triglyceride synthesis, such as DGAT2. An alternative pathway has also been shown to form triglycerides from two diacylglycerols by the action of diacylglycerol transacylase (see Lehner and Kuksis, Progress in Lipid Research (1996) 35, 169-210).

Dgat-/- mice are resistant to diet-induced obesity and remain lean. When fed a high fat diet, Dgat-/- mice maintain weights comparable to mice fed a diet with regular fat content. Dgat-/- mice also have lower tissue triglyceride levels. The resistance to weight gain seen in the knockout mice, which have a slightly higher food intake, is due to an increased energy expenditure and increased sensitivity to insulin and leptin (see Smith et al, Nature Genetics (2000) 25, 87-90, Chen and Farese, Trends in Cardiovascular Medicine (2000) 10, 188-192, Chen and Farese, Current Opinions in Clinical Nutrition and Metabolic Care (2002) 5, 359-363 and Chen et al, Journal of Clinical Investigation (2002) 109, 1049-1055). Dgat-/- mice have reduced rates of triglyceride absorption, improved triglyceride metabolism, and improved glucose metabolism, with lower glucose and insulin levels following a glucose load, in comparison to wild-type mice (see Buhman et al, Journal of Biological Chemistry (2002) 277, 25474-25479 and Chen and Farese, Trends in Cardiovascular Medicine (2000) 10, 188-192).

Disorders or imbalances in triglyceride metabolism, both absorption as well as de novo synthesis, have been implicated in the pathogenesis of a variety of diseases risk. These include obesity, insulin resistance syndrome, type II diabetes, metabolic syndrome (syndrome X) and coronary heart disease (see Kahn, Nature Genetics (2000) 25, 6-7, Yanovski and Yanovski, New England Journal of Medicine (2002) 346, 591-602, Lewis et al, Endocrine Reviews (2002) 23, 201, Brazil, Nature Reviews Drug Discovery (2002) 1, 408, Malloy and Kane, Advances in Internal Medicine (2001) 47, 111, Subauste and

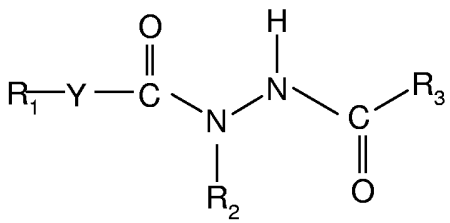
Burant, Current Drug Targets – Immune, Endocrine & Metabolic Disorders (2003) 3, 263-270 and Yu and Ginsberg, Annals of Medicine (2004) 36, 252-261). Compounds that can decrease the synthesis of triglycerides from diacylglycerol by inhibiting or lowering the activity of the DGAT enzyme would be of value as therapeutic agents for the treatment diseases associated with abnormal metabolism of triglycerides.

Known inhibitors of DGAT include: dibenzoxazepinones (see Ramharack, et al, EP 1219716 and Burrows et al, 26th National Medicinal Chemistry Symposium (1998) poster C-22), substituted amino-pyrimidino-oxazines (see Fox et al, WO 2004047755), chalcones such as xanthohumol (see Tabata et al, Phytochemistry (1997) 46, 683-687 and Casaschi et al, Journal of Nutrition (2004) 134, 1340-1346), and substituted benzyl-phosphonates (see Kurogi et al, Journal of Medicinal Chemistry (1996) 39, 1433-1437, Goto, et al, Chemistry and Pharmaceutical Bulletin (1996) 44, 547-551, Ikeda, et al, Thirteenth International Symposium on Athersclerosis (2003), abstract 2P-0401, and Miyata, et al, JP 2004067635).

Also known to be inhibitors of DGAT are: 2-bromo-palmitic acid (see Colman et al, Biochimica et Biophysica Acta (1992) 1125, 203-9), 2-bromo-octanoic acid (see Mayorek and Bar-Tana, Journal of Biological Chemistry (1985) 260, 6528-6532), roselipins (see Noriko et al, (Journal of Antibiotics (1999) 52, 815-826), amidepsin (see Tomoda et al, Journal of Antibiotics (1995) 48, 942-7), isochromophilone, prenylflavonoids (see Chung et al, Planta Medica (2004) 70, 258-260), polyacetylenes (see Lee et al, Planta Medica (2004) 70, 197-200), cochlioquinones (see Lee et al, Journal of Antibiotics (2003) 56, 967-969), tanshinones (see Ko et al, Archives of Pharmaceutical Research (2002) 25, 446-448), gemfibrozil (see Zhu et al, Atherosclerosis (2002) 164, 221-228), and substituted quinolones (see Ko, et al, Planta Medica (2002) 68, 1131-1133).

A need exits in the art, however, for additional DGAT inhibitors that have efficacy for the treatment of metabolic disorders such as, for example, obesity, type II diabetes mellitus and metabolic syndrome. Further, a need exists in the art for DGAT inhibitors having IC_{50} values less than about 1 μM.

In an embodiment of the present invention, a compound of the formula (I) is provided:

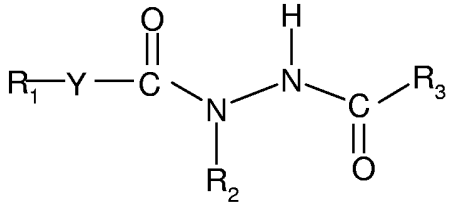


I

In another embodiment of the present invention, a method for the treatment of obesity, type II diabetes or metabolic syndrome in a patient in need thereof is provided, which comprises administering to said patient a therapeutically effective amount of a compound of the formula (I).

In a further embodiment of the present invention, a pharmaceutical composition is provided having a therapeutically effective amount of a compound or a pharmaceutically acceptable salt or ester thereof according to the compound of formula (I) above, and a pharmaceutically acceptable carrier.

The present invention pertains to DGAT inhibitors that are derivatives of, for example, phenyl acrylic and propionic acid. In a preferred embodiment, the invention provides compounds of the formula I

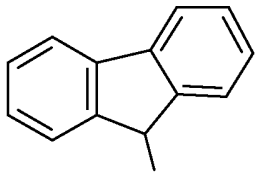


I

wherein

Y is (C_1-C_6) alkylene or (C_1-C_6) alkylene substituted with aryl;

R_1 is substituted or unsubstituted aryl or



;

R_2 is (C_1-C_6) alkyl;

R_3 is unsubstituted aryl,
substituted aryl with a group independently selected from the group consisting of halogen, (C_1-C_6) alkyl, and $-O(CH_2)_mOCH_3$,
unsubstituted saturated, unsaturated or partially saturated heterocycyl which is a 5- or 6- membered heteroaromatic ring connected by a ring carbon atom which has from 1 to 3 hetero ring atoms selected from the group consisting of S, N and O,
substituted saturated, unsaturated or partially saturated heterocycyl substituted with (C_1-C_6) alkyl, or
substituted or unsubstituted 5-10-membered cycloalkyl ring; and

m is 0, 1, 2 or 3,

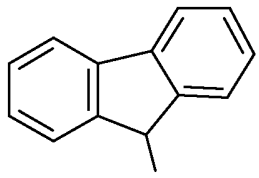
as well as pharmaceutically acceptable salts thereof.

Preferably, Y is (C_1-C_6) alkylene or (C_1-C_6) alkylene substituted with aryl, more preferably Y is CH=CH, $(CH_2)_n$, or –CH(Ar)CH_2, wherein n is 1 or 2. Ar means aryl, more preferably Ar means phenyl. Especially preferred is a compound of formula I, wherein Y is $(CH_2)_n$ and n is 2.

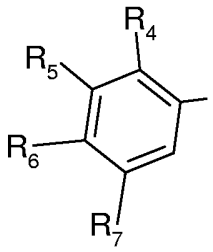
Also preferred is a compound of formula I, wherein

R_1 is unsubstituted aryl or substituted aryl with a group independently selected from the group consisting of H, (C_1-C_6) alkyl, halogen,
unsubstituted aryl,
aryl which is mono-, di- or tri-substituted with a group independently selected from the group consisting of halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, $-CF_3$, $-OCF_3$, $-SCH_3$, $-CN$, $-SO_2CH_3$, $-NO_2$, and $-(CH)_2Ar$, $-O$-phenyl, $-O(CH_2)_pCH_3$, or
unsubstituted or substituted 4-10 membered cycloalkyl ring attached to the aryl ring by oxygen or methyloxy;

and p is 0, 1, 2, or 3; or

R_1 is  .

In another preferred embodiment, R_1 is



wherein R_4 is H, (C_1-C_6) alkyl, unsubstituted aryl, aryl which is mono-, di- or tri-substituted with a group independently selected from the group consisting of halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, $-O(CH)(CH_3)_2$, $-CF_3$, $-O(CH_2)_mCH_3$, $-OCF_3$, $-SCH_3$, -

$CH(CH_3)_2$, -CN, $-SO_2CH_3$, $-NO_2$, and $-(CH)_2Ar$, O-phenyl, $-O(CH_2)_pCH_3$, or unsubstituted or substituted 4-10 membered cycloalkyl ring attached to the aryl ring by oxygen or methyloxy;

R_5, R_6, R_7 independently of each other are H, halogen, phenyl or (C_1-C_6) alkyl; and p is 0, 1, 2 or 3.

In a preferred embodiment, R_4 is selected from the group consisting of -O-phenyl, $-O(CH_2)_pCH_3$, or an unsubstituted or substituted 4-10 membered cycloalkyl ring attached to the aryl ring by oxygen or methyloxy; and p is 1, 2, or 3.

Especially preferred is a compound of formula I, wherein R_4 is a cyclopentyloxy or cyclobutylmethoxy group.

In another preferred embodiment, R_4 is phenyl which is mono-, di- or tri-substituted with a group independently selected from the group consisting of halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, $-CF_3$ and –CN.

Most preferably, R_2 is isopropyl.

In one preferred embodiment, R_3 is unsubstituted phenyl or substituted phenyl with a group independently selected from the group consisting of halogen, (C_1-C_6) alkyl, and $–O(CH_2)_mOCH_3$, and m is 0, 1, 2, or 3.

More preferably, R_3 is phenyl.

In another preferred embodiment, R_3 is a 5- or 6- membered heteroaromatic ring connected by a ring carbon atom which has from 1 to 3 hetero ring atoms selected from the group consisting of S, N and O and which is unsubstituted or substituted with (C_1-C_6) alkyl.

More preferably, R_3 is a 5- or 6- membered heteroaromatic ring selected from the group consisting of thiophene, furane and pyridine.

Especially preferred is a compound of formula I, wherein R_1 and R_3, independently of each other, are phenyl.

More preferably, compounds of formula I according to the present invention are selected from the group consisting of

benzoic acid N'-[3-biphenyl-2-yl-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'- isopropyl-N'-[3-(3'-trifluoromethyl-biphenyl-2-yl)-propionyl]-hydrazide,

benzoic acid N'-[3-(3'-ethoxy-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(3'-cyano-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(5'-chloro-2'-methoxy-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'- isopropyl-N'-[3-(3'-nitro-biphenyl-2-yl)-propionyl]-hydrazide,

benzoic acid N'-[3-(3'-chloro-4'-fluoro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(5'-isopropyl-2'-methoxy-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2',5'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(5'-fluoro-2'-methoxy-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(3'-isopropyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(4'-fluoro-2'-methyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-isopropyl-N'-[3-(3'-methyl-biphenyl-2-yl)-propionyl]-hydrazide,

benzoic acid N'-isopropyl-N'-[3-(3'-methoxy-biphenyl-2-yl)-propionyl]-hydrazide,

benzoic acid N'-[3-(3'-chloro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(3'-fluoro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2'-fluoro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-isopropyl-N'-[3-(2'-methyl-biphenyl-2-yl)-propionyl]-hydrazide,

benzoic acid N'-[3-(2'-chloro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(4'-chloro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-isopropyl-N'-[3-(2'-methoxy-biphenyl-2-yl)-propionyl]-hydrazide,

benzoic acid N'-isopropyl-N'-[3-(4'-methoxy-biphenyl-2-yl)-propionyl]-hydrazide,

benzoic acid N'-[3-(4'-fluoro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-biphenyl-3-yl-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-biphenyl-4-yl-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-(2-9H-fluoren-9-yl-acetyl)-N'-isopropyl-hydrazide,

benzoic acid N'-(3,3-diphenyl-propionyl)-N'-isopropyl-hydrazide,

benzoic acid N'-isopropyl-N'-[3-(2-phenoxy-phenyl)-propionyl]-hydrazide,

benzoic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-acryloyl]-N'-isopropyl-hydrazide,

2-(2-methoxy-ethoxy)-benzoic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

4-(2-methoxy-ethoxy)-benzoic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

thiophene-2-carboxylic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

thiophene-3-carboxylic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

furan-2-carboxylic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

furan-3-carboxylic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

isonicotinic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(5-fluoro-2-propoxy-phenyl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2-butoxy-5-fluoro-phenyl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2-cyclopentyloxy-5-fluoro-phenyl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2- cyclobutylmethoxy-5-fluoro-phenyl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(3-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide,

and all pharmaceutically acceptable salts thereof.

Most preferably, the compound of formula I is selected from the group consisting of

benzoic acid N'-isopropyl-N'-[3-(3'-methoxy-biphenyl-2-yl)-propionyl]-hydrazide,

benzoic acid N'-[3-(2-cyclopentyloxy-5-fluoro-phenyl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(3'-chloro-4'-fluoro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2'-chloro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2',5'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2-butoxy-5-fluoro-phenyl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(5'-isopropyl-2'-methoxy-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-acryloyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2- cyclobutylmethoxy-5-fluoro-phenyl)-propionyl]-N'-isopropyl-hydrazide,

and all pharmaceutically acceptable salts thereof.

It is to be understood that the terminology employed herein is for the purpose of describing particular embodiments, and is not intended to be limiting. Further, although any methods, devices and materials similar or equivalent to those described herein can be used in the practice or testing of the invention, the preferred methods, devices and materials are now described.

As used herein, the term "alkyl" means, for example, a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical which may be substituted or unsubstituted. Where cyclic, the alkyl group is preferably C_3 to C_{12}-cycloalkyl, more preferably C_4 to C_{10}-cycloalkyl, more preferably C_4 to C_7-cycloalkyl. Where acyclic, the alkyl group is preferably C_1 to C_{10}-alkyl, more preferably C_1 to C_6-alkyl, more preferably methyl, ethyl, propyl (n-propyl or isopropyl), butyl (n-butyl, isobutyl or tertiary-butyl) or pentyl (including n-pentyl and isopentyl), more preferably methyl. It will be appreciated therefore that the term "alkyl" as used herein includes alkyl

(branched or unbranched), substituted alkyl (branched or unbranched), alkenyl (branched or unbranched), substituted alkenyl (branched or unbranched), alkynyl (branched or unbranched), substituted alkynyl (branched or unbranched), cycloalkyl, substituted cycloalkyl, cycloalkenyl, substituted cycloalkenyl, cycloalkynyl and substituted cycloalkynyl.

As used herein, the term "lower alkyl" means, for example, a branched or unbranched, cyclic or acyclic, saturated or unsaturated (e.g. alkenyl or alkynyl) hydrocarbyl radical wherein said cyclic lower alkyl group is C_4, C_5, C_6 or C_7 (e.g. C_4-C_7-cycloalkyl), and wherein said acyclic lower alkyl group is (C_1-C_6)-alkyl, most preferably C_1, C_2, C_3 or C_4-alkyl, and is preferably selected from methyl, ethyl, propyl (n-propyl or isopropyl) or butyl (n-butyl, isobutyl or tertiary-butyl). It will be appreciated therefore that the term "lower alkyl" as used herein includes, for example, lower alkyl (branched or unbranched), lower alkenyl (branched or unbranched), lower alkynyl (branched or unbranched), cyclololoweralkyl, cyclololoweralkenyl and cyclololoweralkynyl.

As used herein, the term "lower alkylene" or "(C_1-C_6)-alkylene" means a divalent saturated hydrocarbyl radical of one to six carbon atoms, a branched saturated divalent hydrocarbyl radical of three to six carbon atoms or an unsaturated divalent hydrocarbyl radical. (C_1-C_6)-alkylenes can be substituted by e.g. an aryl group and include, by way of example, the groups CH=CH, $(CH_2)_n$ with n being from 1 to 6, or –CH(Ar)CH_2, wherein Ar is an aryl, more preferably a phenyl group.

As used herein, the term "aryl" means, for example, a substituted or unsubstituted carbocyclic aromatic group, such as phenyl or naphthyl.

The term "heteroaryl" means a substituted or unsubstituted heteroaromatic group containing one or more, preferably one, heteroatom, such as pyridyl, pyrrolyl, furanyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl pyrazolyl, imidazolyl, triazolyl, pyrimidinyl pyridazinyl, pyrazinyl, triazinyl, indolyl, indazolyl, quinolyl, quinazolyl, benzimidazolyl, benzothiazolyl, benzisoxazolyl and benzisothiazolyl.

The alkyl , aryl and heteroaryl groups may be substituted or unsubstituted. Where substituted, there will generally be, for example, 1 to 3 substituents present, preferably 1 substituent. Substituents may include, for example: carbon-containing groups such as alkyl, aryl, arylalkyl (e.g. substituted and unsubstituted phenyl, substituted and unsubstituted benzyl); halogen atoms and halogen-containing groups such as haloalkyl (e.g. trifluoromethyl); oxygen-containing groups such as alcohols (e.g. hydroxyl, hydroxyalkyl, aryl(hydroxyl)alkyl), ethers (e.g. alkoxy, aryloxy, alkoxyalkyl, aryloxyalkyl), aldehydes (e.g. carboxaldehyde), ketones (e.g. alkylcarbonyl, alkylcarbonylalkyl,

arylcarbonyl, arylalkylcarbonyl, arycarbonylalkyl), acids (e.g. carboxy, carboxyalkyl), acid derivatives such as esters(e.g. alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, alkylcarbonyloxyalkyl), amides (e.g. aminocarbonyl, mono- or di-alkylaminocarbonyl, aminocarbonylalkyl, mono-or di-alkylaminocarbonylalkyl, arylaminocarbonyl), carbamates (e.g. alkoxycarbonylamino, arloxycarbonylamino, aminocarbonyloxy, mono- or di-alkylaminocarbonyloxy, arylminocarbonloxy) and ureas (e.g. mono- or di-alkylaminocarbonylamino or arylaminocarbonylamino); nitrogen-containing groups such as amines (e.g. amino, mono- or di-alkylamino, aminoalkyl, mono- or di-alkylaminoalkyl), azides, nitriles (e.g. cyano, cyanoalkyl), nitro; sulfur-containing groups such as thiols, thioethers, sulfoxides and sulfones (e.g. alkylthio, alkylsulfinyl, alkylsulfonyl, alkylthioalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, arylthio, arysulfinyl, arysulfonyl, arythioalkyl, arylsulfinylalkyl, arylsulfonylalkyl); and heterocyclic groups containing one or more, preferably one, heteroatom, (e.g. thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, aziridinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, hexahydroazepinyl, piperazinyl, morpholinyl, thianaphthyl, benzofuranyl, isobenzofuranyl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolinyl, isoquinolinyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxalinyl, chromenyl, chromanyl, isochromanyl, phthalazinyl and carbolinyl).

The lower alkyl groups may be substituted or unsubstituted, preferably unsubstituted. Where substituted, there will generally be, for example, 1 to 3 substitutents present, preferably 1 substituent.

As used herein, the term “saturated, unsaturated or partially saturated heterocycyl which is a 5- or 6- membered heteroaromatic ring connected by a ring carbon atom which has from 1 to 3 hetero ring atoms selected from the group consisting of S, N and O” means a 5- or 6- membered heteroaromatic ring connected by a ring carbon atom which has from 1 to 3 hetero ring atoms selected from the group consisting of S, N and O such as pyrrolyl, thienyl, furanyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, pyridyl, pyrazinyl and piperazinyl. Especially preferred are thienyl, furanyl and pyridyl.

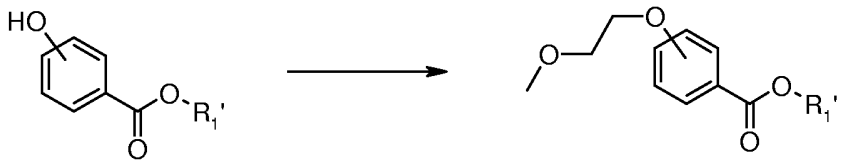
As used herein, the term “alkoxy” meansalkyl-O- wherein alkyl has the meaning as defined above..

As used herein, the term "halogen" means, for example, a fluorine, chlorine, bromine or iodine radical, preferably a fluorine, chlorine or bromine radical, and more preferably a fluorine or chlorine radical.

As used herein, the term "pharmaceutically acceptable salt" means any pharmaceutically acceptable salt of the compound of formula (I). Salts may be prepared from pharmaceutically acceptable non-toxic acids and bases including inorganic and organic acids and bases. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, dichloroacetic, formic, fumaric, gluconic, glutamic, hippuric, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, oxalic, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, oxalic, p-toluenesulfonic and the like. Particularly preferred are fumaric, hydrochloric, hydrobromic, phosphoric, succinic, sulfuric and methanesulfonic acids. Acceptable base salts include alkali metal (e.g. sodium, potassium), alkaline earth metal (e.g. calcium, magnesium) and aluminium salts.

Compounds of the present invention can be prepared beginning with commercially available starting materials and utilizing general synthetic techniques and procedures known to those skilled in the art. Outlined below are reaction schemes suitable for preparing such compounds. Further exemplification is found in the specific Examples detailed below.

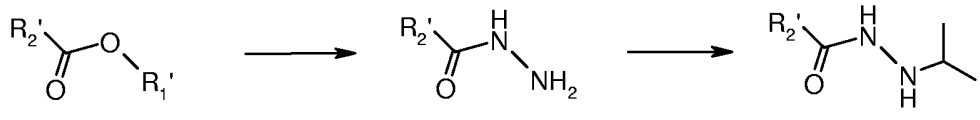
Scheme 1



i ii

As shown in Scheme 1, hydroxy-substituted benzoate esters i can be alkylated with 2-bromoethyl methyl ether by heating in the presence of potassium carbonate to give the alkoxy-ether substituted benzoate esters ii, where R_1' is lower alkyl.

Scheme 2

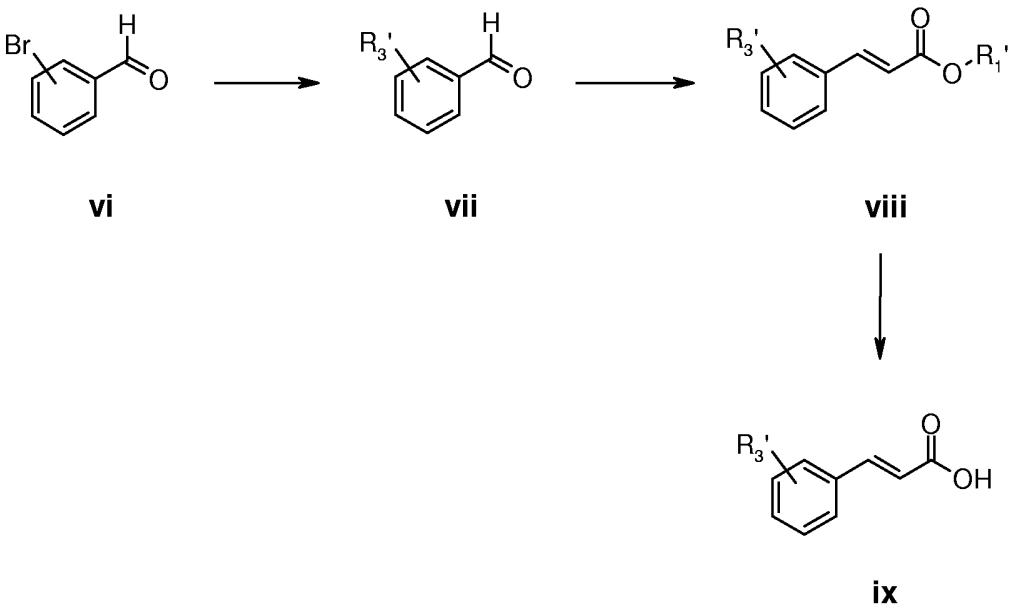


iii iv v

As shown in scheme 2, esters iii, where R_1' is lower alkyl and R_2' is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl or cycloheteroalkyl can be treated with hydrazine monohydrate in an appropriate solvent with heating to yield hydrazide iv.

Hydrazide iv can be dissolved in acetone, heated and then concentrated to dryness. The residue can be dissolved in TFA and treated with triethylsilane, with warming, to yield alkyl hydrazide v, where R_2' is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl or cycloheteroalkyl.

Scheme 3



vi vii viii

ix

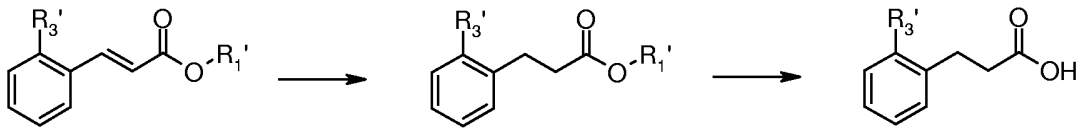
As shown in Scheme 3, using standard palladium catalyzed "cross coupling" procedures, a bromo-benzaldehyde vi can be heated, preferably in a microwave reactor, with a commercially available substituted phenylboronic acid in the presence of a base, typically an aqueous solution of sodium carbonate, in an appropriate solvent, typically, DME, DMF or toluene, with a catalytic amount of palladium, typically $Pd[PPh_3]_4$, to yield vii, where R_3' is H, halogen, lower alkyl, nitro, alkoxy, thioalkoxy, haloalkoxy, lower alkyl carboxylate, or alkyl sulfonyl.

Substituted benzaldehyde vii can be treated with a solution of triethylphosphonoacetate and sodium hydride in an appropriate solvent, typically THF, to yield viii, where R_3' is H, halogen, lower alkyl, nitro, alkoxy, thioalkoxy, haloalkoxy, lower alkyl carboxylate, or alkyl sulfonyl and R_1' is lower alkyl.

The phenyl-acrylate ester viii can be hydrolyzed by heating with a strong base, typically sodium hydroxide in an aqueous/organic mixed solvent, typically THF to give

the phenyl-acrylic acid viii, where R_3' is H, halogen, lower alkyl, nitro, alkoxy, thioalkoxy, haloalkoxy, lower alkyl carboxylate, or alkyl sulfonyl.

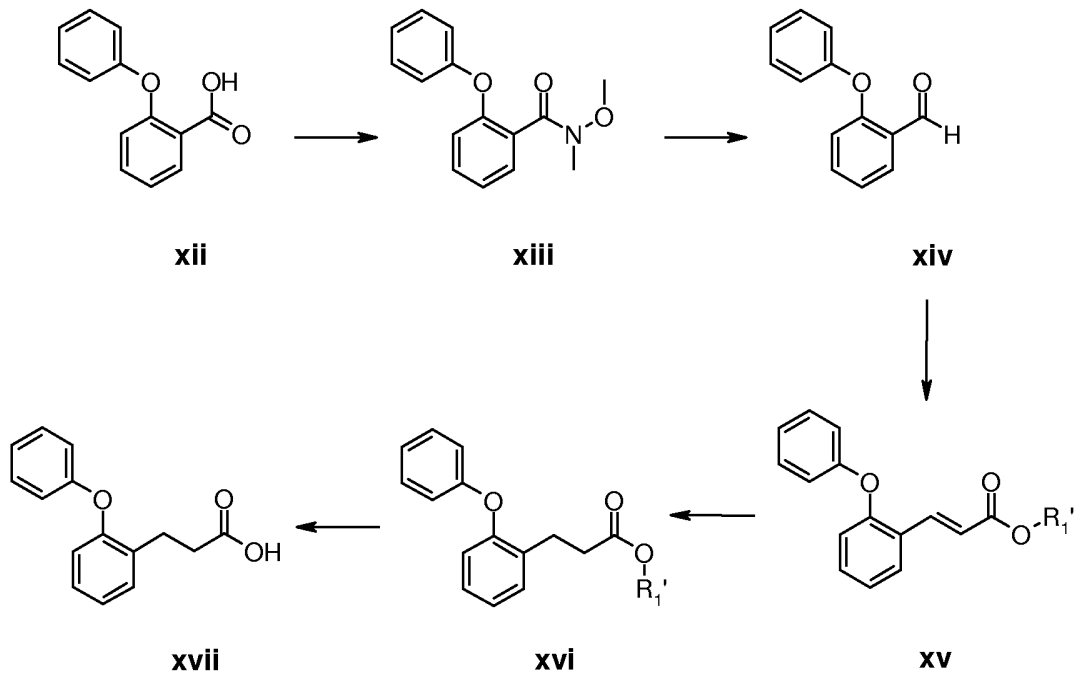
Scheme 4



viii x xi

As shown in scheme 4, phenyl-acrylate ester viii can be hydrogenated in an appropriate solvent with a catalyst, typically 10% palladium on carbon, under an atmosphere of hydrogen, typically 50 psi, to give substituted phenyl-propionate ester x, where R_3' is H, halogen, lower alkyl, nitro, alkoxy, thioalkoxy, haloalkoxy, lower alkyl carboxylate, or alkyl sulfonyl and R_1' is lower alkyl. Phenyl-propionate ester x can be hydrolyzed by heating with a strong base, typically sodium hydroxide in an aqueous/organic mixed solvent, typically THF to give the phenyl-propionic acid xi, where R_3' is H, halogen, lower alkyl, nitro, alkoxy, thioalkoxy, haloalkoxy, lower alkyl carboxylate, or alkyl sulfonyl.

Scheme 5



xii xiii xiv xv xvi xvii

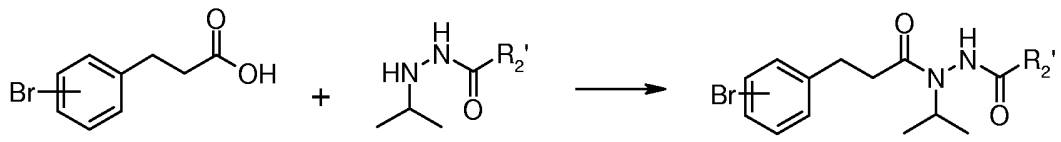
As shown in Scheme 5, a solution of 2-phenoxybenzoic acid xii and N,O-dimethylhydroxylamine hydrochloride in an appropriate solvent, typically DMF, with a

base, typically triethylamine, can be reacted with a suitable coupling reagent, typically HBTU, to form the "Weinreb" amide xiii.

Amide xiii can be reduced with lithium aluminum hydride in THF to afford aldehyde xiv. Without purification, aldehyde xiv can be treated with a solution of triethylphosphonoacetate and sodium hydride in an appropriate solvent, typically THF, to yield xv, where R_1' is lower alkyl.

Phenyl-acrylate ester xv can be hydrogenated in an appropriate solvent with a catalyst, typically 10% palladium on carbon, under an atmosphere of hydrogen, typically 50 psi, to give substituted phenyl-propionate ester xvi, where R_1' is lower alkyl. Phenyl-propionate ester xvi can be hydrolyzed by heating with a strong base, typically lithium hydroxide in an aqueous/organic mixed solvent, typically THF, to give the o-phenoxy-phenyl-propionic acid xvii.

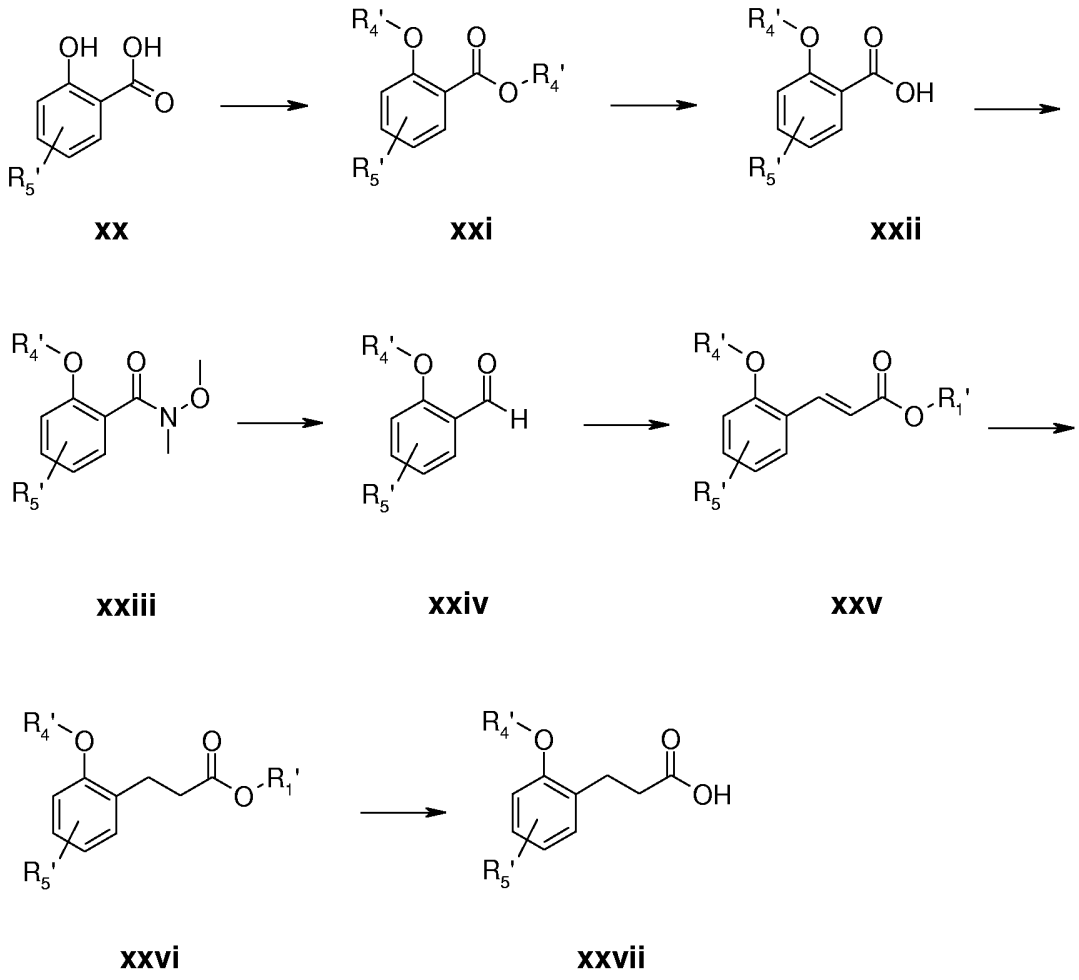
Scheme 6



xviii **v** **xix**

As shown in Scheme 6, a bromo-phenyl-propionic acid xviii can be used to acylate a hydrazide v from Scheme 2, where R_2' is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl or cycloheteroalkyl. Various standard amide bond forming conditions, as practiced by those skilled in the art, may be used. Typically xviii and hydrazide v, in an appropriate solvent, may be treated with a base, such as triethyl amine, and PyBroP or EDCI and HOBT to yield acyl hydrazide xix, where R_2' is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl or cycloheteroalkyl.

Scheme 7



As shown in Scheme 7, a solution of substituted salicylic acid xx, where R_5' is H, halogen, lower alkyl, or alkoxy, in a solvent such as DMF can be reacted with a base, typically potassium carbonate, and an alkyl halide with heating to give xxi. This ester can be hydrolyzed by heating with a strong base, typically lithium hydroxide in an aqueous/organic mixed solvent, typically THF, to give the substituted-benzoic acid xxii, where R4' is lower alkyl or cycloalkyl and R_5' is H, halogen, lower alkyl, or alkoxy.

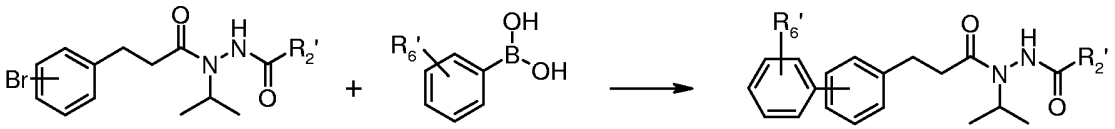
A solution of substituted-benzoic acid xxii and N,O-dimethylhydroxylamine hydrochloride in an appropriate solvent, typically DMF, with a base, typically triethylamine, can be reacted with a suitable coupling reagent, typically HBTU, to form the "Weinreb" amide xxiii.

Amide xxiii can be reduced with lithium aluminum hydride in THF to afford aldehyde xxiv. Without purification, aldehyde xiv can be treated with a solution of triethylphosphonoacetate and sodium hydride in an appropriate solvent, typically THF,

to yield acrylate ester xxv, where R_1' is lower alkyl , R4' is lower alkyl or cycloalkyl and R_5' is H, halogen, lower alkyl, or alkoxy.

Phenyl-acrylate ester xxv can be hydrogenated in an appropriate solvent with a catalyst, typically 10% palladium on carbon, under an atmosphere of hydrogen, typically 50 psi, to give substituted phenyl-propionate ester xxvi, where R_1' is lower alkyl. Phenyl-propionate ester xxvi can be hydrolyzed by heating with a strong base, typically lithium hydroxide in an aqueous/organic mixed solvent, typically THF, to give the o-substituted-phenyl-propionic acid xxvii where R4' is lower alkyl or cycloalkyl and R_5' is H, halogen, lower alkyl, or alkoxy.

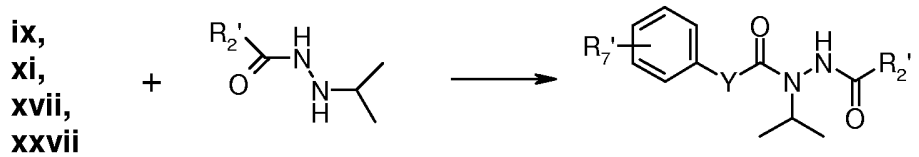
Scheme 8



xix **xxviii** **xxix**

As shown in Scheme 8, using standard palladium catalyzed "cross coupling" procedures, xix can be heated with a substituted arylboronic acid xxviii in the presence of a base, typically an aqueous solution of sodium carbonate in an appropriate solvent, typically, DME, DMF or toluene, with a catalytic amount of palladium, typically $Pd[PPh_3]_4$, to yield xxix, where R_6' is H, halogen, lower alkyl, nitro, alkoxy, thioalkoxy, haloalkoxy, lower alkyl carboxylate, alkyl sulfonyl, or substituted aryl.

Scheme 9



ix, xi, xvii, xxvii **v** **xxx**

As shown in Scheme 9, a substituted aryl-acrylic or aryl-propionic acid ix, xi, xvii, or xxvii from Schemes 3, 4, 5, or 7, can be used to acylate a hydrazide v from Scheme 2, where R_2' is aryl, substituted aryl, heteroaryl, substituted heteroaryl, cycloalkyl or cycloheteroalkyl. Various standard amide bond forming conditions, as practiced by those skilled in the art, may be used. Typically, ix, xi, xvii, or xxvii and hydrazide v, in an appropriate solvent, may be treated with a base, such as triethyl amine, and PyBroP or EDCI and HOBT to yield acyl hydrazide xxx, where R_7' is aryl, substituted aryl,

heteroaryl, substituted heteroaryl, cycloalkyl or cycloheteroalkyl and Y is ethyl or ethylene.

In the practice of the method of the present invention, an effective amount of any one of the compounds of this invention or a combination of any of the compounds of this invention or a pharmaceutically acceptable salt thereof, is administered via any of the usual and acceptable methods known in the art, either singly or in combination. The compounds or compositions can thus be administered orally (e.g., buccal cavity), sublingually, parenterally (e.g., intramuscularly, intravenously, or subcutaneously), rectally (e.g., by suppositories or washings), transdermally (e.g., skin electroporation) or by inhalation (e.g., by aerosol), and in the form or solid, liquid or gaseous dosages, including tablets and suspensions. The administration can be conducted in a single unit dosage form with continuous therapy or in a single dose therapy ad libitum. The therapeutic composition can also be in the form of an oil emulsion or dispersion in conjunction with a lipophilic salt such as pamoic acid, or in the form of a biodegradable sustained-release composition for subcutaneous or intramuscular administration.

Useful pharmaceutical carriers for the preparation of the compositions hereof, can be solids, liquids or gases; thus, the compositions can take the form of tablets, pills, capsules, suppositories, powders, enterically coated or other protected formulations (e.g. binding on ion-exchange resins or packaging in lipid-protein vesicles), sustained release formulations, solutions, suspensions, elixirs, aerosols, and the like. The carrier can be selected from the various oils including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, and the like. Water, saline, aqueous dextrose, and glycols are preferred liquid carriers, particularly (when isotonic with the blood) for injectable solutions. For example, formulations for intravenous administration comprise sterile aqueous solutions of the active ingredient(s) which are prepared by dissolving solid active ingredient(s) in water to produce an aqueous solution, and rendering the solution sterile. Suitable pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, talc, gelatin, malt, rice, flour, chalk, silica, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, glycerol, propylene glycol, water, ethanol, and the like. The compositions may be subjected to conventional pharmaceutical additives such as preservatives, stabilizing agents, wetting or emulsifying agents, salts for adjusting osmotic pressure, buffers and the like. Suitable pharmaceutical carriers and their formulation are described in Remington's Pharmaceutical Sciences by E. W. Martin. Such compositions will, in any event, contain an effective amount of the active compound together with a suitable carrier so as to prepare the proper dosage form for proper administration to the recipient.

The dose of a compound of the present invention depends on a number of factors, such as, for example, the manner of administration, the age and the body weight of the subject, and the condition of the subject to be treated, and ultimately will be decided by the attending physician or veterinarian. Such an amount of the active compound as determined by the attending physician or veterinarian is referred to herein, and in the claims, as an "effective amount". For example, the dose of a compound of the present invention is typically in the range of about 10 to about 1000 mg per day.

The invention will now be further described in the Examples below, which are intended as an illustration only and do not limit the scope of the invention.

EXAMPLES

General Methods: Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer model 241 polarimeter. 1H-NMR spectra were recorded with Varian XL-200, Mercury-300 or Unityplus 400 MHz spectrometers, using tetramethylsilane (TMS) as internal standard. Electron impact (El, 70 ev) and fast atom bombardment (FAB) mass spectra were taken on VG Autospec or VG 70E-HF mass spectrometers. Silica gel used for column chromatography was Mallinkrodt SiliCar 230-400 mesh silica gel for flash chromatography; columns were run under a 0-5 psi head of nitrogen to assist flow. Thin layer chromatograms were run on glass thin layer plates coated with silica gel as supplied by E. Merck (E. Merck # 1.05719) and were visualized by viewing under 254 nm UV light in a view box, by exposure to I2 vapor, or by spraying with either phosphomolybdic acid (PMA) in aqueous ethanol, or after exposure to Cl_2, with a 4,4'-tetramethyldiamino-diphenylmethane reagent prepared according to E. Von Arx, M. Faupel and M Brugger, *J. Chromatography,* 1976, 220, 224-228.

Reversed phase high pressure liquid chromatography (RP-HPLC) was carried out using a Rainin HPLC employing a 41.4 x 300 mm, 8 uM, Dynamax™C-18 column at a flow of 49 mL/min employing a gradient of acetonitrile:water (each containing 0.75% TFA) typically from 5 to 95% acetonitrile over 35-40 min. HPLC conditions are typically described in the format (5-95-35-214); this refers to a linear gradient of from 5% to 95% acetonitrile in water over 35 min while monitoring the effluent with a UV detector at a wavelength of 214 nM.

Methylene chloride (dichloromethane), 2-propanol, DMF, THF, toluene, hexane, ether, and methanol, were Fisher or Baker reagent grade and were used without

additional purification except as noted, acetonitrile was Fisher or Baker HPLC grade and was used as is.

Definitions as used herein:

DGAT is diacylglycerol:acyl CoA O-acyltransferase,

THF is tetrahydrofuran,

DMF is N,N-dimethylformamide,

DMA is N,N-dimethylacetamide,

DMSO is dimethylsulfoxide,

DCM is dichloromethane,

DME is dimethoxyethane,

MeOH is methanol,

EtOH is ethanol,

$Pd[PPh_3]_4$ is tetrakis(triphenylphosphine)palladium (0),

NaOH is sodium hydroxide,

TFA is 1,1,1-trifluoroacetatic acid,

HOBT is 1-hydroxybenzotriazole,

HBTU is O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate,

PyBroP is bromotripyrrolidinophosphonium hexafluorophosphate,

EDCI is 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride,

DIPEA is diisopropylethylamine,

brine is saturated aqueous sodium chloride solution,

DAG is 1,2-dioleoyl-sn-glycerol,

TLC is thin layer chromatography,

RP HPLC is reversed phase high performance liquid chromatography,

APCI-MS is atmospheric pressure chemical ionization mass spectrometry,

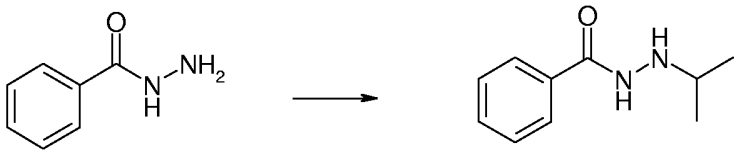
ES-MS is electrospray mass spectrometry,

RT is room or ambient temperature.

Silica gel chromatography on Biotage columns refers to use of a flash chromatography system supplied by the Biotage Division of the Dyax Corporation employing prepacked 40g (40s columns), 90g (40m columns) or 800g (75m columns). Elution is carried out with hexane-ethyl acetate mixtures under 10-15 psi nitrogen pressure.

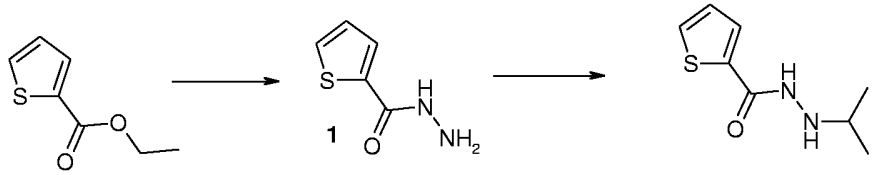
PART I: PREPARATION OF PREFERRED INTERMEDIATES

Benzoic acid N'-isopropyl-hydrazide



A solution of benzoylhydrazine (10 g, 73.45 mmol) in hexane (200 ml) was treated with acetone (54 mL, 734.5 mmol) and refluxed overnight. The precipitate was collected by suction filtration to afford a white solid which was treated with TFA (200 ml) and triethylsilane (24 mL, 149.24 mmol) at 60 °C overnight. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between DCM and 1N NaOH. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to afford the product as a white solid (9.31 g, 71%).

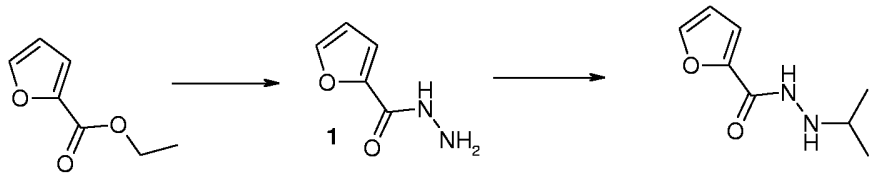
Thiophene-2-carboxylic acid N'-isopropyl-hydrazide



A solution of ethyl-2-thiophene carboxylate (2 g, 12.8 mmol) and hydrazine monohydrate (6.2 ml, 128 mmol) in EtOH (10 ml) was refluxed overnight. The mixture was concentrated to dryness to afford intermediate 1 as an off white solid (1.81 g). A portion of this material (500 mg) was dissolved in acetone (5 ml) and the solution was

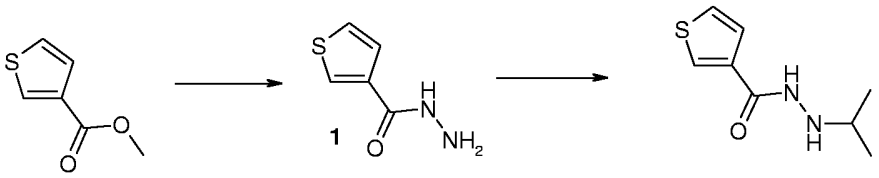
heated to 50 °C overnight. The solution was concentrated to dryness. The residue was dissolved in TFA (5 ml) and treated with triethylsilane (1.1 ml, 6.74 mmol) at 60 °C overnight. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between saturated aqueous bicarbonate and DCM. The organic layer was washed with brine, dried over sodium sulfate and concentrated under vacuum to afford the product as a white solid (516 mg, 80%).

Furan-2-carboxylic acid N'-isopropyl-hydrazide



A solution of ethyl-2-furoate (2 g, 14.3 mmol) and hydrazine monohydrate (6.9 ml, 143 mmol) in EtOH (10 ml) was refluxed overnight. The mixture was concentrated to dryness to afford intermediate 1 (1.65 g). A portion of this material (500 mg) was dissolved in acetone (5 ml) and the solution was heated to 50 °C overnight. The solution was concentrated to dryness. The residue was dissolved in TFA (5 ml) and treated with triethylsilane (1.30 ml, 8.18 mmol) at 60 °C overnight. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between saturated aqueous bicarbonate and DCM. The organic layer was washed with brine, dried over sodium sulfate and concentrated under vacuum to afford the product as a white solid (511 mg, 74%).

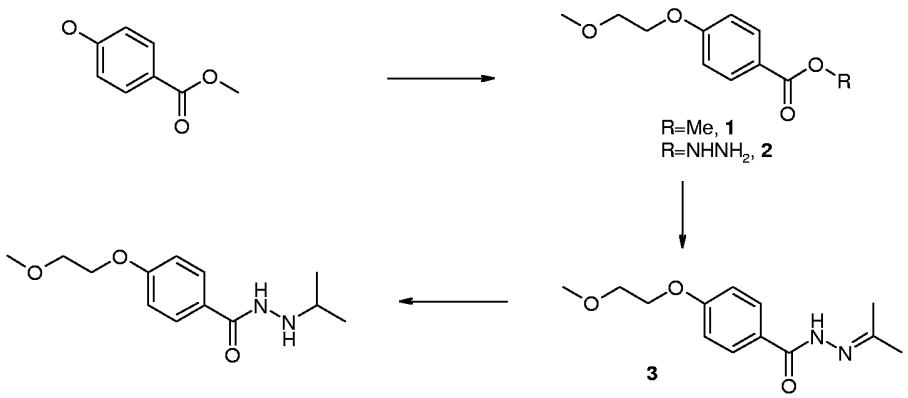
Thiophene-3-carboxylic acid N'-isopropyl-hydrazide



A solution of ethyl-3-thiophene carboxylate (2 g, 12.8 mmol) and hydrazine monohydrate (6.2 ml, 128 mmol) in EtOH (10 ml) was refluxed overnight. The mixture was concentrated to dryness to afford intermediate 1 (1.86 g, 100%). A portion of this material (500 mg) was dissolved in acetone (5 ml) and the solution was heated to 60 °C overnight. The solution was concentrated to dryness. The residue was dissolved in TFA (5 ml) and treated with triethylsilane (1.16 ml, 7.24 mmol) at 60 °C overnight. The reaction mixture was concentrated under reduced pressure and the residue was partitioned between saturated aqueous bicarbonate and DCM. The organic layer was washed with

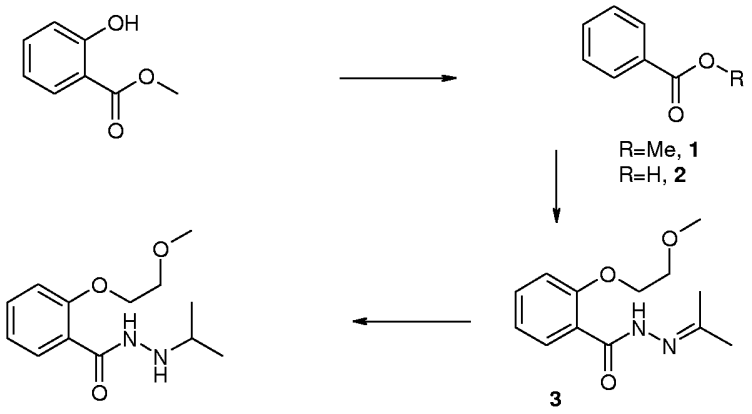
brine, dried over sodium sulfate and concentrated under vacuum to afford the product as a white solid (484 mg, 75%).

4-(2-Methoxy-ethoxy)-benzoic acid-N'-isopropyl hydrazide



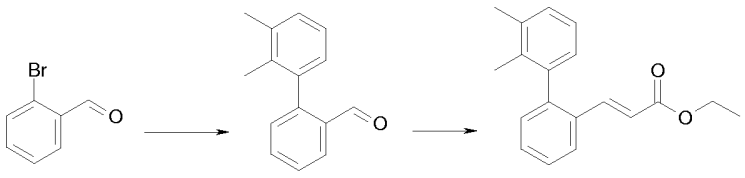
A DMF (20 ml) solution of methyl-p-hydroxybenzoate (1.0 g, 6.57 mmol), potassium carbonate (9.08 g, 65.72 mmol) and 2-bromoethyl methyl ether (6.17 ml, 65.72 mmol) was heated to 150 °C for 20 minutes in a microwave oven. The reaction mixture was filtered through celite, and partitioned between 1 N NaOH and ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to afford intermediate 1 as pale yellow oil (1.28 g, 93%). A solution of ester 1 (1.0 g, 4.76 mmol) and hydrazine monohydrate (4.61 ml, 95.12 mmol) in MeOH (8 ml) was heated to 160 °C for 20 minutes in a microwave oven. The reaction mixture was concentrated under reduced pressure to afford hydrazide 2 as a yellow solid (790 mg, 79%). A solution of hydrazide 2 (200 mg, 0.95 mmol) in acetone (4 ml) was refluxed overnight. The reaction mixture was concentrated under reduced pressure to afford intermediate 3 as brown oil (240 mg, 100%). Compound 3 (240mg, 0.95 mmol) was then treated with EtSiH (0.35 ml, 2.1 mmol) in TFA (5 ml) at 60 °C overnight. The reaction mixture was concentrated and the residue was partitioned between DCM and 1N NaOH. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to afford the product as oil (170 mg, 62%).

2-(2-Methoxy-ethoxy)-benzoic acid-N'-isopropyl hydrazide



A DMF (20 ml) solution of methyl-o-hydroxybenzoate (1.0 g, 6.57 mmol), potassium carbonate (9.08 g, 65.72 mmol) and 2-bromoethyl methyl ether (6.17 ml, 65.72 mmol) was heated to 150 °C for 20 minutes in a microwave oven. The reaction mixture was filtered through celite, and partitioned between 1 N NaOH and ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to afford intermediate 1 as brown oil (807 mg, 58%). A solution of ester 1 (0.8 g, 3.8 mmol) and hydrazine monohydrate (4.0 ml, 76.0 mmol) in MeOH (8 ml) was heated to 160 °C for 20 minutes in a microwave oven. The reaction mixture was concentrated under reduced pressure to afford hydrazide 2 as oil (840 mg, 88%). A solution of hydrazide 2 (840 mg, 3.99 mmol) in acetone (10 ml) was refluxed overnight. The reaction mixture was concentrated under reduced pressure to afford intermediate 3 as brown oil (1.1 g, 100%). This crude material was then treated with EtSiH (1.5 ml, 9.25mmol) in TFA (25 ml) at 60 °C overnight. The reaction mixture was concentrated and the residue was partitioned between DCM and 1N NaOH. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to afford the product as oil (460 mg, 40%).

3-(2',3'-Dimethyl-biphenyl-2-yl)-acrylic acid ethyl ester



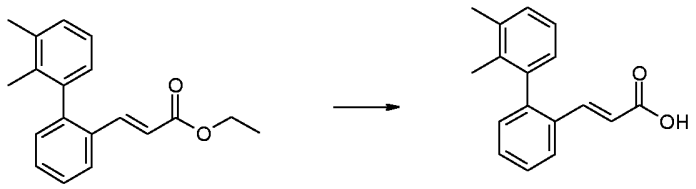
1

A solution of 2-bromo-benzaldehyde (150 mg, 0.81 mmol) in DME (2 ml)/ 2M Na_2CO_3 (1.4 ml, 2.84 mmoles) was treated with 3-dimethyl-phenylboronic acid (243 mg, 1.62 mmol) and $Pd[PPh_3]_4$ (93 mg, 0.081 mmol) for 10 min at 150 °C in a microwave reactor. The reaction mixture was partitioned between water and ethyl acetate. The

organic layer was washed successively with water and brine, then dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 1-5% ethyl acetate/hexanes gradient to afford 1 (746 mg, 87%).

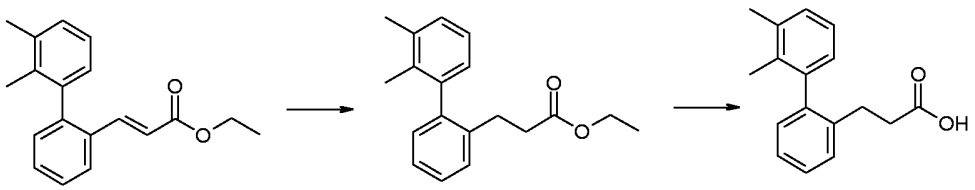
A solution of triethylphosphonoacetate (0.226 ml, 1.14 mmoles) in THF (10ml) was treated with 60% sodium hydride (87 mg, 2.18 mmoles) at rt for 10 min. The aldehyde 1 (200 mg, 0.95 mmoles) was then added and the solution was stirred at rt for 2.5 h. The reaction mixture was partitioned between 1 N HCl and ethyl acetate. The organic layer was washed successively with water, saturated sodium carbonate and brine, then dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 5-10% ethyl acetate/hexanes gradient to afford 3-(2',3'-dimethyl-biphenyl)-acrylic acid ethyl ester (234 mg, 88%).

3-(2',3'-Dimethyl-biphenyl-2-yl)-acrylic acid



A solution of 3-(2',3'-dimethyl-biphenyl-2-yl)-acrylic acid ethyl ester (110 mg, 0.39 mmoles) in THF (3ml)/2N NaOH (3ml) was heated to 160 °C for 10 min in a microwave reactor. The mixture was cooled to rt and partitioned between 1N HCl and ethyl acetate. The organic layer was washed with water and brine, then dried over sodium sulfate and concentrated to afford the desired acid (100 mg, 100%).

3-(2',3'-Dimethyl-biphenyl-2-yl)-propionic acid

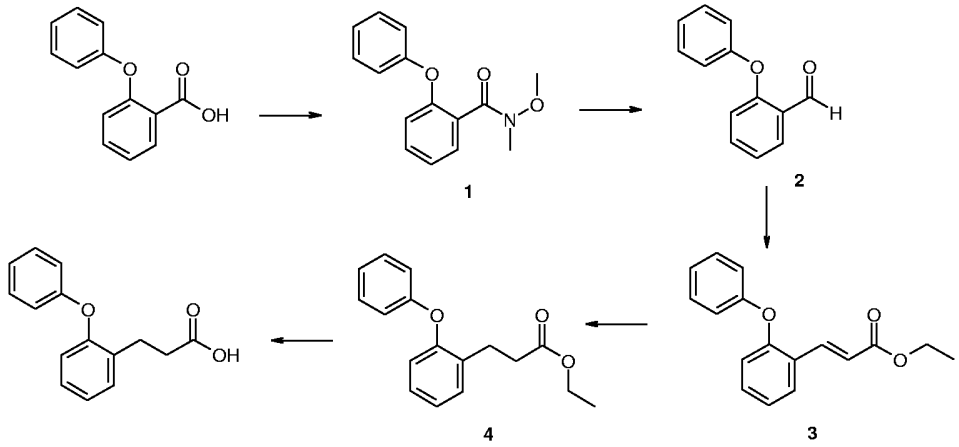


1

A solution of 3-(2',3'-dimethyl-biphenyl-2-yl)-acrylic acid ethyl ester (2.3 g, 8.2 mmoles) in MeOH (35 ml) was placed in the Parr apparatus. A catalytic amount of 10% Pd/C (230 mg) was added and the mixture was shaken under an atmosphere of hydrogen (50 psi) for 1.5 h. The heterogeneous mixture was filtered through a cake of celite and concentrated to afford ester 1 (2.17 g). This intermediate was dissolved in THF (40ml)/ water (20 ml) and treated with lithium hydroxide monohydrate (3.23 g, 76.8 mmoles) for 5 h at reflux. The mixture was cooled to rt and partitioned between 1N HCl and ethyl

acetate. The organic layer was washed with water and brine, then dried over sodium sulfate and concentrated to afford the desired acid (1.94g, 93%).

3-(2-Phenoxy-phenyl)-propionic acid



A solution of 2-phenoxybenzoic acid (660 mg, 3.08 mmoles) and N,O-dimethylhydroxylamine hydrochloride (451 mg, 4.62 mmoles) in DMF (15 ml) was treated at rt for 18 h with triethylamine (1.3 ml, 9.24 mmoles) and HBTU (1.75 g, 4.62 mmoles). The reaction mixture was partitioned between 1N NaOH and ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford 1 which was not further purified (827 mg, 100%).

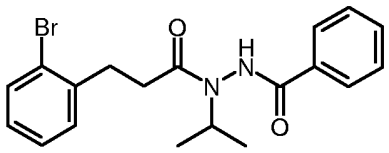
A 1M solution of lithium aluminum hydride in THF (3.18 ml, 3.18 mmoles) was slowly added to a cold (-20 °C) solution of 1 (410 mg, 1.59 mmoles) in THF (8 ml). The solution was stirred at -20 °C for 45 min and then quenched slowly with water. The mixture was filtered through a cake of celite and the filtrate was partitioned between ethyl acetate and saturated bicarbonate. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford aldehyde 2 (278 mg, 88%) which was not further purified.

A solution of triethylphosphonoacetate (0.334 ml, 1.68 mmoles) in THF (2ml) was treated with 60% sodium hydride (132 mg, 3.3 mmoles) at rt for 10 min. The aldehyde 2 (278 mg, 1.40 mmoles) was then added and the solution was stirred at rt for 4 h. The reaction mixture was partitioned between 1 N HCl and ethyl acetate. The organic layer was washed successively with water, saturated sodium carbonate and brine, then dried over sodium sulfate, filtered and concentrated. The crude was adsorbed on silica and purified on a silica gel column with a 5-10% ethyl acetate/hexanes gradient to afford ester 3 (258 mg, 59%).

A solution of ester 3 (136 mg, 0.51 mmoles) in EtOH (5 ml) was placed in the Parr apparatus. A catalytic amount of 10% Pd/C (25 mg) was added and the mixture was shaken under an atmosphere of hydrogen (50 psi) for 1.5 h. The heterogeneous mixture was filtered through a cake of celite and concentrated to afford ester 4 (127 mg, 93%).

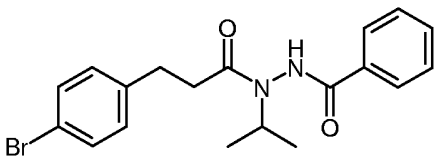
This ester (127 mg, 0.47 mmoles) was dissolved in THF (10 ml)/ water (5 ml) and treated with lithium hydroxide monohydrate (197 mg, 4.7 mmoles) for 5 h at reflux. The mixture was cooled to rt and partitioned between 1N HCl and ethyl acetate. The organic layer was washed with water and brine then dried over sodium sulfate and concentrated to afford the desired acid (112 mg, 98%).

Benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide



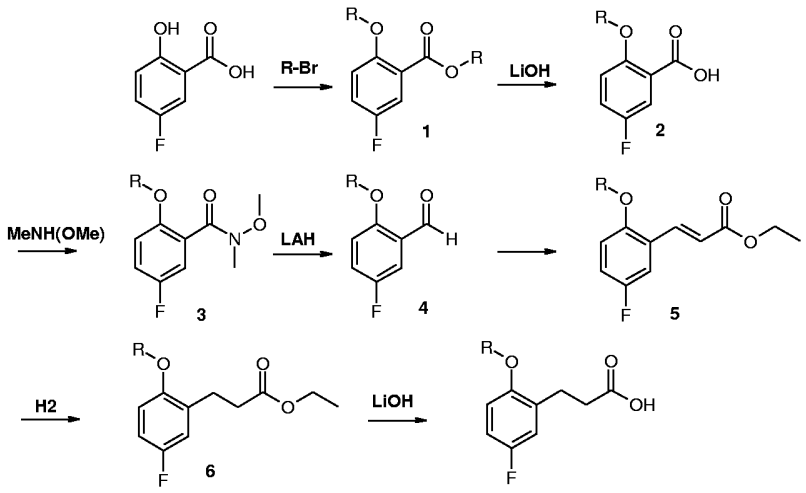
A solution of (3-(2-bromophenyl)propionic acid (257 mg, 1.12 mmoles) and benzoic acid N'-isopropyl-hydrazide (200 mg, 1.12 mmoles) in DMF (6 mL) was treated with triethylamine (0.47 mL, 3.36 mmol), HOBT (182 mg, 1.34 mmoles) and EDCI (2.58 g, 1.34 mmol) at room temperature for 72 h. The reaction mixture was partitioned between water and dichloromethane. The organic layer was successively washed with water and brine, then dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-30% ethyl acetate/hexanes gradient to afford the product as a solid (258 mg, 59%).

Benzoic acid N'-[3-(4-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide



A solution of (3-(4-bromophenyl)propionic acid (387 mg, 1.68 mmoles) and benzoic acid N'-isopropyl-hydrazide (300 mg, 1.68 mmoles) in DMF (10 mL) was treated with triethylamine (0.70 mL, 5.05 mmol), HOBT (273 mg, 2.02 mmoles) and EDCI (387 mg, 2.02 mmoles) at room temperature for 72 h. The reaction mixture was partitioned between 1N HCl and ethyl acetate. The organic layer was successively washed with water, 1N NaOH and brine, then dried over sodium sulfate, filtered and concentrated to afford the product as a solid (476 mg, 73%). The product was not further purified.

General procedure for 3-(2-alkoxy-3-fluoro-phenyl)-propionic acids



A solution of 5-fluoro-salicylic acid in DMF (0.2M) was reacted with potassium carbonate (5 eq) and an alkyl bromide (4 eq) at 80 °C for 2-3 h. The reaction mixture was partitioned between 1N HCl and ethyl acetate. The organic layer was washed successively with 1N NaOH and brine, then dried over sodium sulfate, filtered, and concentrated to afford intermediate 1 which was not further purified.

This compound was dissolved in THF (0.2M) and treated with lithium hydroxide monohydrate (10 eq) at reflux overnight. The reaction mixture was partitioned between 1N HCl and ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to afford acid 2 which was not further purified.

A solution of 2 in DMF (0.2M) was treated with triethylamine (5 eq), N,O-dimethylamine hydrochloride (1.5 eq) and HBTU (1.5 eq) at rt overnight. The reaction mixture was partitioned between 1N HCl and ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to afford amide 3 which was not further purified.

A solution of 3 in anhydrous THF (0.2M) was cooled to -30 °C and then treated with a THF solution of lithium aluminum hydride (1M, 2 eq) for 10 min. The reaction was quenched at -30 °C with 1N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to afford aldehyde 4 which was not further purified.

A THF solution of triethylphosphonoacetate (0.2M) was treated at rt for 10 min with 60% sodium hydride (2 eq). A THF solution of 4 (0.2M, 1eq) was then added at rt and the mixture was stirred for 2-3h. The reaction was quenched at rt with 1N HCl and extracted with ethyl acetate. The organic layer was washed successively with saturated

aqueous sodium bicarbonate and brine, then dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with 5% ethyl acetate/hexanes to afford ester 5.

A solution of 5 in ethanol (0.2M) was placed in the Parr apparatus. A catalytic amount of 10% Pd/C (50 mg/mmol) was added and the mixture was shaken under an atmosphere of hydrogen (50 psi) for 2-3h. The heterogeneous mixture was filtered through a cake of celite and concentrated to afford ester 6 which was not further purified.

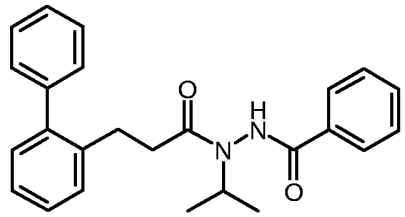
This compound was dissolved in THF/H_2O (2/1) (0.2M) and treated with lithium hydroxide monohydrate (10 eq) at reflux for 4-5h. The reaction mixture was partitioned between 1N HCl and ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated to afford the corresponding phenyl propionic acid which was not further purified.

Phenyl propionic acids were prepared by this method where R = n-propyl, n-butyl, cyclopentyl, and cyclobutylmethyl.

PART II: PREPARATION OF PREFERRED COMPOUNDS

Example 1

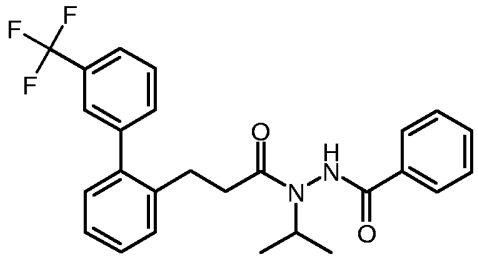
Benzoic acid N'-[3-biphenyl-2-yl-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (100 mg, 0.26 mmol) in DME (5 ml)/ 2M Na_2CO_3 (450 µL, 0.90 mmol) was treated with phenylboronic acid (47 mg, 0.39 mmol) and $Pd[PPh_3]_4$ (30 mg, 0.026 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 30-50% ethyl acetate/hexanes gradient to afford the product as a solid (98 mg, 98%). LC-MS m/e 387.16 ($M+H^+$)

Example 2

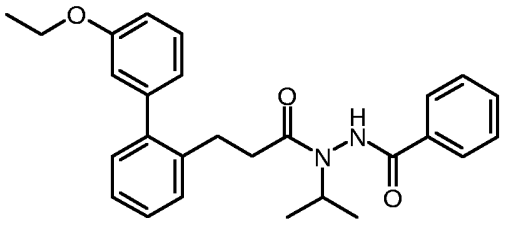
Benzoic acid N'- isopropyl-N'-[3-(3'-trifluoromethyl-biphenyl-2-yl)-propionyl]-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 3-trifluoro-phenylboronic acid (49 mg, 0.26 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient and then by RP HPLC to afford the product as a solid (15 mg, 26%). LC-MS m/e 455.21 ($M+H^+$)

Example 3

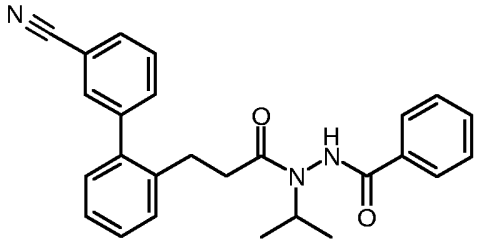
Benzoic acid N'-[3-(3'-ethoxy-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 3-ethoxy-phenylboronic acid (42 mg, 0.26 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient and then by RP HPLC to afford the product as a solid (12 mg, 22%). LC-MS m/e 431.27 ($M+H^+$)

Example 4

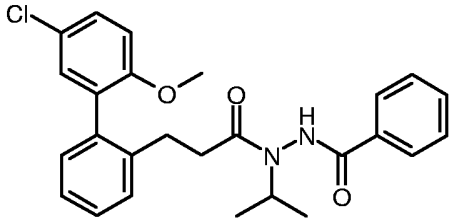
Benzoic acid N'-[3-(3'-cyano-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 3-cyano-phenylboronic acid (38 mg, 0.26 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (13 mg, 25%). LC-MS m/e 412.21 ($M+H^+$)

Example 5

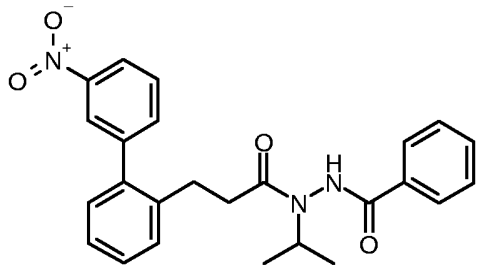
Benzoic acid N'-[3-(5'-chloro-2'-methoxy-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 5-chloro-2-methoxy-phenylboronic acid (48 mg, 0.26 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (22 mg, 38%). LC-MS m/e 451.31 ($M+H^+$)

Example 6

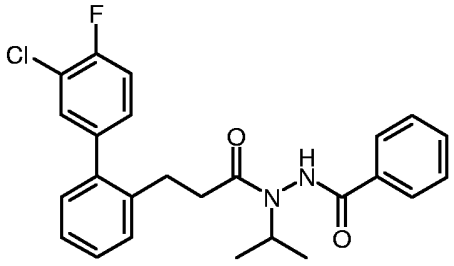
Benzoic acid N'- isopropyl-N'-[3-(3'-nitro-biphenyl-2-yl)-propionyl]-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 3-nitro-phenylboronic acid (43 mg, 0.26 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (12 mg, 22%). LC-MS m/e 432.31 ($M+H^+$)

Example 7

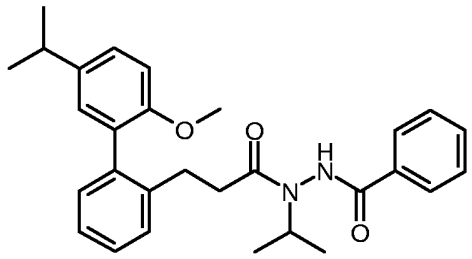
Benzoic acid N'-[3-(3'-chloro-4'-fluoro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 3-chloro-4-fluoro-phenylboronic acid (34 mg, 0.19 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient and then by RP HPLC to afford the product as a solid (23 mg, 41%). LC-MS m/e 439.25 ($M+H^+$)

Example 8

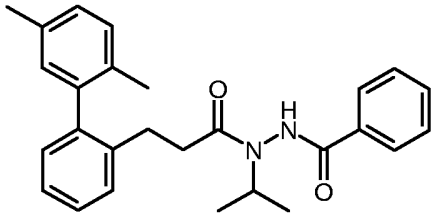
Benzoic acid N'-[3-(5'-isopropyl-2'-methoxy-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 5-isopropyl-2-methoxy-phenylboronic acid (37 mg, 0.19 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient and then by RP HPLC to afford the product as a solid (18 mg, 31%). LC-MS m/e 459.35 ($M+H^+$)

Example 9

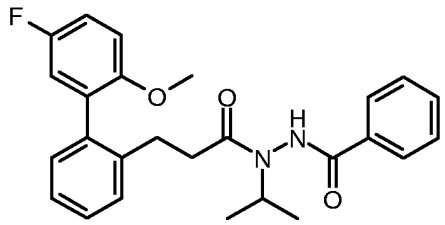
Benzoic acid N'-[3-(2',5'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 2,5-dimethyl-phenylboronic acid (29 mg, 0.19 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (14 mg, 26%). LC-MS m/e 415.36 ($M+H^+$)

Example 10

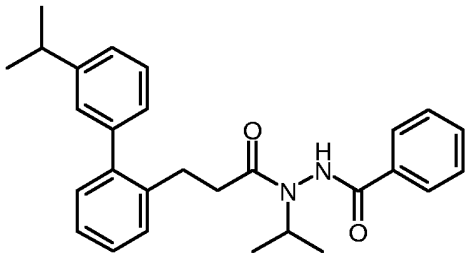
Benzoic acid N'-[3-(5'-fluoro-2'-methoxy-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 5-fluoro-2-methoxy-phenylboronic acid (33 mg, 0.19 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (18 mg, 32%). LC-MS m/e 435.33 ($M+H^+$)

Example 11

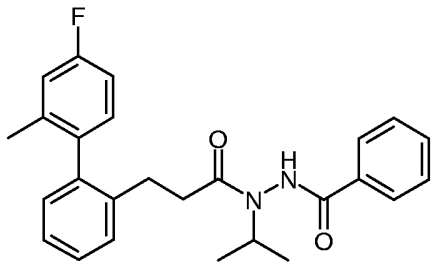
Benzoic acid N'-[3-(3'-isopropyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 3-isopropyl-phenylboronic acid (32 mg, 0.19 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (17 mg, 31%). LC-MS m/e 429.39 ($M+H^+$)

Example 12

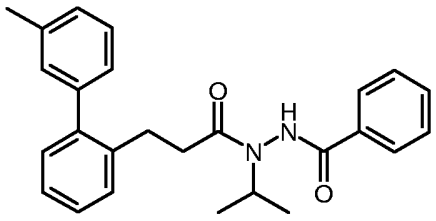
Benzoic acid N'-[3-(4'-fluoro-2'-methyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 4-fluoro-2-methyl-phenylboronic acid (30 mg, 0.19 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 72 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient and then by RP HPLC to afford the product as a solid (5 mg, 9%). LC-MS m/e 419.28 ($M+H^+$)

Example 13

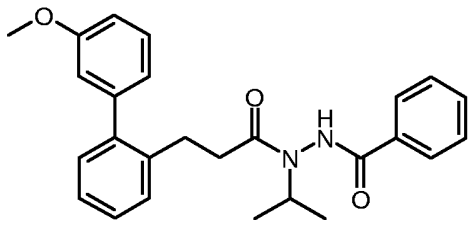
Benzoic acid N'-isopropyl-N'-[3-(3'-methyl-biphenyl-2-yl)-propionyl]-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 3-methyl-phenylboronic acid (26 mg, 0.19 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (48 mg, 93%). LC-MS m/e 401.37 ($M+H^+$)

Example 14

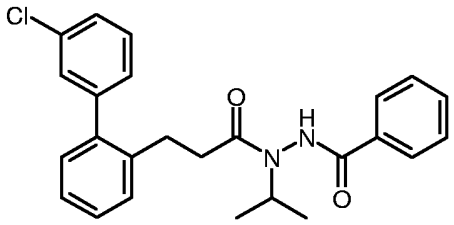
Benzoic acid N'-isopropyl-N'-[3-(3'-methoxy-biphenyl-2-yl)-propionyl]-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 3-methoxy-phenylboronic acid (29 mg, 0.19 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (32 mg, 60%). LC-MS m/e 417.35 ($M+H^+$)

Example 15

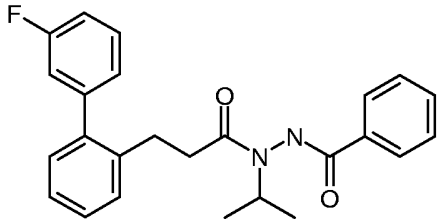
Benzoic acid N'-[3-(3'-chloro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 3-chloro-phenylboronic acid (30 mg, 0.19 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (39 mg, 72%). LC-MS m/e 421.26 ($M+H^+$)

Example 16

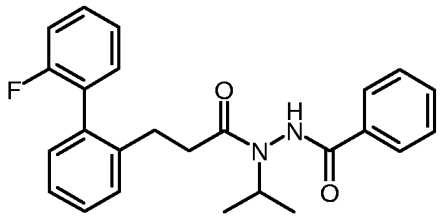
Benzoic acid N'-[3-(3'-fluoro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 3-fluoro-phenylboronic acid (27 mg, 0.19 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (38 mg, 73%). LC-MS m/e 405.28 ($M+H^+$)

Example 17

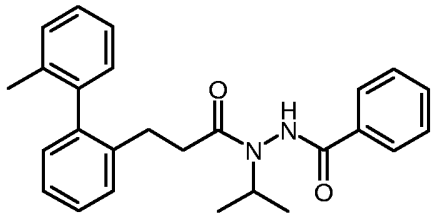
Benzoic acid N'-[3-(2'-fluoro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 2-fluoro-phenylboronic acid (27 mg, 0.19 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (13 mg, 25%). LC-MS m/e 405.28 ($M+H^+$)

Example 18

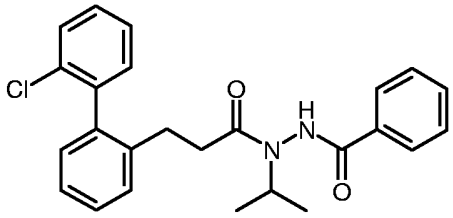
Benzoic acid N'-isopropyl-N'-[3-(2'-methyl-biphenyl-2-yl)-propionyl]-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 2-methyl-phenylboronic acid (27 mg, 0.19 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (9 mg, 18%). LC-MS m/e 401.29 ($M+H^+$)

Example 19

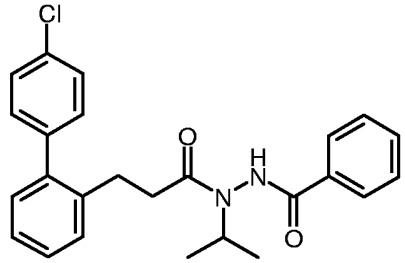
Benzoic acid N'-[3-(2'-chloro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (45 mg, 0.12 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 2-chloro-phenylboronic acid (27 mg, 0.17 mmol) and $Pd[PPh_3]_4$ (13 mg, 0.012 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 30-50% ethyl acetate/hexanes gradient to afford the product as a solid (46 mg, 94%). LC-MS m/e 421.27 ($M+H^+$)

Example 20

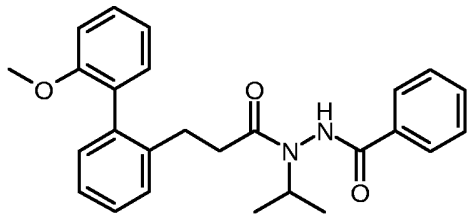
Benzoic acid N'-[3-(4'-chloro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (45 mg, 0.12 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 4-chloro-phenylboronic acid (27 mg, 0.17 mmol) and $Pd[PPh_3]_4$ (13 mg, 0.012 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 30-50% ethyl acetate/hexanes gradient to afford the product as a solid (30 mg, 61%). LC-MS m/e 421.26 ($M+H^+$)

Example 21

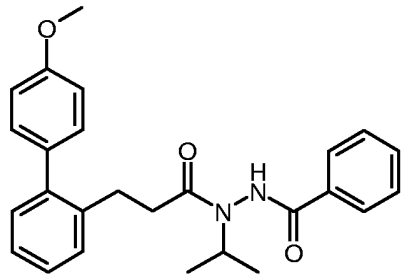
Benzoic acid N'-isopropyl-N'-[3-(2'-methoxy-biphenyl-2-yl)-propionyl]-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 2-methoxy-phenylboronic acid (29 mg, 0.19 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (21 mg, 39%). LC-MS m/e 417.30 ($M+H^+$)

Example 22

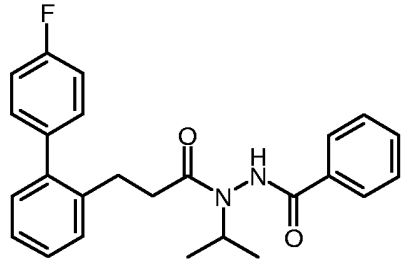
Benzoic acid N'-isopropyl-N'-[3-(4'-methoxy-biphenyl-2-yl)-propionyl]-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 4-methoxy-phenylboronic acid (29 mg, 0.19 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (35 mg, 66%). LC-MS m/e 417.29 ($M+H^+$)

Example 23

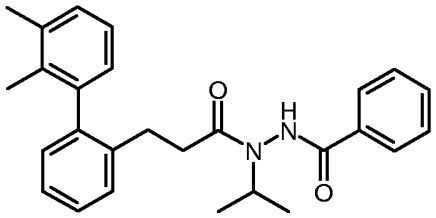
Benzoic acid N'-[3-(4'-fluoro-biphenyl-2-yl)-propionyl]-N'-isopropyl--hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 4-fluoro-phenylboronic acid (29 mg, 0.19 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (41 mg, 79%). LC-MS m/e 405.25 ($M+H^+$)

Example 24

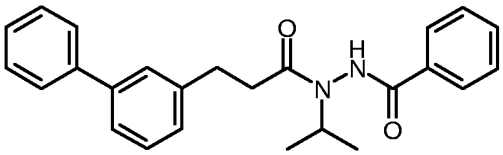
Benzoic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(2-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (50 mg, 0.13 mmol) in DME (4 ml)/ 2M Na_2CO_3 (225 µL, 0.45 mmol) was treated with 2,3-dimethyl-phenylboronic acid (38 mg, 0.26 mmol) and $Pd[PPh_3]_4$ (15 mg, 0.013 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient and then by RP HPLC to afford the product as a solid (14 mg, 27%). LC-MS m/e 415.35 ($M+H^+$)

Example 25

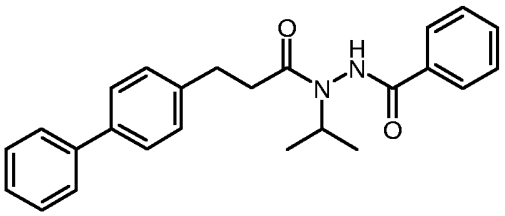
Benzoic acid N'-[3-biphenyl-3-yl-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(3-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (100 mg, 0.26 mmol) in DME (5 ml)/ 2M Na_2CO_3 (450 µL, 0.90 mmol) was treated with phenylboronic acid (47 mg, 0.39 mmol) and $Pd[PPh_3]_4$ (30 mg, 0.026 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 30-50% ethyl acetate/hexanes gradient to afford the product as a solid (69 mg, 70%). LC-MS m/e 387.19 ($M+H^+$)

Example 26

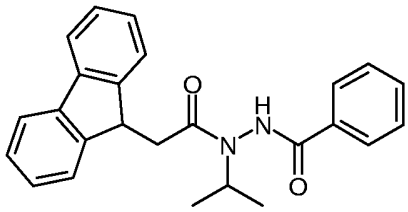
Benzoic acid N'-[3-biphenyl-4-yl-propionyl]-N'-isopropyl-hydrazide



A solution of benzoic acid N'-[3-(4-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide (100 mg, 0.26 mmol) in DME (5 ml)/ 2M Na_2CO_3 (450 µL, 0.90 mmol) was treated with phenylboronic acid (47 mg, 0.39 mmol) and $Pd[PPh_3]_4$ (30 mg, 0.026 mmol) for 18 hours at 90 °C. The reaction mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 30-50% ethyl acetate/hexanes gradient to afford the product as a solid (56 mg, 56%). LC-MS m/e 387.17 ($M+H^+$)

Example 27

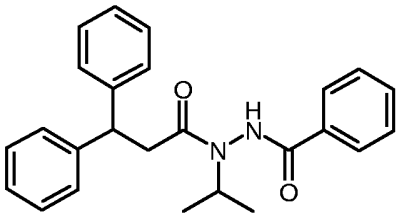
Benzoic acid N'-(2-9H-fluoren-9-yl-acetyl)-N'-isopropyl-hydrazide



A solution of 9-fluoreneacetic acid (126 mg, 0.56 mmoles) and benzoic acid N'-isopropyl-hydrazide (100 mg, 0.56 mmoles) in DMF (5 mL) was treated with triethylamine (0.23 mL, 1.68 mmol), HOBT (91 mg, 0.67 mmoles) and EDCI (129 mg, 0.67 mmol) at room temperature for 72 h. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with water and brine, then dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 10-30% ethyl acetate/hexanes gradient to afford the product as a solid (87 mg, 40%). LC-MS m/e 385.19 ($M+H^+$)

Example 28

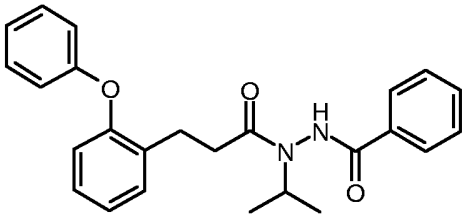
Benzoic acid N'-(3,3-diphenyl-propionyl)-N'-isopropyl-hydrazide



A solution of 3,3-diphenylpropionic acid (127 mg, 0.56 mmoles) and benzoic acid N'-isopropyl-hydrazide (100 mg, 0.56 mmoles) in DMF (5 mL) was treated with triethylamine (0.23 mL, 1.68 mmol), HOBT (91 mg, 0.67 mmoles) and EDCI (129 mg, 0.67 mmol) at room temperature for 18 h. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with water, dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 30-50% ethyl acetate/hexanes gradient to afford the product as a solid (59 mg, 27%). LC-MS m/e 387.26 ($M+H^+$)

Example 29

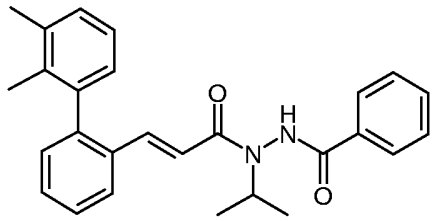
Benzoic acid N'-isopropyl-N'-[3-(2-phenoxy-phenyl)-propionyl]-hydrazide



A solution of 3-(2-phenoxy-phenyl)-propionic acid (110 mg, 0.45 mmoles) and benzoic acid N'-isopropyl-hydrazide (97 mg, 0.54 mmoles) in DMF (5 mL) was treated with diisopropylethylamine (0.20 mL, 1.13 mmol), and PyBroP (315 mg, 0.68 mmol) at room temperature for 18 h. The reaction mixture was partitioned between 1N HCl and ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 30-50% ethyl acetate/hexanes gradient to afford the product as a solid (40 mg, 22%). LC-MS m/e 425.44 ($M+H^+$)

Example 30

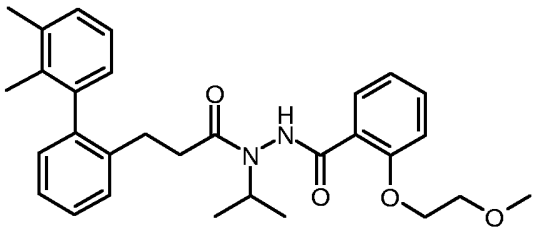
Benzoic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-acryloyl]-N'-isopropyl-hydrazide



A solution of 3-(2',3'-dimethyl-biphenyl-2-yl)-acrylic acid (120 mg, 0.40 mmoles) and benzoic acid N'-isopropyl-hydrazide (71 mg, 0.40 mmoles) in DMF (4 mL) was treated with triethylamine (0.16 mL, 1.19 mmoles), HOBT (64 mg, 0.48 mmoles) and EDCI (91 mg, 0.48 mmol) at room temperature for 48 h. The reaction mixture was partitioned between 1N HCl and ethyl acetate. The organic layer was washed successively with water, 1N NaOH and brine, then dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (30 mg, 18%). LC-MS m/e 403.49($M+H^+$)

Example 31

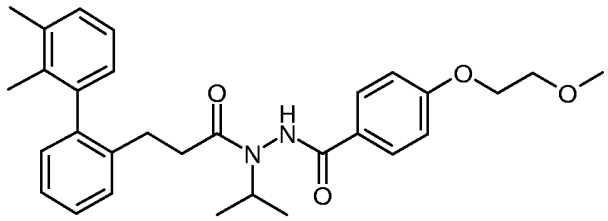
2-(2-methoxy-ethoxy)-benzoic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of 3-(2',3'-dimethyl-biphenyl-2-yl)-propionic acid (110 mg, 0.44 mmoles) and 2-(2-methoxy-ethoxy)-benzoic acid-N'-isopropyl hydrazide (100 mg, 0.40 mmoles) in DMF (3 mL) was treated with triethylamine (0.16 mL, 1.19 mmoles), HOBT (64 mg, 0.48 mmoles) and EDCI (91 mg, 0.48 mmoles) at room temperature for 48 h. The reaction mixture was partitioned between 1N HCl and ethyl acetate. The organic layer was washed successively with water, 1N NaOH and brine, then dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with 10% ethyl acetate/hexanes to afford the product (70 mg, 36%). LC-MS m/e 489.39 ($M+H^+$)

Example 32

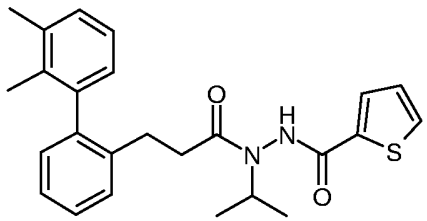
4-(2-methoxy-ethoxy)-benzoic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of 3-(2',3'-dimethyl-biphenyl-2-yl)-propionic acid (110 mg, 0.44 mmoles) and 4-(2-methoxy-ethoxy)-benzoic acid-N'-isopropyl hydrazide (100 mg, 0.40 mmoles) in DMF (3 mL) was treated with triethylamine (0.16 mL, 1.19 mmoles), HOBT (64 mg, 0.48 mmoles) and EDCI (91 mg, 0.48 mmoles) at room temperature for 48 h. The reaction mixture was partitioned between 1N HCl and ethyl acetate. The organic layer was washed successively with water, 1N NaOH and brine, then dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with 10% ethyl acetate/hexanes to afford the product (30 mg, 16%). LC-MS m/e 489.40 ($M+H^+$)

Example 33

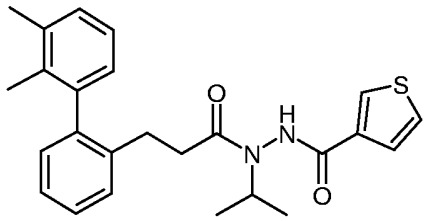
Thiophene-2-carboxylic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of 3-(2',3'-dimethyl-biphenyl-2-yl)-propionic acid (207 mg, 0.81 mmoles) and thiophene-2-carboxylic acid N'-isopropyl-hydrazide (150 mg, 0.81 mmoles) in DMF (8 mL) was treated with triethylamine (0.34 mL, 2.44 mmoles), HOBT (132 mg, 0.98 mmoles) and EDCI (156 mg, 0.98 mmoles) at room temperature for 48 h. The reaction mixture was partitioned between 1N HCl and dichloromethane. The organic layer was washed successively with 1N NaOH and brine, then dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product (173 mg, 51%). LC-MS m/e 421.46 ($M+H^+$)

Example 34

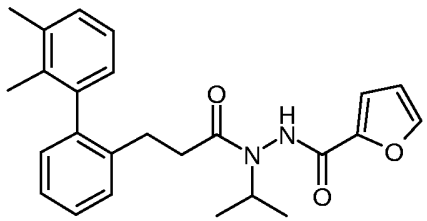
Thiophene-3-carboxylic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of 3-(2',3'-dimethyl-biphenyl-2-yl)-propionic acid (207 mg, 0.81 mmoles) and thiophene-3-carboxylic acid N'-isopropyl-hydrazide (150 mg, 0.81 mmoles) in DMF (8 mL) was treated with triethylamine (0.34 mL, 2.44 mmoles), HOBT (132 mg, 0.98 mmoles) and EDCI (156 mg, 0.98 mmoles) at room temperature for 48 h. The reaction mixture was partitioned between 1N HCl and dichloromethane. The organic layer was washed successively with 1N NaOH and brine, then dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product (172 mg, 50%). LC-MS m/e 421.46 ($M+H^+$)

Example 35

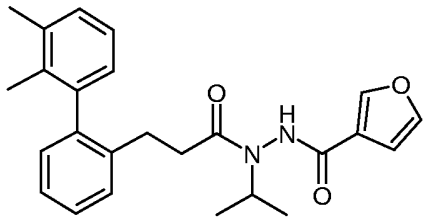
Furan-2-carboxylic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of 3-(2',3'-dimethyl-biphenyl-2-yl)-propionic acid (227 mg, 0.89 mmoles) and furan-2-carboxylic acid N'-isopropyl-hydrazide (150 mg, 0.89 mmoles) in DMF (8 mL) was treated with triethylamine (0.37 mL, 2.67 mmoles), HOBT (144 mg, 1.07 mmoles) and EDCI (205 mg, 1.07 mmoles) at room temperature for 48 h. The reaction mixture was partitioned between 1N HCl and dichloromethane. The organic layer was washed successively with 1N NaOH and brine, then dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product (193 mg, 54%). LC-MS m/e 405.46 ($M+H^+$)

Example 36

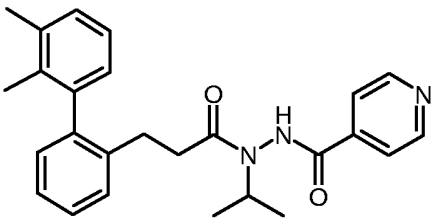
Furan-3-carboxylic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of 3-(2',3'-dimethyl-biphenyl-2-yl)-propionic acid (227 mg, 0.89 mmoles) and furan-3-carboxylic acid N'-isopropyl-hydrazide (150 mg, 0.89 mmoles) in DMF (8 mL) was treated with triethylamine (0.37 mL, 2.67 mmoles), HOBT (144 mg, 1.07 mmoles) and EDCI (205 mg, 1.07 mmoles) at room temperature for 48 h. The reaction mixture was partitioned between 1N HCl and dichloromethane. The organic layer was washed successively with 1N NaOH and brine, then dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product (149 mg, 41%). LC-MS m/e 405.52 ($M+H^+$)

Example 37

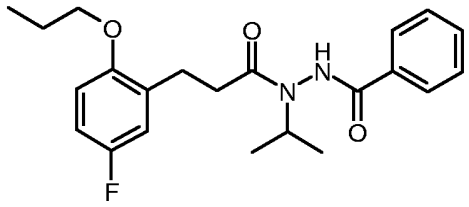
Isonicotinic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide



A solution of 3-(2',3'-dimethyl-biphenyl-2-yl)-propionic acid (127 mg, 0.50 mmoles) and isonicotinic acid N'-isopropyl-hydrazyde (ACROS) (167 mg, 0.60 mmoles) in DMF (5 mL) was treated with diisopropylethylamine (0.35 mL, 2.0 mmoles), and PyBroP (350 mg, 0.75 mmoles) at room temperature for 16 h. The reaction mixture was partitioned between 1N NaOH and ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with 100% ethyl acetate to afford the product (17 mg, 8%). LC-MS m/e 416.49 ($M+H^+$)

Example 38

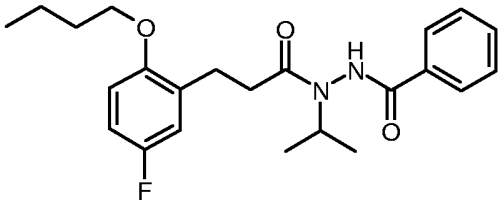
Benzoic acid N'-[3-(5-fluoro-2-propoxy-phenyl)-propionyl]-N'-isopropyl-hydrazide



A solution of 3-(5-fluoro-2-propoxy-phenyl)-propionic acid (160 mg, 0.71 mmoles) and benzoic acid N'-isopropyl-hydrazide (106 mg, 0.60 mmoles) in DMF (3 mL) was treated with diisopropylethylamine (0.26 mL, 1.49 mmoles), and PyBroP (416 mg, 0.89 mmoles) at room temperature for 16 h. The reaction mixture was partitioned between 1N HCl and ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate and brine, then dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-50% ethyl acetate/hexanes gradient to afford the product as a solid (84 mg, 30%). LC-MS m/e 387.26 ($M+H^+$)

Example 39

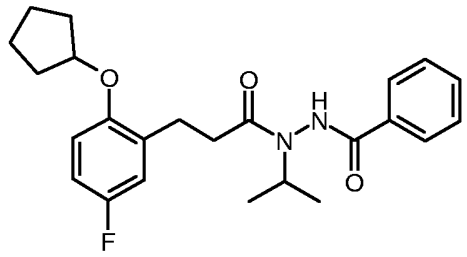
Benzoic acid N'-[3-(2-butoxy-5-fluoro-phenyl)-propionyl]-N'-isopropyl-hydrazide



A solution of 3-(2-butoxy-5-fluoro-phenyl)-propionic acid (300 mg, 1.37 mmoles) and benzoic acid N'-isopropyl-hydrazide (203 mg, 1.14 mmoles) in DMF (3 mL) was treated with diisopropylethylamine (0.50 mL, 2.85 mmoles), and PyBroP (800 mg, 1.71 mmoles) at room temperature for 16 h. The reaction mixture was partitioned between 1N HCl and ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate and brine, then dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-40% ethyl acetate/hexanes gradient to afford the product as a solid (20 mg, 5%). LC-MS m/e 401.28 ($M+H^+$)

Example 40

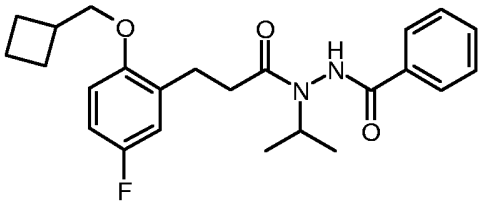
Benzoic acid N'-[3-(2-cyclopentyloxy-5-fluoro-phenyl)-propionyl]-N'-isopropyl-hydrazide



A solution of 3-(2-cyclopentyloxy-5-fluoro-phenyl)-propionic acid (220 mg, 0.87 mmoles) and benzoic acid N'-isopropyl-hydrazide (130 mg, 0.73 mmoles) in DMF (5mL) was treated with diisopropylethylamine (0.32 mL, 1.81 mmoles), and PyBroP (507 mg, 1.09 mmoles) at room temperature for 48 h. The reaction mixture was partitioned between 1N HCl and ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate and brine, then dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-40% ethyl acetate/hexanes gradient to afford the product as a solid (90 mg, 30%). LC-MS m/e 413.32 ($M+H^+$)

Example 41

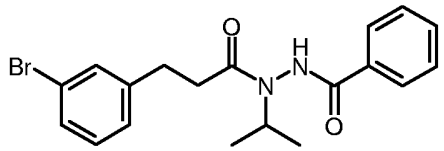
Benzoic acid N'-[3-(2- cyclobutylmethoxy-5-fluoro-phenyl)-propionyl]-N'-isopropyl-hydrazide



A solution of 3-(2-cyclobutylmethoxy-5-fluoro-phenyl)-propionic acid (195 mg, 0.77 mmoles) and benzoic acid N'-isopropyl-hydrazide (115 mg, 0.64 mmoles) in DMF (5mL) was treated with diisopropylethylamine (0.28 mL, 1.61 mmoles), and PyBroP (450 mg, 0.97 mmoles) at room temperature for 48 h. The reaction mixture was partitioned between 1N HCl and ethyl acetate. The organic layer was washed successively with saturated aqueous sodium bicarbonate and brine, then dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-40% ethyl acetate/hexanes gradient to afford the product as a solid (45 mg, 14%). LC-MS m/e 413.32($M+H^+$)

Example 42

Benzoic acid N'-[3-(3-bromo-phenyl)-propionyl]-N'-isopropyl-hydrazide



A solution of (3-(3-bromophenyl)propionic acid (257 mg, 1.12 mmoles) and benzoic acid N'-isopropyl-hydrazide (200 mg, 1.12 mmoles) in DMF (6 mL) was treated with triethylamine (0.47 mL, 3.36 mmoles), HOBT (182 mg, 1.34 mmoles) and EDCI (2.58 mg, 1.34 mmoles) at room temperature for 18 h. The reaction mixture was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated. The crude was absorbed on silica and purified on a silica gel column with a 20-40% ethyl acetate/hexanes gradient to afford the product as a solid (293 mg, 67%).

Example 43

DGAT Phospholipid FlashPlate Assay

Materials for the assay were: PL-FlashPlate: Phospholipid FlashPlates from PerkinElmer, catalog number SMP108; DAG (1,2-Dioleoyl-sn-glycerol) 10 mM suspended in water containing 0.1% Triton X-100; ^{14}C-Pal-CoA (palmitoyl coenzyme A, [palmitoyl-1-^{14}C]) from PerkinElmer, catalog number NEC-555 with a specific activity of 55 mCi/mmol; and DGAT pellet, with a protein concentration of 9.85 mg/ml.

Aqueous buffers were prepared or purchased as follows: The coating buffer (CB) was purchased from PerkinElmer, catalog number SMP900A; the reaction buffer (RB) was 50 mM Tris-HCl, pH 7.5, 100 mM NaCl, 0.01 % BSA in water; the washing buffer (WB) is 50 mM Tris-HCl, pH 7.5, 100 mM NaCl, 0.05 % deoxycholic acid sodium salt in water; the dilution buffer (DB) was 50 mM Tris-HCl, pH 7.5, 100 mM NaCl, 1 mM EDTA, 0.2 % Triton X-100 in water.

1,2-Dioleoyl-sn-glycerol (DAG, 10 mmoles) was diluted to 500 µM with coating buffer (CB). The diluted DAG solution was then added to 384-well PL-FlashPlates at 60 µl per well, and incubated at room temperature for 2 days. The coated plates were then washed twice with washing buffer (WB) before use. Test compounds were serial diluted to 2000, 666.7, 222.2, 74.1, 24.7, 8.2, 2.7 and 0.9 µM in 100 % DMSO. Diluted compound were further diluted 10 fold with reaction buffer (RB). ^{14}C-Pal-CoA was diluted to 8.3 µM with RB. The DGAT pellet was diluted to 0.13 mg protein/ml with dilution buffer

(DB) immediately before it was added to the PL-FlashPlates to start the reaction. 20 µl of the RB-diluted compounds (or 10% DMSO in RB for Total and Blank), 15 µl of RB diluted 14C-Pal-CoA and 15 µl of DB diluted DGAT pellet (DB without DGAT for Blanks) were transferred to each well of the PL-FlashPlates. The reaction mixtures were incubated at 37°C for 1 hour. The reactions were stopped by washing 3 times with WB. Plates were sealed with Top-seal and read on a Topcount instrument.

Calculation of IC_{50}: The IC_{50} values for each compound were generated using an Excel template. The Topcount rpm readings of Total and Blank were used as 0 % and 100 % inhibition. The percent inhibition values of reactions in the presence of compounds were calculated, and plotted against compound concentrations. All data were fitted into a Dose Response One Site model (4 parameter logistic model) as the following:

(A+((B-A)/(1+((x/C)^D)))),

with A and B as the bottom and top of the curve (highest and lowest inhibition), respectively, and C as IC_{50} and D as Hill Coefficient of the compound. The results are summarized in Table 1 below:

Table 1

Compound of Example	Activity in DGAT Phospholipid FlashPlate Assay (A = IC_{50} < 0.3 µM, B = IC_{50} < 1 µM)
1	A
2	A
3	A
4	B
5	A
6	A
7	A
8	A
9	A

Compound of Example	Activity in DGAT Phospholipid FlashPlate Assay (A = IC_{50} < 0.3 μM, B = IC_{50} < 1 μM)
10	A
11	A
12	B
13	A
14	A
15	A
16	A
17	A
18	A
19	A
20	A
21	B
22	A
23	A
24	A
25	B
26	B
27	B
28	B
29	A

Compound of Example	Activity in DGAT Phospholipid FlashPlate Assay (A = IC_{50} < 0.3 µM, B = IC_{50} < 1 µM)
30	A
31	B
32	A
33	A
34	A
35	B
36	B
37	B
38	A
39	A
40	A
41	A
42	B

In Table 2 below specific data for three preferred examples are given:

Table 2

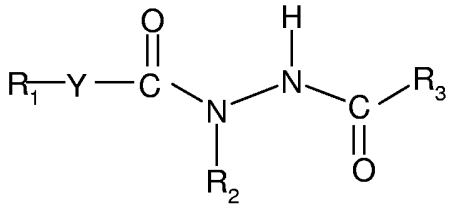
Compound of Example	Activity in DGAT Phospholipid FlashPlate Assay (µM)
9	0.048
18	0.092
3	0.072

It is to be understood that the invention is not limited to the particular embodiments of the invention described above, as variations of the particular embodiments may be made and still fall within the scope of the appended claims.

***

Claims

1. A compound of the formula I



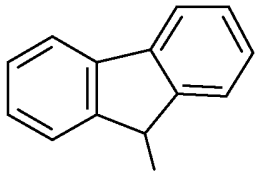
I

,

wherein

Y is (C_1-C_6) alkylene or (C_1-C_6) alkylene substituted with aryl;

R_1 is substituted or unsubstituted aryl or



;

R_2 is (C_1-C_6) alkyl;

R_3 is unsubstituted aryl,
substituted aryl with a group independently selected from the group consisting of halogen, (C_1-C_6) alkyl, and $-O(CH_2)_mOCH_3$,
unsubstituted saturated, unsaturated or partially saturated heterocycyl which is a 5- or 6- membered heteroaromatic ring connected by a ring carbon atom which has from 1 to 3 hetero ring atoms selected from the group consisting of S, N and O,
substituted saturated, unsaturated or partially saturated heterocycyl substituted with (C_1-C_6) alkyl, or
substituted or unsubstituted 5-10-membered cycloalkyl ring; and

m is 0, 1, 2 or 3,

and pharmaceutically acceptable salts thereof.

2. The compound of formula I according to claim 1, wherein

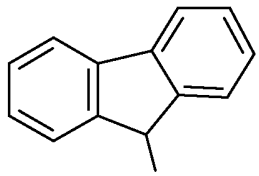
Y is CH=CH, $(CH_2)_n$, or $-CH(Ar)CH_2$; and n is 1 or 2.

3. The compound of formula I according to claims 1 or 2, wherein Y is $(CH_2)_n$ and n is 2.

4. The compound of formula I according to any one of claims 1 to 3, wherein

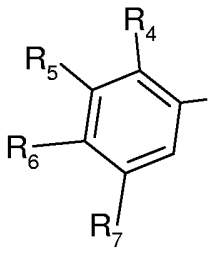
R_1 is unsubstituted aryl or substituted aryl with a group independently selected from the group consisting of H, $(C_1\text{-}C_6)$ alkyl, halogen,
unsubstituted aryl,
aryl which is mono-, di- or tri-substituted with a group independently selected from the group consisting of halogen, $(C_1\text{-}C_6)$ alkyl, $(C_1\text{-}C_6)$ alkoxy, $-CF_3$, $-OCF_3$, $-SCH_3$, $-CN$, $-SO_2CH_3$, $-NO_2$, and $-(CH)_2Ar$,
$-O$-phenyl, $-O(CH_2)_pCH_3$, or
unsubstituted or substituted 4-10 membered cycloalkyl ring attached to the aryl ring by oxygen or methyloxy;

and p is 0, 1, 2, or 3; or

R_1 is  .

5. The compound of formula I according to any one of claims 1 to 4, wherein

R_1 is



;

R_4 is H, $(C_1\text{-}C_6)$ alkyl,
unsubstituted aryl, aryl which is mono-, di- or tri-substituted with a group independently selected from the group consisting of halogen, $(C_1\text{-}C_6)$ alkyl, $(C_1\text{-}C_6)$ alkoxy, $-CF_3$, - $-OCF_3$, $-SCH_3$,
, $-CN$, $-SO_2CH_3$, $-NO_2$, and $-(CH)_2Ar$,
$-O$-phenyl, $-O(CH_2)_pCH_3$, or

unsubstituted or substituted 4-10 membered cycloalkyl ring attached to the aryl ring by oxygen or methyloxy;

R_5, R_6, R_7 independently of each other are H, halogen, phenyl or (C_1-C_6) alkyl; and

p is 0, 1, 2 or 3,

and pharmaceutically acceptable salts thereof.

6. The compound of formula I according to any one of claims 1 to 5, wherein R_4 is selected from the group consisting of -O-phenyl, $-O(CH_2)_pCH_3$, or an unsubstituted or substituted 4-10 membered cycloalkyl ring attached to the aryl ring by oxygen or methyloxy; and p is 1, 2, or 3.

7. The compound of formula I according to any one of claims 1 to 6, wherein R_4 is a cyclopentyloxy or cyclobutylmethoxy group.

8. The compound of formula I according to any one of claims 1 to 5, wherein R_4 is phenyl which is mono-, di- or tri-substituted with a group independently selected from the group consisting of halogen, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, $-CF_3$ and –CN.

9. The compound of formula I according to any one of claims 1 to 8, wherein R_2 is isopropyl.

10. The compound of formula I according to any one of claims 1 to 9, wherein R_3 is unsubstituted phenyl or substituted phenyl with a group independently selected from the group consisting of halogen, (C_1-C_6) alkyl, and $–O(CH_2)_mOCH_3$, and m is 0, 1, 2, or 3.

11. The compound of formula I according to any one of claims 1 to 9, wherein R_3 is a 5- or 6- membered heteroaromatic ring connected by a ring carbon atom which has from 1 to 3 hetero ring atoms selected from the group consisting of S, N and O and which is unsubstituted or substituted with (C_1-C_6) alkyl.

12. The compound of formula I according to any one of claims 1 to 9 and 11, wherein R_3 is a 5- or 6- membered heteroaromatic ring selected from the group consisting of thiophene, furane and pyridine.

13. The compound of formula I according to any one of claims 1 to 10, wherein R_1 and R_3, independently of each other, are phenyl.

14. A compound of formula I according to claim 1, selected from the group consisting of

benzoic acid N'-isopropyl-N'-[3-(3'-methoxy-biphenyl-2-yl)-propionyl]-hydrazide,

benzoic acid N'-[3-(2-cyclopentyloxy-5-fluoro-phenyl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(3'-chloro-4'-fluoro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2'-chloro-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2',5'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2-butoxy-5-fluoro-phenyl)-propionyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(5'-isopropyl-2'-methoxy-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide,

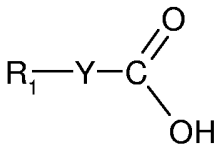
benzoic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-acryloyl]-N'-isopropyl-hydrazide,

benzoic acid N'-[3-(2',3'-dimethyl-biphenyl-2-yl)-propionyl]-N'-isopropyl-hydrazide, and

benzoic acid N'-[3-(2- cyclobutylmethoxy-5-fluoro-phenyl)-propionyl]-N'-isopropyl-hydrazide.

15. A process for the manufacture of compounds according to any one of claims 1 to 14, which process comprises

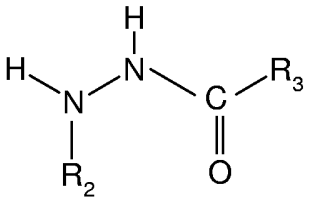
coupling a compound of the general formula



II

,

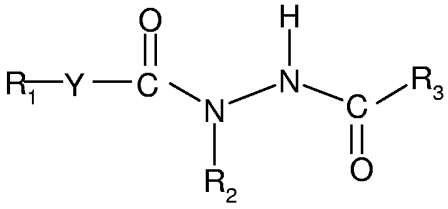
wherein Y and R_1 are as defined in claim 1,
with a hydrazide of the formula



III

,

wherein R_2 and R_3 are as defined in claim 1,
under basic conditions to obtain a compound of the formula



I

and, if desired, converting the compound of formula I into a pharmaceutically acceptable salt.

16. Compounds according to any one of claims 1 to 14 when manufactured by a process according to claim 15.

17. Compounds according to any one of claims 1 to 14 for use as therapeutically active substances.

18. The use of compounds according to any one of claims 1 to 14 for the preparation of medicaments for the treatment and/or prevention of diseases which are associated with inhibition of diacylglycerol acyltransferase.

19. The use according to claim 18 for the treatment of obesity, type II diabetes or metabolic syndrome.

20. A method for the treatment of obesity, type II diabetes or metabolic syndrome in a patient in need thereof, which comprises administering to said patient a therapeutically effective amount of a compound of the formula I according to claim 1.

21. The method according to claim 20, wherein said therapeutically effective amount of said compound is from about 10 mg to about 1000 mg per day.

22. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof according to claim 1, and a pharmaceutically acceptable carrier.

23. The pharmaceutical composition according to claim 22 for use in the treatment of obesity, type II diabetes or metabolic syndrome.

24. The novel compounds, processes and methods as well as the use of such compounds substantially as described herein before.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/061900

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C243/38 C07C255/56 C07D333/38 C07D307/68 C07D213/56
A61P3/00 A61K31/166 A61K31/277 A61K31/4409 A61K31/341
A61K31/381

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D C07C A61P A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 424 333 A (WING ET AL) 13 June 1995 (1995-06-13) compounds 689,693,694,700,706,708,879,881-886,940,94 2	1,2,4,5, 10,13
X	US 6 013 836 A (HSU ET AL) 11.January 2000 (2000-01-11) compounds 694,881-886,939,942	1,2,4,5, 10,13
X	GOTTSCHLING, DIRK ET AL: "Combinatorial and rational strategies to develop non-peptidic .alpha.4.beta.7-integrin antagonists from cyclic peptides" ANGEWANDTE CHEMIE, INTERNATIONAL EDITION , 41(16), 3007-3011 CODEN: ACIEF5; ISSN: 1433-7851, 2002, XP002385990 compound 12	1,9

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 June 2006	04/07/2006

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/061900

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WANG, QINGMIN ET AL: "Alkylgermasesquioxide derivatives of tert-butyl-diacylhydrazines" HETEROATOM CHEMISTRY , 14(4), 293-297 CODEN: HETCE8; ISSN: 1042-7163, 2003, XP002385991 compound 8	1,2,4,5, 10,13
X	EP 0 347 216 A2 (ROHM AND HAAS CO., USA) 20 December 1989 (1989-12-20) page 18, lines 37,39	1,4,5, 10,13
X	MUKHERJEE, R.: "Conversion of thioamides and N2-acyl-N1-thioacylhydrazines into amides and N1,N2-diacyl-N1-methylhydrazines by trimethyloxonium fluoroborate" JOURNAL OF THE CHEMICAL SOCIETY [SECTION] D: CHEMICAL COMMUNICATIONS , (18), 1113-4 CODEN: CCJDAO; ISSN: 0577-6171, 1971, XP008065519 compound (6)D	1,2,4,5, 10,13
X	TAKAMIZAWA, AKIRA ET AL: "Pyrimidine derivatives and related compounds. LXXXVIII. Reactions of 1,3,4-oxadiazolium salts with dialkyl acylphosphonates. Novel synthesis of 1,3,4-oxadiazin-5-one derivatives" CHEMICAL & PHARMACEUTICAL BULLETIN , 23(5), 948-54 CODEN: CPBTAL; ISSN: 0009-2363, 1975, XP008065520 compounds XVa-f	1,5,10, 13
A	PATENT ABSTRACTS OF JAPAN vol. 2003, no. 12, 5 December 2003 (2003-12-05) & JP 2004 067635 A (OTSUKA PHARMACEUT FACTORY INC), 4 March 2004 (2004-03-04) abstract	1-24

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/061900

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

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

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

Although claims 20 and 21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

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

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

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

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

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

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

Remark on Protest

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

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/061900

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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US 6013836 A	11-01-2000	NONE		
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		AU	3645489 A	21-12-1989
		BR	8902892 A	20-03-1990
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		EG	18874 A	30-06-1994
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		NZ	229536 A	26-05-1992
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		ZA	8904510 A	28-02-1990
JP 2004067635 A	04-03-2004	NONE		