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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 July 2015 (02.07.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/097713 A1

(51) International Patent Classification:
C07D 491/08 (2006.01) *A61K 31/472* (2006.01)
A61K 31/404 (2006.01) *A61K 31/4985* (2006.01)
A61K 31/407 (2006.01) *A61K 31/519* (2006.01)
A61K 31/4162 (2006.01) *C07D 215/06* (2006.01)
A61K 31/4365 (2006.01) *C07D 215/20* (2006.01)
A61K 31/437 (2006.01) *C07D 217/04* (2006.01)
A61K 31/439 (2006.01) *C07C 229/14* (2006.01)
A61K 31/47 (2006.01)

(21) International Application Number:
PCT/IN2014/000704

(22) International Filing Date:
3 November 2014 (03.11.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
3577/MUM/2013 14 November 2013 (14.11.2013) IN

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

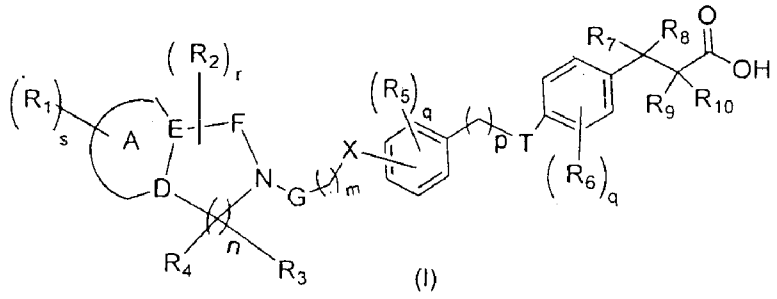
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) Title: NOVEL HETEROCYCLIC COMPOUNDS



(I)

(57) Abstract: The present invention relates to novel GPR 40 agonists of the general formula (I), their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, pharmaceutical compositions containing them, methods for their preparation, use of these compounds in medicine and the intermediates involved in their preparation.

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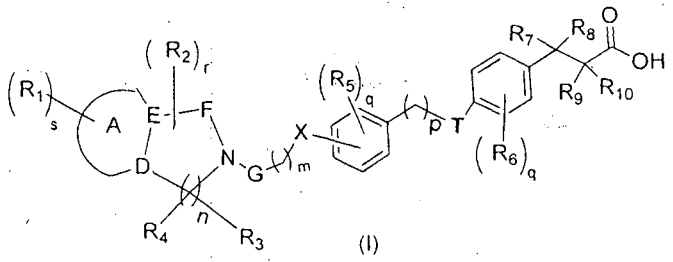
NOVEL HETEROCYCLIC COMPOUNDS

FIELD OF INVENTION

The present invention relates to novel GPR 40 agonists of the general formula (I), their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, pharmaceutical compositions containing them, methods for their preparation, use of these compounds in medicine and the intermediates involved in their preparation.



(I)

The present invention is directed to G-protein coupled receptor (GPCR) agonists that are useful for the treatment of obesity, diabetes and related metabolic disorders.

The compounds of the general formula (I) lower blood glucose, regulate peripheral satiety, lower or modulate triglyceride levels and/or cholesterol levels and/or low-density lipoproteins (LDL) and raises the high-density lipoproteins (HDL) plasma levels and hence are useful in combating different medical conditions, where such lowering (and raising) is beneficial. Thus, it could be used in the treatment and/or prophylaxis of obesity, hyperlipidemia, hypercholesteremia, hypertension, atherosclerotic disease events, vascular restenosis, diabetes and many other related conditions.

The compounds of general formula (I) are useful to prevent or reduce the risk of developing atherosclerosis, which leads to diseases and conditions such as arteriosclerotic cardiovascular diseases, stroke, coronary heart diseases, cerebrovascular diseases, peripheral vessel diseases and related disorders.

These compounds of general formula (I) are useful for the treatment and/or prophylaxis of metabolic disorders loosely defined as Syndrome X. The characteristic features of Syndrome X include initial insulin resistance followed

by hyperinsulinemia, dyslipidemia and impaired glucose tolerance. The glucose intolerance can lead to non-insulin dependent diabetes mellitus (NIDDM, Type 2 diabetes), which is characterized by hyperglycemia, which if not controlled may lead to diabetic complications or metabolic disorders caused by insulin resistance. Diabetes is no longer considered to be associated only with glucose metabolism, but it affects anatomical and physiological parameters, the intensity of which vary depending upon stages/duration and severity of the diabetic state. The compounds of this invention are also useful in prevention, halting or slowing progression or reducing the risk of the above mentioned disorders along with the resulting secondary diseases such as cardiovascular diseases, like arteriosclerosis, atherosclerosis; diabetic retinopathy, diabetic neuropathy and renal disease including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal diseases, like microalbuminuria and albuminuria, which may be result of hyperglycemia or hyperinsulinemia.

BACKGROUND OF THE INVENTION

Diabetes mellitus is a serious disease afflicting over 100 million people worldwide. In the United States, there are more than 12 million diabetics, with 600,000 new cases diagnosed each year.

Diabetes mellitus is a diagnostic term for a group of disorders characterized by abnormal glucose homeostasis resulting in elevated blood sugar. There are many types of diabetes, but the two most common are Type I (also referred to as insulin-dependent diabetes mellitus or IDDM) and Type II (also referred to as non-insulin-dependent diabetes mellitus or NIDDM).

The etiology of the different types of diabetes is not the same; however, everyone with diabetes has two things in common: overproduction of glucose by the liver and little or no ability to move glucose out of the blood into the cells where it becomes the body's primary fuel.

People who do not have diabetes rely on insulin, a hormone made in the pancreas, to move glucose from the blood into the cells of the body. However, people who

have diabetes either don't produce insulin or can't efficiently use the insulin they produce; therefore, they can't move glucose into their cells. Glucose accumulates in the blood creating a condition called hyperglycemia, and over time, can cause serious health problems.

Diabetes is a syndrome with interrelated metabolic, vascular, and neuropathic components. The metabolic syndrome, generally characterized by hyperglycemia, comprises alterations in carbohydrate, fat and protein metabolism caused by absent or markedly reduced insulin secretion and/or ineffective insulin action. The vascular syndrome consists of abnormalities in the blood vessels leading to cardiovascular, retinal and renal complications. Abnormalities in the peripheral and autonomic nervous systems are also part of the diabetic syndrome.

About 5% to 10% of the people who have diabetes have IDDM. These individuals don't produce insulin and therefore must inject insulin to keep their blood glucose levels normal. IDDM is characterized by low or undetectable levels of endogenous insulin production caused by destruction of the insulin-producing β cells of the pancreas, the characteristic that most readily distinguishes IDDM from NIDDM. IDDM, once termed juvenile-onset diabetes, strikes young and older adults alike.

Approximately 90 to 95% of people with diabetes have Type II (or NIDDM). NIDDM subjects produce insulin, but the cells in their bodies are insulin resistant: the cells don't respond properly to the hormone, so glucose accumulates in their blood. NIDDM is characterized by a relative disparity between endogenous insulin production and insulin requirements, leading to elevated blood glucose levels. In contrast to IDDM, there is always some endogenous insulin production in NIDDM; many NIDDM patients have normal or even elevated blood insulin levels, while other NIDDM patients have inadequate insulin production (Rotwein, R. et al. N. Engl. J. Med. 308, 65-71 (1983)). Most people diagnosed with NIDDM are age 30 or older, and half of all new cases are age 55 and older. Compared with whites and Asians, NIDDM is more common among Native Americans, African-Americans, Latinos, and Hispanics. In addition, the onset can be insidious or even clinically non-apparent, making diagnosis difficult.

The primary pathogenic lesion on NIDDM has remained elusive. Many have suggested that primary insulin resistance of the peripheral tissues is the initial event. Genetic epidemiological studies have supported this view. Similarly, insulin secretion abnormalities have been argued as the primary defect in NIDDM. It is likely that both phenomena are important contributors to the disease process (Rimoin, D. L., et. al. Emery and Rimoin's Principles and Practice of Medical Genetics 3rd Ed. 1:1401-1402 (1996)).

Many people with NIDDM have sedentary lifestyles and are obese; they weigh approximately 20% more than the recommended weight for their height and build. Furthermore, obesity is characterized by hyperinsulinemia and insulin resistance, a feature shared with NIDDM, hypertension and atherosclerosis.

The G-protein –coupled receptor GPR 40 functions as a receptor for long-chain free fatty acids (FFAs) in the body and as such is implicated in a large number of metabolic conditions in the body. For example it has been alleged that a GPR 40 agonist promotes insulin secretion whilst a GPR 40 antagonist inhibits insulin secretion and so depending upon the circumstances the agonist and antagonist may be useful as therapeutic agents for the number of insulin related conditions such as type 2 diabetes, obesity, impaired glucose tolerance, insulin resistance, neurodegenerative diseases and the like.

There is increasing evidences that lipids can also serve as extracellular ligands for a specific class of receptors and thus act as "nutritional sensors" (Nolan CJ et al. J. Clinic. Invest., 2006, 116, 1802-1812The free fatty acids can regulate cell function. Free fatty acids have demonstrated as ligands for orphan G protein-coupled receptors (GPCRs) and have been proposed to play a critical role in physiological glucose homeostasis.

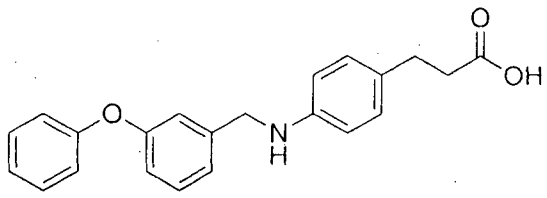
GPR40, GPR120, GPR41 and GPR43 exemplify a growing number of GPCRs that have been shown to be activated by free fatty acids. GPR40 and GPR120 are activated by medium to long-chain free fatty acids whereas GPR 41 and GPR 43 are activated by short-chain fatty acid (Brown AJ et al, 2003).

GPR 40 is highly expressed on pancreatic β-cells, and enhances glucose-stimulated insulin secretion (*Nature*, **2003**, *422*, 173-176, *J. Bio. Chem.* **2003**, *278*, 11303-11311, *Biochem. Biophys. Res. Commun.* **2003**, *301*, 406-410).

Free fatty acids regulate insulin secretion from pancreatic β cells through GPR40 is reported (*Lett. to Nature* **2003**, *422*, 173-176).

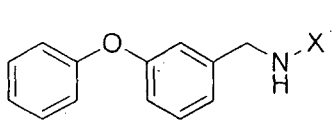
GlaxoSmithKline Research and Development, US published an article in Bioorg. *Med. Chem. Lett.* **2006**, *16*, 1840-1845 titled Synthesis and activity of small molecule GPR40 agonists. (Does this describe GW9508?)Another article titled Pharmacological regulation of insulin secretion in MIN6 cells through the fatty acid receptor GPR40: Identification of agonist and antagonist small molecules is reported in

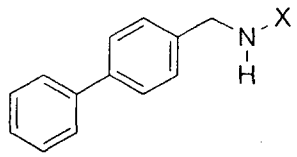
Br. J. Pharmacol. **2006**, *148*, 619-928 from GlaxoSmithKline, USA (Does this describe GW9508?)



GW 9508

Solid phase synthesis and SAR of small molecule agonists for the GPR 40 receptor is published in *Bioorg. Med. Chem. Lett.* **2007**, *16*, 1840-1845 by Glaxo SmithKline Res. & Dev. USA, including those with the following structures.

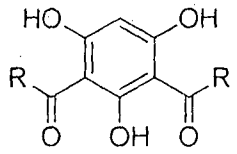




Johnson & Johnson Pharmaceutical Research and development , USA published " Synthesis and Biological Evaluation of 3-Aryl-3-(4-phenoxy)-propanoic acid as a Novel Series of G-protein –coupled receptor 40 agonists(*J. Med. Chem.* **2007**, *16*, 2807-2817)

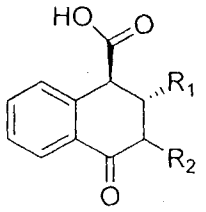
National Institutes of Health, Bethesda, Maryland published "Bidirectional Iterative Approach to the Structural Delineation of the Functional Chemo print in GPR 40 for agonist Recognition (*J. Med. Chem.* **2007**, 50, 2981-2990).

Discovery of diacyl phloroglucinols of the following formula



as a new class of GPR40 (FFAR1) agonists has been published by Piramal Life Sciences, Ltd. in *Bioorg. Med. Chem. Lett.* **2008**, 18, 6357-6361

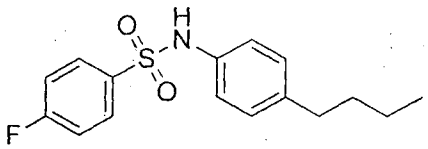
Synthesis and SAR of 1,2,3,4-tetrahydroisoquinoline-1-ones as novel G-protein coupled receptor40(GPR40) antagonists of the following formula has been published in *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2400-2403 by Pfizer



Piramal Life Sciences Ltd. published "Progress in the discovery and development of small molecule modulators of G-protein coupled receptor 40(GPR40/FFA1/FFAR1), an emerging target for type 2 diabetes" in *Exp. Opin. Therapeutic Patents* **2009**, *19*(2), 237-264.

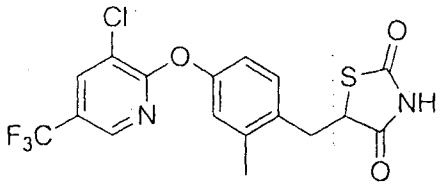
There was a report published in *Zhongguo Bingli Shengli Zazhi* **2009**, *25*(7), 1376-1380 from Sun Yat. Sen University, Guangzhou, which mentions the role GPR 40 on lipoapoptosis.

A novel class of antagonists for the FFA's receptor GPR 40 was published in *Biochem. Biophy. Res. Commun.* **2009**, *390*, 557-563.

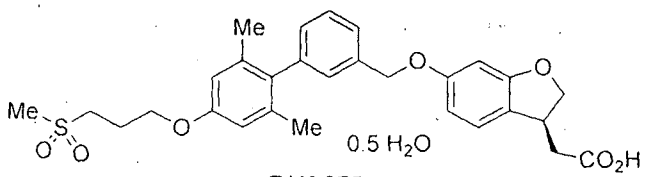


N41(DC260126)

Merck Res. Laboratories published "Discovery of 5-aryloxy-2,4-thiazolidinediones as potent GPR40 agonists" having the following formula in *Bioorg. Med. Chem. Lett.* **2010**, 20, 1298-1301

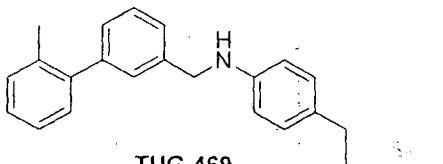


Discovery of TAK-875, a potent, selective, and orally bioavailable GPR 40 agonist is reported by Takeda Pharmaceutical Ltd. *ACS Med. Chem. Lett.* **2010**, *1*(6), 290-294



TAK-875
EC50= 14 nM
Ki= 38 nM

In another report from University of Southern Denmark" Structure –Activity of Dihydrocinnamic acids and discovery of potent FFA1 (GPR40) agonist TUG-469" is reported in *ACS Med. Chem. Lett.* **2010**, 1(7), 345-349.



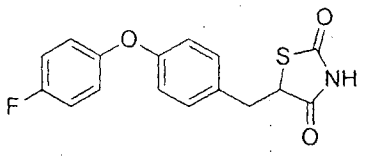
TUG-469

The free fatty acid 1 receptor (FFAR1 or GPR40), which is highly expressed on pancreatic β-cells and amplifies glucose-stimulated insulin secretion, has emerged as an attractive target for the treatment of type 2 diabetes (*ACS Med. Chem. Lett. 2010, 1(6), 290-294*).

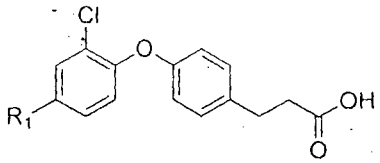
G-protein coupled receptor (GPR40) expression and its regulation in human pancreatic islets: The role of type 2 diabetes and fatty acids is reported in *Nutrition Metabolism & Cardiovascular diseases* **2010**, *20*(1), 22-25

Ranbaxy reported "Identification of Berberine as a novel agonist of fatty acid receptor GPR40" in *Phytother Res.* **2010**, *24*, 1260-63.

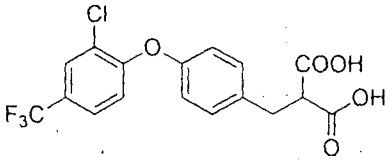
The following substituted 3-(4-aryloxyaryl)-propanoic acids as GPR40 agonists are reported by Merck Res. Lab. in *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3390-3394



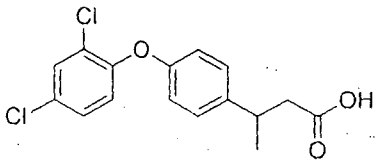
1. EC_{50}=0.74 μM



2.R_1= Cl (EC_{50}=1.358 μM)
3.R_1= CF_3 (EC_{50}=0.686 μM)



4. EC_{50}=0.970 μM

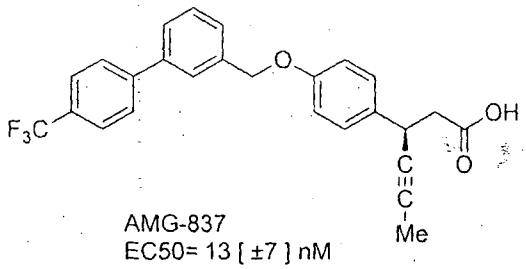


5. EC_{50}=2.484 μM

CoMSIA study on substituted aryl alkanoic acid analogs as GPR 40 agonists is reported *Chem. Bio. Drug. Des.* **2011**, *77*, 361-372

Takeda further published "Design, Synthesis and biological activity of potential and orally available G-protein coupled receptor 40 agonists" in *J. Med. Chem.* **2011**, *54*(5), 1365-1378.

Amgen disclosed a potent orally bioavailable GPR 40 agonist AMG-837 in *Bioorg. Med. Chem. Lett.* **2012**, *22*, 1267-1270



AMG-837
EC50= 13 [±7] nM

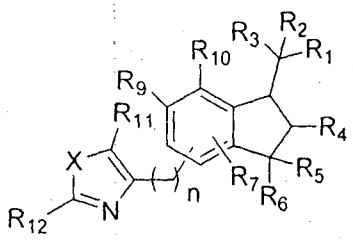
Discovery of phenylpropanoic acid derivatives containing polar functionalities as Potent and orally bioavailable G protein-coupled receptor 40 Agonist for the treatment of type 2 Diabetes is reported in *J. Med. Chem.* **2012**, *55*, 3756-3776 by Takeda.

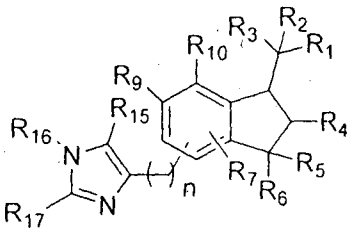
Discovery of AM-1638: A potent and orally bioavailable GPR40/FFA1 full agonist is reported in *ACS Med. Chem. Lett.* **2012**, *3*(9), 726-730.

Optimization of (2,3-Dihydro-1-benzofuran-3-yl)acetic acids: Discovery of a Non-free Fatty acid like, highly bioavailable G protein-coupled receptor 40/free

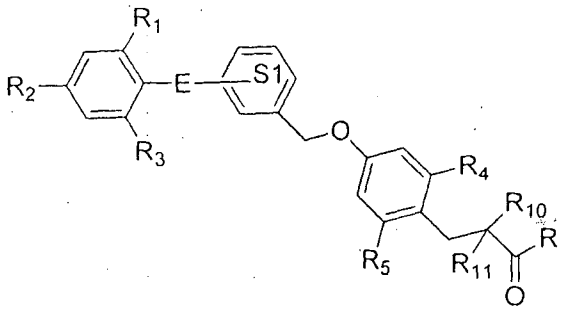
acid receptor 1 agonist as a glucose –dependent insulinotropic agent is reported by Takeda in *J. Med. Chem.* **2012**, *55*, 3960-3974.

Bayer disclosed indane, dihydrobenzofuran, and tetrahydronaphthalene carboxylic acid derivatives and their use as antidiabetics in patent application no. WO 2004011446 with the following formulae





Takeda disclosed 3-(4-Benzyloxyphenyl) propanoic acid derivatives in a patent WO 2005063729 with the following general formula:

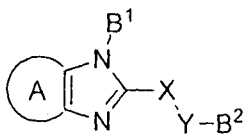


WO 2005086661 A1 (22 September 2005, Amgen Inc.) disclosed compounds, pharmaceutical compositions and methods for use in treating metabolic disorders, having the following formula:

$$Q\text{-}L^1\text{-}P\text{-}L^2\text{-}M\text{-}X\text{-}L^3\text{-}A$$

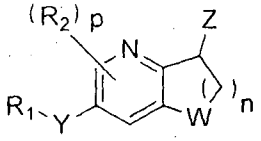
US 2006/0004012, Akerman et al. disclosed certain compounds, pharmaceutical compositions and methods for use in treating metabolic disorders, the said compounds being GPR 40 agonists.

WO 06/ 038738 A1 (13th April 2006, Takeda Pharmaceutical Ltd., Japan) disclosed certain receptor function regulating agent with the following general structure

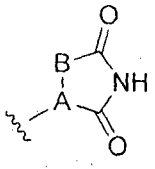


Merck & Co. disclosed antidiabetic bicyclic compounds in WO2006083781. Disclosed therein are bicyclic compounds containing a phenyl or pyridyl ring fused to a cycloalkyl or heterocyclic ring, to which is attached a 5-membered heterocyclic ring, including pharmaceutically acceptable salts and prodrugs thereof, as agonists of G protein coupled receptor 40(GPR40) and are useful as therapeutic compounds, particularly in the treatment of Type 2 diabetes mellitus, and of conditions that are often associated with the disease, including obesity and lipid disorders, such as mixed or diabetic dyslipidemia, hyperlipidemia, hypercholesterolemia, and hypertriglyceridemia are disclosed.

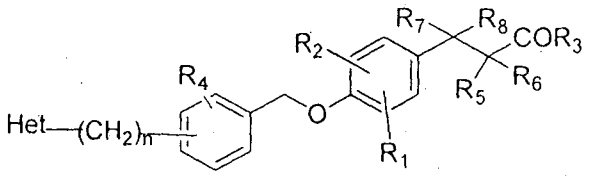
Merck & Co., in another patent application WO 2006083612 disclosed antidiabetic bicyclic compounds, wherein, the bicyclic compounds contain a fused pyridine ring including pharmaceutically acceptable salts and prodrugs thereof, as agonists of G protein coupled receptor 40 (GPR40) and are useful as therapeutic compounds, particularly in the treatment of Type 2 diabetes mellitus, and of conditions that are often associated with the disease, including obesity and lipid disorders, such as mixed or diabetic dyslipidemia, hyperlipidemia, hypercholesterolemia, and hypertriglyceridemia. The compounds disclosed in the patent application has the following general structure:



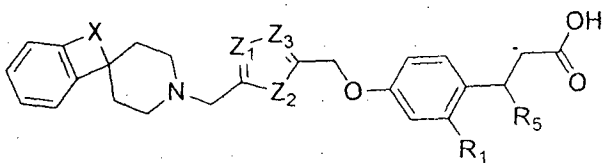
wherein Z is selected from the group consisting of $CR_3R_4CO_2R_5$, $-OCR_3R_4CO_2R_5$, N (R_6) ($CR_3R_4CO_2R_5$), $-SCR_3R_4CO_2R_5$, tetrazole, and the heterocyclic ring II.



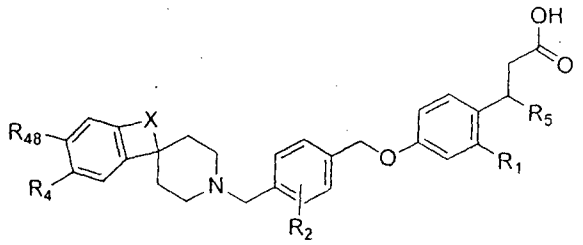
Condensed ring compounds have been disclosed by Yasum et al. in a patent US 7820837. The following formula mentioned in US 7517910 claims compounds having a GPR 40 receptor function modulating action, which are useful as insulin secretagogues, agents for the prophylaxis or treatment of diabetes and the like



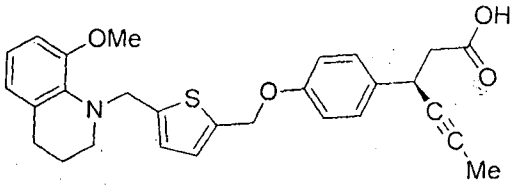
Novel Spiropiperidine compounds have been mentioned by Eli Lilly & Company in WO 2011066183



Eli Lilly also disclosed the following Spiropiperidines in patent application no. US20110092531

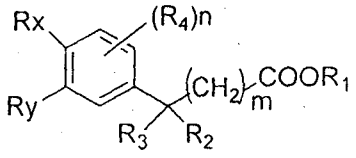


Novel 1,2,3,4-tetrahydroquinoline derivatives useful for the treatment of diabetes have been described by Eli Lilly & Company in patent application no. WO 2013025424

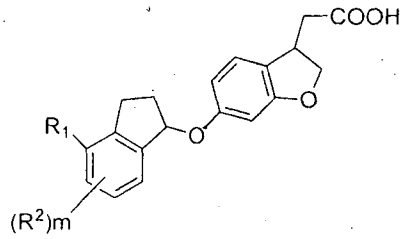


A patent application, WO 2013147443 titled "Preparation of β- substituted carboxylic acid derivatives for the treatment of diabetes" has been published by Daichi Sankyo.

Piramal Enterprises Limited has published a patent application no. WO 2013/128378 for phenyl alkanoic acid derivatives as GPR agonists with the structure below



Boehringer Ingelheim has published patent application numbers WO 2013/144097 & WO 2013/144098 titled "New indanyloxy dihydrobenzofuranyl acetic acid derivatives and their use as GPR receptor agonists" with the structures defined below



Novel therapeutic target for treatment of cancers and related therapies and methods are disclosed in patent application no. WO 2014145817 by Children's Medical Center Corporation.

WO 2014146604 disclosed certain fused ring compounds having GPR40 receptor function regulating action.

Tricyclic compound and use thereof has been published by SK Chemicals Co., Ltd. in patent application no. WO2014133361.

Certain antidiabetic bicyclic compounds have been disclosed in patent application no. WO2014130608.

Boehringer Ingelheim International disclosed certain other indanyloxy dihydrobenzofuranyl acetic acids in patent application nos. WO2013164292, WO2014122067, WO2014086712, and WO2014082918 & US20140148462, US20140221349 & US20140163025.

Takeda Pharmaceutical Company Limited have disclosed, fused cyclic compounds as GPR40 receptor modulators in a patent application no. EP2743268.

Bristol-Myers Squibb has disclosed Dihydropyrazole GPR40 modulators in patent application nos. WO2014078611, WO2014078610, WO2014078609 & WO2014078608.

LG Life Sciences Limited has disclosed certain GPR40 receptor agonist in patent WO2014073904. Hancke Orozco et al. have disclosed compounds, compositions, and methods for decreasing intestinal glucose uptake and inducing incretin release in patent application no. US20140128333. Merck Sharp & Dohme Corp.

disclosed antidiabetic tricyclic compounds in patents application nos. US20140045746, WO2014022528 and in another application disclosed certain bridged and fused antidiabetic compounds in patent US 20140038970.

Novel fluoro-substituted compounds capable of modulating the G-protein coupled receptor

GPR40 have been disclosed in patent application no. US20140058125.

Mochida Pharmaceutical Co. has disclosed Cyclic amide derivative in patent US20140057871. Negoro et al. have disclosed certain carboxylic acid compounds in patent application no. US20120035196. Several other patent applications have disclosed a varied number of compounds as GPR40 modulators. Some of the representative literature is provided below:

Chandra Sekhar Gudla et al have disclosed some new 3-substituted 3-(aryloxyaryl)-propanoic acid in IJCPS, 2014, Vol.2(5), 852-861.

WO 2005095338, WO 2006038738, WO 2006083612, WO 2006083781, WO 2007013679, WO 2007136572, WO 2007136573, WO 2007049050, WO 20070123225, WO 2008002931, WO 2008054674, WO 2008054675, WO 200830520, WO 2008130514, WO 2008139987, WO 2009058237, WO 2009048527, WO 2009054423, US 7968552, WO 2009038204, WO 2010045258, WO 2010012650, WO 2010085522, WO 2010085525, WO 2010085528, WO 2010091176, WO 2011044073, WO 2011052756, WO 2011078371, WO 2011069958, WO 2011083752, WO 2012111849, WO 2012108478, WO 2012074126, WO 2012020738, WO 2012004261, WO 2012010413, WO 2012010413 , WO 2012011125 etc.

Drugs aimed at the pathophysiology associated with insulin dependent Type I diabetes and non-insulin dependent Type II diabetes have many potential side effects and do not adequately address the dyslipidemia and hyperglycemia in a high proportion of patients. Treatment is often focused at individual patient needs using diet, exercise, hypoglycaemic agents and insulin, but there is a continuing need for novel antidiabetic agents, particularly ones that may be better tolerated with fewer adverse effects.

Similarly, metabolic syndrome (syndrome X) which is characterized by hypertension and its associated pathologies including atherosclerosis, lipidemia, hyperlipidemia and hypercholesterolemia have been associated with decreased insulin sensitivity which can lead to abnormal blood sugar levels when challenged. Myocardial ischemia and microvascular disease is an established morbidity associated with untreated or poorly controlled metabolic syndrome.

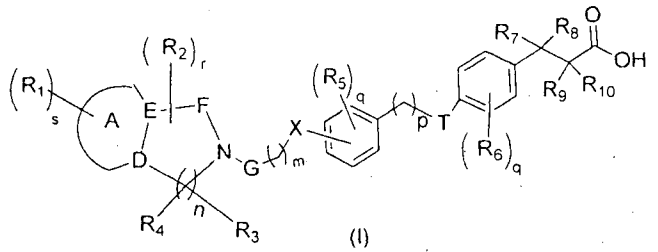
There is a continuing need for novel antiobesity and antidiabetic agents, particularly ones that are well tolerated with few adverse effects.

The present invention is directed to agonists of GPR 40 that are useful for the treatment of diabetes. In humans, GPR 40 is expressed in the pancreas. As discussed above, several GPR 40 agonists have been developed and are continuing to be developed. However, the therapeutic potential of these compounds to treat diseases has not yet been proved and so there remains the need to develop newer medicines which are better or of comparable efficacy with the present treatment regimes, have lesser side effects and require a lower dosage regime.

We herein disclose novel compounds of formula (I) useful as antidiabetic, anti-obesity, hypolipidaemic, hypolipoproteinemic, and antihyperglycemic agents which may have beneficial effect in the treatment and/or prophylaxis of diseases caused by hyperlipidemia, diseases classified under Syndrome X and atherosclerosis, and methods for their preparation.

SUMMARY OF THE INVENTION

The main objective of the present invention is to provide novel GPR40 agonists represented by the general formula (I), their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them or their mixtures thereof.



(I)

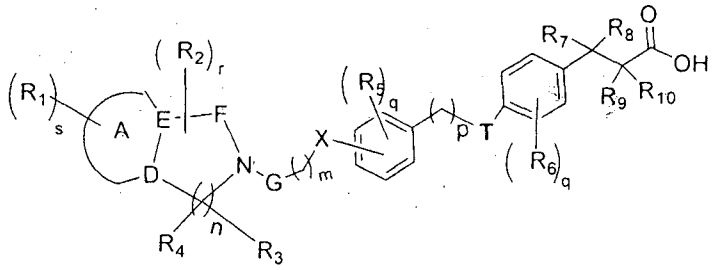
In an embodiment of the present invention is provided processes for the preparation of compounds represented by the general formula (I), their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts.

In a further embodiment of the present invention is provided pharmaceutical compositions containing compounds of the general formula (I), their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, or their mixtures in combination with suitable carriers, solvents, diluents and other media normally employed in preparing such compositions.

In yet another embodiment is provided a pharmaceutical composition comprising the compound of formula (I) and a second suitable therapeutic agent for the treatment of diabetes, obesity and other related disorders.

DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention relates to compounds of the general formula (I)



Formula (I)

their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them wherein

each of R_1, R_2, R_3, R_4, R_5, R_6, at each occurrence independently represents H, halogen, hydroxyl, CN, NO_2, CHO, COOH, CO, optionally substituted groups selected from, alkyl, alkoxy, thiol, sulphoxide, sulphone, acyl, NH_2 or optionally substituted NHCO-linear or branched (C_1-C_6)alkyl, aralkyl, cycloalkyl,

cycloalkylalkyl, heterocyclyl, hetererocyclylalkyl, heteroaryl, heteroaralkyl or the groups OR, C(O)OR, C(O)R, and SO_2R wherein 'R' at each occurrence independently represents optionally substituted groups selected from H, linear or branched (C_1-C_6)alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, hetrerocyclylalkyl, heteroaryl, heteroaralkyl groups; In an alternate embodiment, R_3 and R_4 together may form an oxo group;

'A' is selected from 3-7 member partially saturated, unsaturated or saturated ring which may further be having one or more than one heteroatom selected from O, S, or N;

Each of 'E' & 'D' may independently be either nitrogen or carbon. 'F' may be selected from C, N or O; 'G' may be present or absent and when present represents either a bond or is selected from O, S, NR_a, wherein 'R_a' represents linear or branched (C_1-C_6) alkyl;

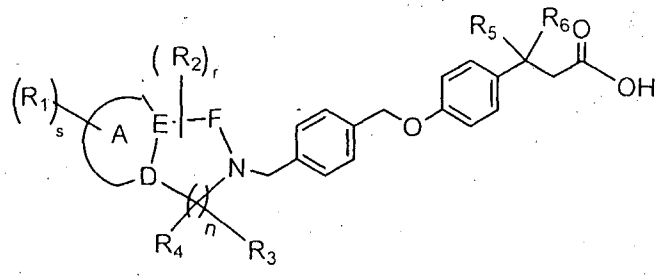
m =1-3; each of 'n', 'r', 'p' and's' independently represents an integer ranging from 0 to 6; q = 0-4;

'X' may be present or absent and when present is selected from CH_2, O, S, and NR_a, SO_2NH; wherein R_a is as defined earlier;

'T' is selected from oxygen, -NH, S, SO, SO_2 or NR_a, wherein R_a is as defined earlier; each of R_7 and R_8 independently may be selected (C_2-C_4)alkyne, nitrile, or a cycloalkyl; Alternatively R_7 and R_8 may combine with the carbon atom to which it is attached to form a 3-7 membered cyclic ring which may optionally further have one or more than one heteroatom selected from S, N, or O;

R_9 & R_{10} may be selected from hydrogen, alkyl, alkoxy, and halogen groups.

A preferred embodiment of the present invention relates to compound of the general Formula (I')



Formula (I')

their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them wherein

Each of R_1, R_2, R_3 and R_4 at each occurrence independently represents H, halogen, hydroxyl, CN, NO_2, CHO, COOH, CO, optionally substituted groups selected from, alkyl, alkoxy, thiol, sulphoxide, sulphone, acyl, NH_2 or optionally substituted NHCO-linear or branched $(C_1$-$C_6)$alkyl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, hetererocyclylalkyl, heteroaryl, heteroaralkyl or the groups OR, C(O)OR, C(O)R, and SO_2R wherein 'R' at each occurrence independently represents optionally substituted groups selected from H, linear or branched $(C_1$-$C_6)$alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, hetrerocyclylalkyl, heteroaryl, heteroaralkyl groups;

In an alternate embodiment, R_3 and R_4 together may form an oxo group;

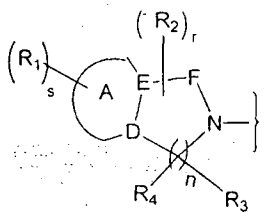
'A' is selected from 3-7 member partially saturated, unsaturated or saturated ring which may further be having one or more than one heteroatom selected from O, S, or N;

Each of 'E' & 'D' may independently be either nitrogen or carbon. 'F' may be selected from C, N or O;

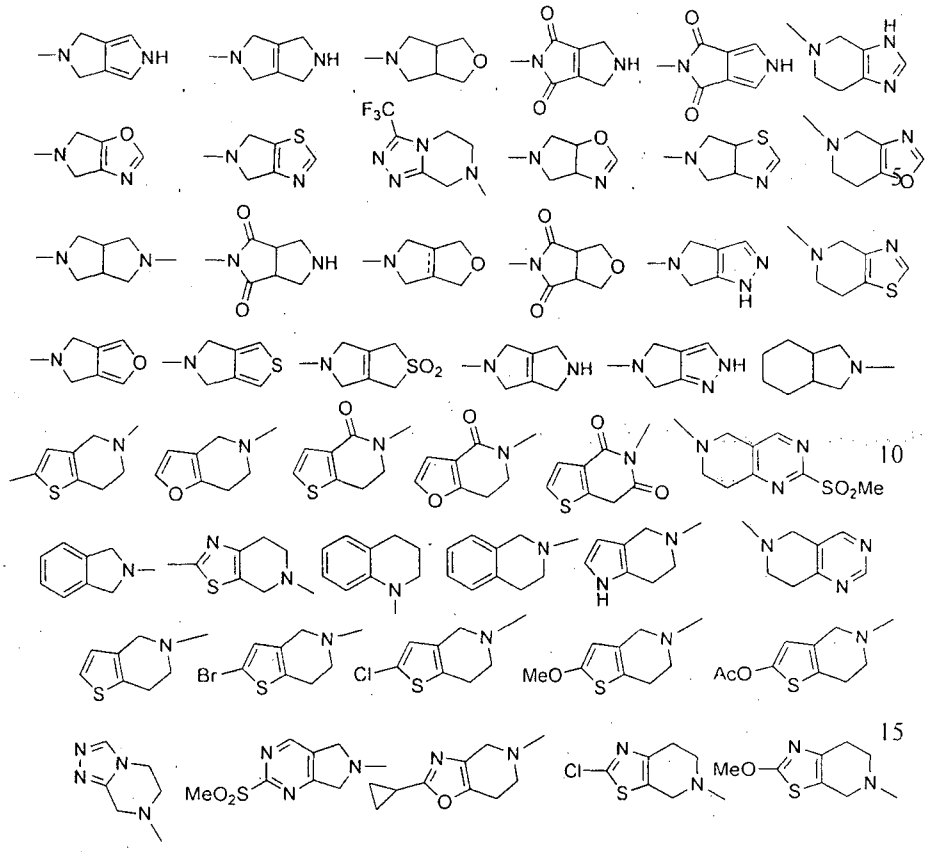
Each of 'n', 'r' and's' independently represents an integer ranging from 0 to 6;

each of R_5 and R_6 independently may be selected $(C_2$-$C_4)$alkyne, nitrile, or a cycloalkyl; Alternatively R_5 and R_6 may combine with the carbon atom to which it is formed to form a 3-7 membered cyclic ring which may optionally further have one or more than one heteroatom selected from S, N, or O;

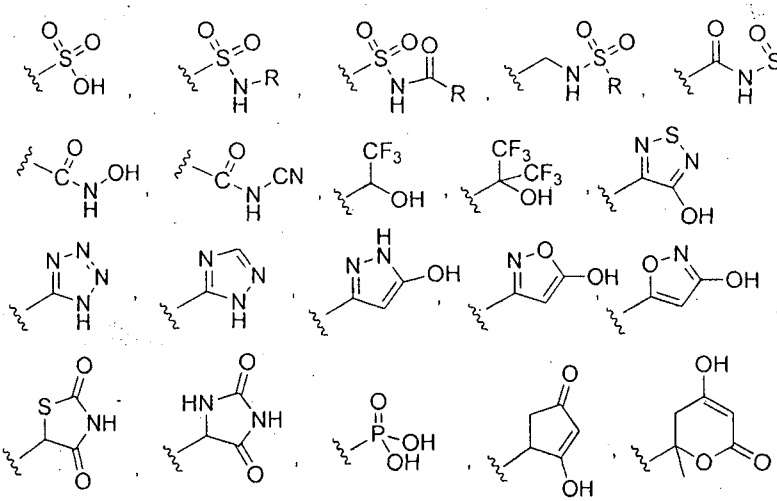
The preferred heterocycles representing



may be selected from the following bicyclic rings mentioned below



The substituent –COOH may be optionally replaced wherever possible with bioisosteric replacements such as:



and the like;

When any of the groups from R_1 to R_{10} are substituted with one or many groups, the substituents may be independently selected from the groups comprising hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocylyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylalkoxyacyl, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives such as esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkylsulfonylamino, alkylsulfonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfenyl derivatives, sulfonyl derivatives, sulfonic acid and its derivatives.

The aryl group may be an aromatic system containing one, two or three rings wherein such rings may be attached together in a dependent manner or may be fused; in a preferred embodiment such aryl group may be selected from phenyl, naphthyl, tetrahydronaphthyl, indane, biphenyl groups;

The heteroaryl group represents 5 to 8 membered aromatic radicals, which may be single or fused containing one or more hetero atoms selected from O, N or S; in a preferred embodiment such groups may be selected from pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, isothiazolyl, imidazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzothienyl, indolinyl, indolyl, azaindolyl, azaindolinyl, benzodihydrofuranyl, benzodihydrothienyl, pyrazolopyrimidinyl, pyrazolopyrimidonyl, azaquinazolinyl, azaquinazolinoyl, pyridofuranyl, pyridothienyl, thienopyrimidyl, thienopyrimidonyl, quinolinyl, pyrimidinyl, pyrazolyl, quinazolinyl, quinazolonyl, pyrimidonyl, pyridazinyl, triazinyl, benzoxazinyl, benzoxazinonyl, benzothiazinyl, benzothiazinonyl, benzoxazolyl, benzothiazolyl, benzimidazolyl,

benzotriazolyl, phthalazynil, naphthylidinyl, purinyl, carbazolyl, phenothiazinyl, phenoxazinyl groups;

The term "heterocyclyl" represents saturated, partially saturated or unsaturated ring-shaped radicals, the heteroatoms being selected from nitrogen, sulfur or oxygen; in a preferred embodiment such groups may be selected from aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, 2-oxopiperidinyl, 4-oxopiperidinyl, 2-oxopiperazinyl, 3-oxopiperazinyl, morpholinyl, thiomorpholinyl, 2-oxomorpholinyl, azepinyl, diazepinyl, oxapinyl, thiazepinyl, oxazolidinyl, thiazolidinyl, and the like; examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole groups.

The "alkyl" group used either alone or in combination with other radicals, denotes a linear or branched radical containing one to six carbons, selected from methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, amyl, *t*-amyl, *n*-pentyl, *n*-hexyl, and the like;

- the "alkenyl" group used either alone or in combination with other radicals, is selected from a radical containing from two to six carbons, more preferably groups selected from vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl and the like; the "alkenyl" group includes dienes and trienes of straight and branched chains;
- the "alkynyl" group used either alone or in combination with other radicals, is selected from a linear or branched radical containing two to six carbon atoms, more preferably thienyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, and the like. The term "alkynyl" includes di- and tri-ynes;
- the "cycloalkyl", or "alicyclic" group used either alone or in combination with other radicals, is selected from a cyclic radical containing three to six carbons, more preferably cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like;

The terms "bicycloalkyl" means more than one cycloalkyl groups fused together;

- the "cycloalkenyl" group used either alone or in combination with other radicals, are preferably selected from cyclopropenyl, 1-cyclobutenyl, 2-cyclobutenyl, 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl and the like;
- the "alkoxy" group used either alone or in combination with other radicals, is selected from groups containing an alkyl radical, as defined above, attached directly to an oxygen atom, more preferably groups selected from methoxy, ethoxy, *n*-propoxy, *iso*-propoxy, *n*-butoxy, *t*-butoxy, *iso*-butoxy, pentyloxy, hexyloxy, and the like;
- the "cycloalkoxy" group used either alone or in combination with other radicals, is selected from groups containing an cycloalkyl radical, as defined above, attached directly to an oxygen atom, more preferably groups selected from cyclopropoxy, cyclobutoxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy and the like;
- the "aryloxy" group used either alone or in combination with other radicals, is selected from groups containing an aryl radical, as defined above, attached directly to an oxygen atom, more preferably groups selected from phenoxy, naphthyloxy, tetrahydronaphthyloxy, biphenyloxy, and the like;
- the "aralkyl" group used either alone or in combination with other radicals, is selected from groups containing an aryl radical, as defined above, attached directly to an alkyl radical, as define above, more preferably groups selected from benzyl, phenethyl, and the like;
- the "aralkoxy" group used either alone or in combination with other radicals, is selected from groups containing an aralkyl radical, as defined above, attached directly to an oxygen atom, more preferably groups selected from benzyloxy, phenethyloxy, and the like;
- the "heteroaralkyl" group used either alone or in combination with other radicals, is selected from groups containing an heteroaryl radical, as defined above, attached directly to an alkyl radicals, as define above, more preferably groups selected from pyridinealkyl, thiophenealkyl, quinolinealkyl, and the like;

- the "alkenoxy" group used either alone or in combination with other radicals, is selected from groups containing an alkenyl radical, as defined above, attached to an oxygen atom, more preferably selected from vinyloxy, allyloxy, butenoxy, pentenoxy, hexenoxy, and the like;
- the "haloalkyl" group is selected from an alkyl radical, as defined above, suitably substituted with one or more halogens; such as perhaloalkyl, more preferably, perfluoro(C_1-C_6)alkyl such as fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl, difluoroethyl, trifluoroethyl, mono or polyhalo substituted methyl, ethyl, propyl, butyl, pentyl or hexyl groups;
- the "haloalkoxy" group is selected from suitable haloalkyl, as defined above, directly attached to an oxygen atom, more preferably groups selected from fluoromethoxy, chloromethoxy, fluoroethoxy, chloroethoxy and the like;
- the "perhaloalkoxy" group is selected from a suitable perhaloalkyl radical, as defined above, directly attached to an oxygen atom, more preferably groups selected from trifluoromethoxy, trifluoroethoxy, and the like;
- the groups "heteroaryloxy", "heteroaralkoxy", "heterocycloxy", "heterocylylalkoxy" are selected from suitable heteroaryl, heteroarylalkyl, heterocyclyl, heterocylylalkyl groups respectively, as defined above, attached to an oxygen atom;
- the "acyl" group used either alone or in combination with other radicals, is selected from a radical containing one to eight carbons, more preferably selected from formyl, acetyl, propanoyl, butanoyl, *iso*-butanoyl, pentanoyl, hexanoyl, heptanoyl, benzoyl and the like, which may be substituted;
- the "acyloxy" group used either alone or in combination with other radicals, is selected from a suitable acyl group, as defined above, directly attached to an oxygen atom, more preferably such groups are selected from acetyloxy, propionyloxy, butanoyloxy, *iso*-butanoyloxy, benzoyloxy and the like;
- the "acylamino" group used either alone or in combination with other radicals, is selected from a suitable acyl group as defined earlier, attached to an amino radical, more preferably such groups are selected from CH_3CONH,

C_2H_5CONH, C_3H_7CONH, C_4H_9CONH, C_6H_5CONH and the like, which may be substituted;

- the "mono-substituted amino" group used either alone or in combination with other radicals, represents an amino group substituted with one group selected from (C_1-C_6)alkyl, substituted alkyl, aryl, substituted aryl or arylalkyl groups as defined earlier, more preferably such groups are selected from methylamine, ethylamine, *n*-propylamine, *n*-butylamine, *n*-pentylamine and the like;
- the 'disubstituted amino" group used either alone or in combination with other radicals, represents an amino group, substituted with two radicals that may be same or different selected from (C_1-C_6)alkyl, substituted alkyl, aryl, substituted aryl, or arylalkyl groups, as defined above, more preferably the groups are selected from dimethylamino, methylethylamino, diethylamino, phenylmethyl amino and the like;
- the "arylamino" used either alone or in combination with other radicals, represents an aryl group, as defined above, linked through amino having a free valence bond from the nitrogen atom, more preferably the groups are selected from phenylamino, naphthylamino, *N*-methyl anilino and the like;
- the "oxo" or "carbonyl" group used either alone (-C=O-) or in combination with other radicals such as alkyl described above, for e.g. "alkylcarbonyl", denotes a carbonyl radical (–C=O-) substituted with an alkyl radical described above such as acyl or alkanoyl;
- the "carboxylic acid" group, used alone or in combination with other radicals, denotes a –COOH group, and includes derivatives of carboxylic acid such as esters and amides;
- the "ester" group used alone or in combination with other radicals, denotes –COO- group, and includes carboxylic acid derivatives, more preferably the ester moieties are selected from alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, and the like, which may optionally be substituted; aryloxycarbonyl group such as phenoxycarbonyl, napthyloxycarbonyl, and the like, which may optionally be substituted; aralkoxycarbonyl group such as

benzyloxycarbonyl, phenethyloxycarbonyl, napthylmethoxycarbonyl, and the like, which may optionally be substituted; heteroaryloxycarbonyl, heteroaralkoxycarbonyl, wherein the heteroaryl group, is as defined above, which may optionally be substituted; heterocyclyloxycarbonyl, where the heterocyclic group, as defined earlier, which may optionally be substituted;

- the "amide" group used alone or in combination with other radicals, represents an aminocarbonyl radical (H_2N-C=O), wherein the amino group is mono- or di-substituted or unsubstituted, more preferably the groups are selected from methyl amide, dimethyl amide, ethyl amide, diethyl amide, and the like;
- the "aminocarbonyl" group used either alone or in combination with other radicals, may be selected from 'aminocarbonyl', 'aminocarbonylalkyl", "n-alkylaminocarbonyl", "N-arylaminocarbonyl", "N,N-dialkylaminocarbonyl", "N-alkyl-N-arylaminocarbonyl", "N-alkyl-N-hydroxyaminocarbonyl", and "N-alkyl-N-hydroxyaminocarbonylalkyl", each of them being optionally substituted. The terms "N-alkylaminocabonyl" and "N,N-dialkylaminocarbonyl" denotes aminocarbonyl radicals, as defined above, which have been substituted with one alkyl radical and with two alkyl radicals, respectively. Preferred are "lower alkylaminocarbonyl" having lower alkyl radicals as described above attached to aminocarbonyl radical. The terms "N-arylaminocarbonyl" and "N-alkyl-N-arylaminocarbonyl" denote amiocarbonyl radicals substituted, respectively, with one aryl radical, or one alkyl, and one aryl radical. The term "aminocarbonylalkyl" includes alkyl radicals substituted with aminocarbonyl radicals;
- the "hydroxyalkyl" group used either alone or in combination with other radicals, is selected from an alkyl group, as defined above, substituted with one or more hydroxy radicals, more preferably the groups are selected from hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl and the like;
- the "aminoalkyl" group used alone or in combination with other radicals, denotes an amino ($-NH_2$) moiety attached to an alkyl radical, as defined above, which may be substituted, such as mono- and di-substituted aminoalkyl. The

term "alkylamino" used herein, alone or in combination with other radicals, denotes an alkyl radical, as defined above, attached to an amino group, which may be substituted, such as mono- and di-substituted alkylamino;

- the "alkoxyalkyl" group used alone or in combination with other radicals, denotes an alkoxy group, as defined above, attached to an alkyl group as defined above, more preferably the groups may be selected from methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like;
- the "alkylthio" group used either alone or in combination with other radicals, denotes a straight or branched or cyclic monovalent substituent comprising an alkyl group as defined above, linked through a divalent sulfur atom having a free valence bond from the sulfur atom, more preferably the groups may be selected from methylthio, ethylthio, propylthio, butylthio, pentylthio and the like or cyclic alkylthio selected from cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio and the like, which may be optionally substituted;
- the "thioalkyl" group used either alone or in combination with other radicals, denotes an alkyl group, as defined above, attached to a group of formula –SR', where R' represents hydrogen, alkyl or aryl group, e.g. thiomethyl, methylthiomethyl, phenylthiomethyl and the like, which may be optionally substituted.
- the "alkoxycarbonylamino" group used alone or in combination with other radicals, is selected from a suitable alkoxycarbonyl group, as defined above, attached to an amino group, more preferably methoxycarbonylamino, ethoxycarbonylamino, and the like;
- the "aminocarbonylamino", "alkylaminocarbonylamino", "dialkylaminocarbonylamino" groups used alone or in combination with other radicals, is a carbonylamino (-$CONH_2$) group, attached to amino(NH_2), alkylamino group or dialkylamino group respectively, where alkyl group is as defined above;

- the "amidino" group used either alone or in combination with other radicals, represents a $-C(=NH)-NH_2$ radical; the "alkylamidino" group represents an alkyl radical, as described above, attached to an amidino group;
- the "alkoxyamino" group used either alone or in combination with other radicals, represents a suitable alkoxy group as defined above, attached to an amino group;
- the "hydroxyamino" group used either alone or in combination with other radicals, represents a –NHOH moiety, and may be optionally substituted with suitable groups selected from those described above;
- the "sulfenyl" group or "sulfenyl derivatives" used alone or in combination with other radicals, represents a bivalent group, –SO- or R_xSO, where Rx is an optionally substituted alkyl, aryl, heteroaryl, heterocyclyl, group selected from those described above;
- the "sulfonyl" group or "sulfones derivatives" used either alone or in combination with other radicals, with other terms such as alkylsulfonyl, represents a divalent radical $-SO_2-$, or R_xSO_2-, where R_x is as defined above. More preferably, the groups may be selected from "alkylsulfonyl" wherein suitable alkyl radicals, selected from those defined above, is attached to a sulfonyl radical, such as methylsulfonyl, ethylsulfonyl, propylsulfonyl and the like, "arylsulfonyl" wherein an aryl radical, as defined above, is attached to a sulfonyl radical, such as phenylsulfonyl and the like.
- the "sulfonyloxy" group used either alone or in combination with other radicals, with other terms such as alkylsulfonyloxy, represents a divalent radical $-SO_3-$, or R_xSO_3-, where R_x is as defined above. More preferably, the groups may be selected from "alkylsulfonyl" wherein suitable alkyl radicals, selected from those defined above, is attached to a sulfonyloxy radical, such as methanesulfonyloxy, ethanesulfonyloxy, propanesulfonyloxy and the like, "arylsulfonyl" wherein an aryl radical, as defined above, is attached to a sulfonyl radical, such as benzenesulfonyloxy and the like

Suitable groups and substituents on the groups may be selected from those described anywhere in the specification.

Particularly useful compounds may be selected from

(S)-3-(4-((3-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid (1);

Lithium 3-(4-((3-((4H-furo[3,4-c]pyrrol-5(6H)-yl)methyl)benzyl)oxy)phenyl)-3-cyanopropanoic acid;

3-cyano-3-(4-((3-((4-oxo-6,7-dihydrothieno[3,2-c]pyridin-5(4H)yl)methyl)benzyl)oxy)phenyl)propanoic acid;

Lithium 3-cyano-3-(4-((3-((3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methyl)benzyl)oxy)phenyl)propanoic acid;

3-cyano-3-(4-((3-((2,2-dioxido-1H-thieno[3,4-c]pyrrol-5(3H,4H,6H)-yl)methyl)benzyl)oxy)phenyl)propanoic acid;

3-cyano-3-(4-((3-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)propanoic acid;

(S)-3-(4-((3-((2-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((1-(tert-butoxycarbonyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-(isoindolin-2-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((3,4-dihydroquinolin-1(2H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-bromo-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

calcium*(S)*-3-(4-((3-((2-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate*(S)*-3-(4-((3-((2-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate;

calcium*(S)*-3-(4-((3-((2-methyl-6,7-dihydrothiazolo[4,5-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate*(S)*-3-(4-((3-((2-methyl-6,7-dihydrothiazolo[4,5-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate;

(S)-3-(4-((3-((2-(Difluoromethyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

Calcium *(S)*-3-(4-((3-((2-bromo-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate;

Calcium *(S)*-3-(4-((3-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate;

(S)-3-(4-((3-((7,8-Dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((1-Methylpyrrolo[3,4-c]pyrazol-5(1H,4H,6H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(3S)-3-(4-((3-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-(Indolin-1-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((5,6-Dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-Cyclopropyl-6,7-dihydrooxazolo[4,5-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(3S)-3-(4-((3-((5-Benzylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with formic acid;

(S)-3-(4-((3-((4H-Thieno[2,3-c]pyrrol-5(6H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

6-(3-((4-((*S*)-1-carboxypent-3-yn-2-yl)phenoxy)methyl)benzyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-6-ium formate;

1-(3-((4-((*S*)-1-carboxypent-3-yn-2-yl)phenoxy)methyl)benzyl)-7-methoxy-1,2,3,4-tetrahydroquinolin-1-ium formate;

(S)-3-(4-((3-((2-Chloro-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-Bromo-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-(pyrrolo[3,4-c]pyrazol-5(1H,4H,6H)-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-(hydroxymethyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-5-(3-((4-(1-carboxypent-3-yn-2-yl)phenoxy)methyl)benzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid;

3-cyclopropyl-3-(3-((3-((2-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)propanoic acid;

(S)-3-(4-((3-((1-methyl-6,7-dihydro-1H-pyrrolo [3,2-c]pyridin-5(4H)-yl)methyl) benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-amino-6,7-dihydrothiazolo [5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy) phenyl)hex-4-ynoic acid;

Calcium *(S)*-3-(4-((3-((2-chloro-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate;

(S)-3-(4-((3-((2-carbamoyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

((*(S)*-3-(4-((3-((2-isopropylpyrrolo[3,4-c]pyrazol-5(2H,4H,6H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-(methoxycarbonyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-cyano-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-formyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

S)-3-(4-((3-((2-methyl-6,7-dihydropyrazolo [1,5-a]pyrazin-5(4H)-yl)methyl)benzyl) oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-(methylcarbamoyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-(dimethylcarbamoyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(3S)-3-(4-((3-((2-Methyl-5-(4-(methylsulfonyl)phenyl)pyrrolidin-1-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-(Methylsulfonyl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-Methoxy-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(3S)-3-(4-((3-((2-phenylpyrrolidin-1-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-(Pyrrolidin-1-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with formic acid;

(S)-3-(4-((3-(Piperidin-1-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with formic acid;

(S)-3-(4-((3-((1-isopropylpyrrolo[3,4-c]pyrazol-5(1H,4H,6H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with formic acid;

(R)-3-(4-((3-((2-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(R)-3-(4-((3-((2-Methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((6,7-Dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

3-(4-((3-((2-Methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

3-(4-((3-((2-Methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

Calcium *(S)*-3-(4-((3-((2-chloro-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate;

(S)-3-(4-((3-((2-(cyclopropylcarbamoyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-(pyrrolidine-1-carbonyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-Aacetamido-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

Calcium *(S)*-3-(4-((3-((2-cyclopropyl-6,7-dihydrooxazolo[4,5-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate;

(S)-3-(4-((3-((2-Nitro-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-(Dimethylamino)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with 2,2,2-trifluoroacetic acid;

(S)-3-(4-((3-((2-Amino-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with 2,2,2-trifluoroacetic acid;

(S)-3-(4-((3-((7,8-Dihydro-1,6-naphthyridin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-Cyclopropyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with 2,2,2-trifluoroacetic acid;

(S)-3-(4-((3-((2-Acetamido-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with 2,2,2-trifluoroacetic acid;

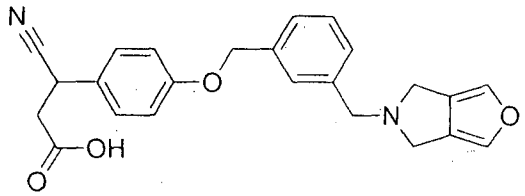
(S)-3-(4-((3-((2-Ethyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-Acetyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

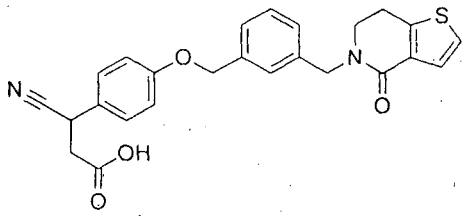
(S)-3-(4-((3-((2-((Methylamino)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with 2,2,2-trifluoroacetic acid;

The following compounds can be synthesized following the similar procedure as described for example 1 with suitable modifications as are well known to a person skilled in the art and are considered to be encompassed within the scope of the present invention.

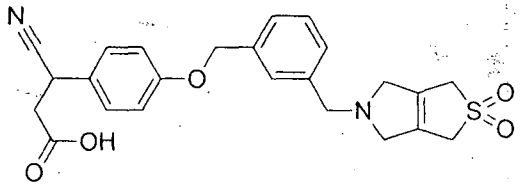
3-(4-((3-((4H-furo[3,4-c]pyrrol-5(6H)-yl)methyl)benzyl)oxy)phenyl)-3-cyanopropanoic acid



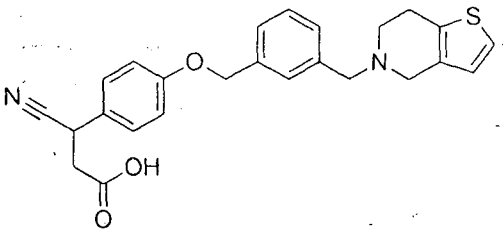
3-cyano-3-(4-((3-((4-oxo-6,7-dihydrothieno[3,2-c]pyridin-5(4H) yl)methyl)benzyl)oxy)phenyl)propanoic acid



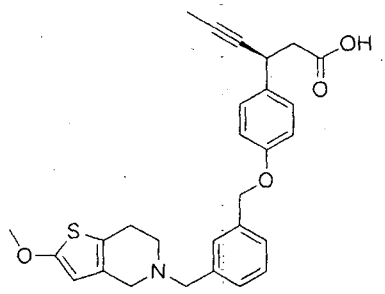
3-cyano-3-(4-((3-((2,2-dioxido-1H-thieno[3,4-c]pyrrol-5(3H,4H,6H)-yl)methyl)benzyl)oxy)phenyl)propanoic acid



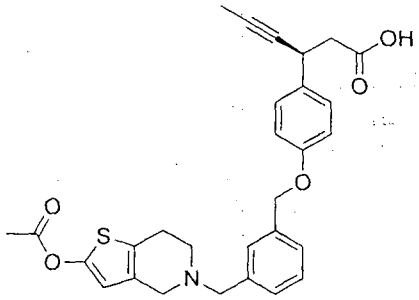
3-cyano-3-(4-((3-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)propanoic acid



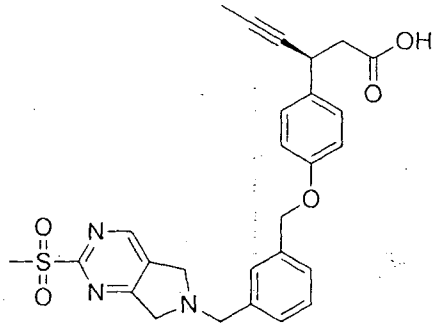
(S)-3-(4-((3-((2-methoxy-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



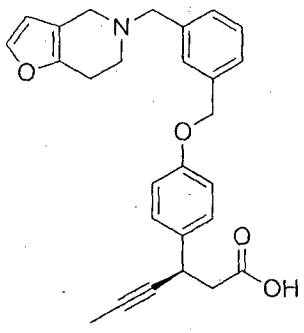
(S)-3-(4-((3-((2-acetoxy-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



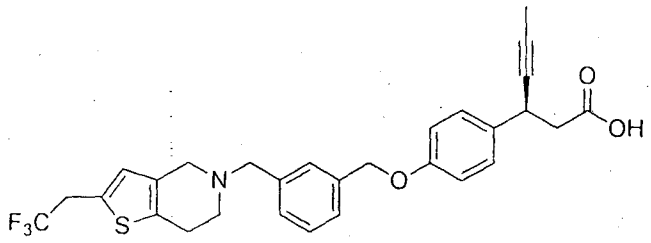
(S)-3-(4-((3-((2-(methylsulfonyl)-5H-pyrrolo[3,4-d]pyrimidin-6(7H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



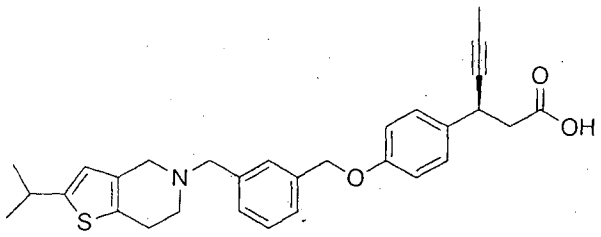
(S)-3-(4-((3-((6,7-dihydrofuro[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



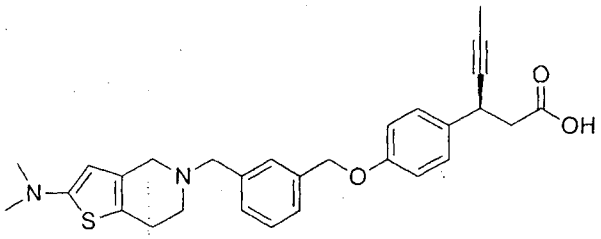
(S)-3-(4-((3-((2-(2,2,2-trifluoroethyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



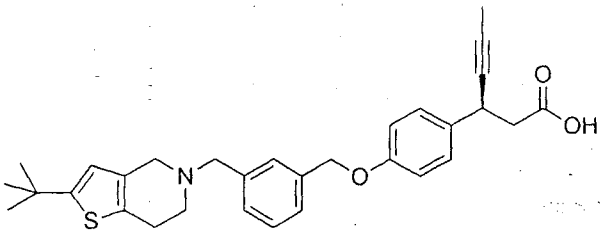
(S)-3-(4-((3-((2-isopropyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



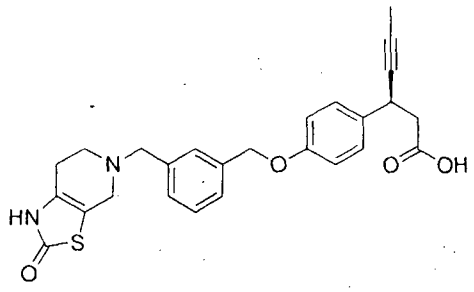
(S)-3-(4-((3-((2-(dimethylamino)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



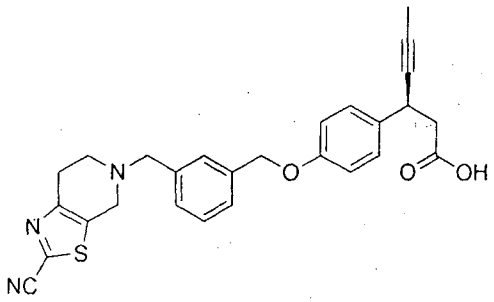
(S)-3-(4-((3-((2-(tert-butyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



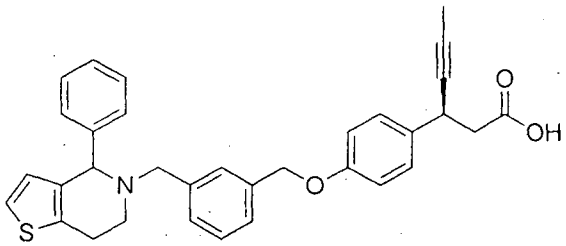
(S)-3-(4-((3-((2-oxo-1,2,6,7-tetrahydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



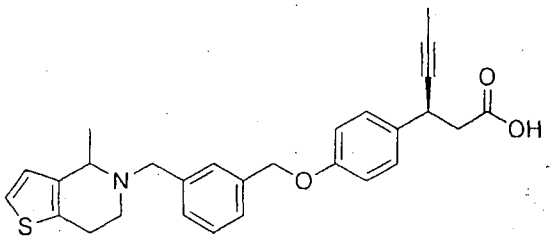
(S)-3-(4-((3-((2-cyano-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



(3S)-3-(4-((3-((4-phenyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



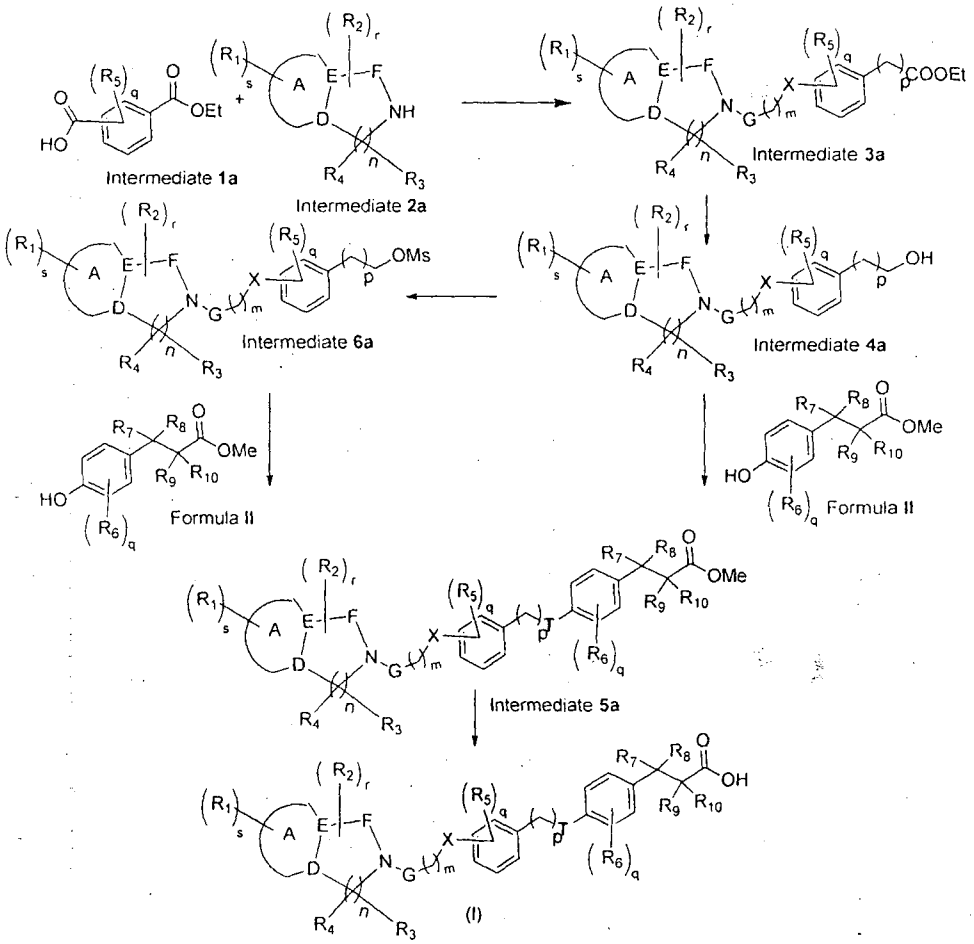
(3S)-3-(4-((3-((4-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



The novel compounds of this invention may be prepared using the reactions and techniques described in the below section along with, whenever appropriate other suitable processes known to a skilled person. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. It is understood by those skilled in the art that

the nature and order of the synthetic steps presented may be varied for the purpose of optimizing the formation of the compounds of the present invention and also that certain steps may be modified, altered, obvious steps added or deleted in order to optimize as well as required for preparing the compounds of the present invention. Such, obvious changes should also be considered as being part of the present invention.

Scheme 1: Compounds of general formula (I) may be prepared according to the scheme described below



A compound of formula (I) can be prepared in accordance with reactions as depicted in scheme 1.

The first step involves the reaction of substituted carboxylic acid (intermediate 1a) with an appropriate substituted heterocycle (intermediate 2a) under peptide bond formation conditions to give intermediate 3a. The ester of intermediate 3a can be reduced using a suitable reducing agent such as diisobutylaluminum hydride,

lithium aluminum hydride or sodium borohydride etc. to give intermediate 4a. Intermediate 4a can be further reacted with compounds of formula II under Mitsunobu conditions to give intermediate 5a. Mitsunobu conditions involve reacting an alcohol intermediate 4a with a nucleophile such as a phenol (formula II), using a suitable phosphine such as tributyl phosphine, triphenyl phosphine, or triethyl phosphine and an azodicarbonyl such as ADDP or an azodicarboxylate (DEAD).

Alternatively, intermediate 4a can be converted to compound having suitable leaving group such as mesylate derivative (intermediate 6a) using an appropriate set of reactants and conditions such as methanesulfonyl chloride and triethylamine.

The intermediate 6a can be reacted with compound of formula II using diisopropyl ethylamine or cesium carbonate to give intermediate 5a.

The intermediate 5a can be hydrolyzed to give carboxylic acid derivative of formula (I) using bases such as lithium hydroxide, sodium hydroxide or potassium hydroxide.

In an optional step, a pharmaceutically acceptable salt of a compound of formula (I) can be formed by reaction of appropriate compound of formula (I) with a pharmaceutically acceptable base or with and acid in a suitable solvent under standard conditions. Optionally, the formation of such salts can occur simultaneously upon hydrolysis of an ester intermediate.

The formation of such salts is well known and appreciated in the art.

The compounds of the present invention can be used either alone or in combination with one or more therapeutic agents selected from insulin, insulin derivatives and mimetics, insulin secretagogues, insulin sensitizers, biguanide agents, alpha-glucosidase inhibitors, insulinotropic sulfonylurea receptor ligands, meglitinides, GLP-1, GLP-1 analogs, DPP-IV inhibitors, GPR-119 activators, sodium-dependent glucose co-transporter (SGLT2) inhibitors, PPAR modulators, non-glitazone type PPAR delta agonist, HMG-CoA reductase inhibitors, cholesterol-lowering drugs, rennin inhibitors, anti-thrombotic and anti-platelet agents and other anti-obesity agents or pharmaceutically acceptable salts thereof.

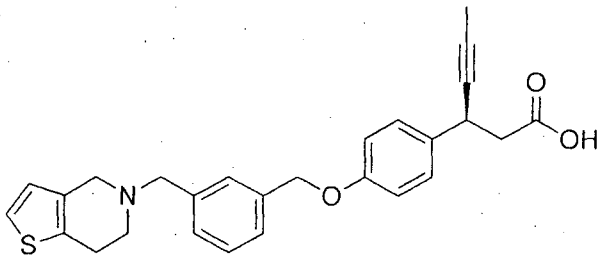
Such use will depend on the condition of the patient being treated and is well within the scope of a skilled practitioner.

Following the general process described above, including suitable modifications and additions which are within the scope of a skilled person, the following compounds of formula **(1)** were prepared as follows:

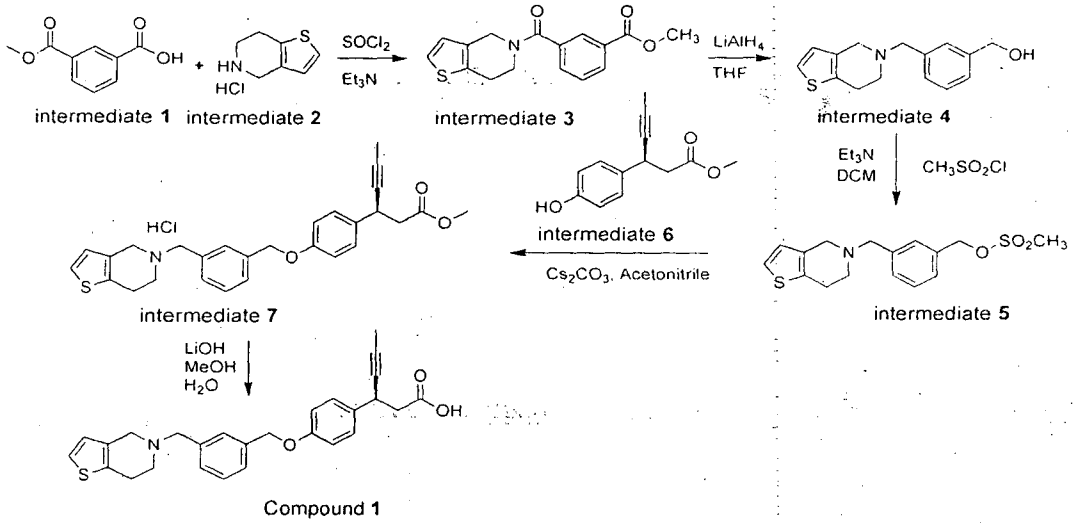
1H NMR spectral data given in the examples (vide infra) are recorded using a 400 MHz spectrometer (Bruker AVANCE-400) and reported in δ scale. Until and otherwise mentioned the solvent used for NMR is $CDCl_3$.

Example 1

(S)-3-(4-((3-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)yl)methyl)benzyl)oxy) phenyl)hex-4-ynoic acid (1)



Scheme 2:



Procedure:

i. **Methyl 3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridine-5-carbonyl)benzoate** (intermediate **3)**

To 3-(methoxycarbonyl)benzoic acid intermediate **1** (10 g, 55.5 mmol) was added thionyl chloride (16.21 mL, 222 mmol) in small portions at 25 °C followed by a drop of dimethylformamide. The reaction mixture was stirred under refluxing for 3 h. Excess thionyl chloride was evaporated under reduced pressure at 100 °C. The 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride intermediate **2** (12.19 g, 69.4 mmol) was dissolved in 100 mL of water, to that added solution of sodium hydroxide (4.44 g, 111 mmol) in 25 mL of water. Free base of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine was extracted in dichloromethane (75 mL), dried over anhydrous potassium carbonate. The acid chloride was dissolved in anhydrous dichloromethane (75 mL) and cooled to 0 °C.

To the reaction mixture added drop wise triethylamine (15.47 mL, 111 mmol) followed by solution of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine in dichloromethane(75 mL) drop by drop at 0 °C. The reaction mixture was warmed to 25 °C and stirred it for 3 h. Progress of the reaction was monitored by TLC. The reaction mixture was poured into ice-water (125 mL), adjusted pH ~4 with 10% HCl and extracted with dichloromethane (3 x 100 mL). The combined organic fractions were washed with 5% sodium hydroxide (100 mL) followed by brine (100 mL), dried over anhydrous Na2SO4 and evaporated on a rotatory evaporator under reduced pressure to afford crude amide intermediate **3**.

The crude product was purified by flash column chromatography using 230-400 mesh silica-gel as a stationary phase and 10-50% ethyl acetate - hexanes as a mobile phase afforded pure methyl 3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridine-5-carbonyl)benzoate (12 g, 39.8 mmol, 71.7 % yield)

ii. (3-((6,7-Dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)phenyl)methanol (intermediate **4)**

To a solution of methyl 3-(4,5,6,7-tetrahydrothieno[3,2-c]pyridine-5-carbonyl)benzoate intermediate **3** (12 g, 39.8 mmol) in dry THF (100 mL) was added $LiAlH_4$ (3.02 g, 80 mmol) in small portions at 25 °C. The reaction mixture was stirred under refluxing for 3 h. The progress of reaction was monitored by TLC by using mobile phase 30% ethyl acetate in hexane. Suspension of aqueous sodium sulfate was added drop wise to the reaction mixture to quench excess

$LiAlH_4$. Ethyl acetate (150 mL) was added to the reaction mixture and refluxed for 30 min and decanted ethyl acetate, this process was repeated three times to ensure no product in white slug of lithium sulfate and aluminum hydroxide. The combined organic fractions were dried over anhydrous Na_2SO_4 and evaporated on a rotatory evaporator under reduced pressure to afford crude product as pale yellow sticky mass of intermediate **4**.

The crude alcohol intermediate **4** was purified by flash column chromatography using 230-400 mesh silica-gel as stationary phase and 10-50% ethyl acetate - hexane as a mobile phase afforded pure (3-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)phenyl)methanol intermediate **4** (5.41 g, 20.86 mmol, 52.4 % yield).

iii. ***(S)*-3-(4-((3-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl) oxy)phenyl)hex-4-ynoic acid (1)**

To a solution of (3-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)phenyl)methanol intermediate **4** (0.16g, 0.617 mmol) in 5 mL of anhydrous tetrahydrofuran was added triethylamine (0.258 ml, 1.851 mmol) followed by methanesulfonyl chloride (141 mg, 1.234 mmol) at 0 °C. The reaction mixture was stirred at 25 °C for 1 h. The progress of the reaction was monitored by TLC. The reaction mixture was poured into ice-water (25 mL) and extracted with dichloromethane (3 x 25 mL). The combined organic fractions were dried over anhydrous Na_2SO_4 and evaporated on a rotatory evaporator under reduced pressure to afford 3-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl mesylate intermediate (**5**) as pale yellow sticky mass.

To a solution of *(S)*-methyl 3-(4-hydroxyphenyl)hex-4-ynoate intermediate **6** (162 mg, 0.740 mmol) in Acetonitrile (5.00 ml) was added cesium carbonate (603 mg, 1.851 mmol) followed by solution of 3-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl mesylate **5** in 2 mL of acetonitrile at 25 °C. Reaction mixture was stirred for 3 h at 75 °C. Progress of the reaction was monitored by TLC. After completion of the reaction, volatiles were evaporated off under reduced pressure. The reaction mixture was poured into ice-water (25 mL) and product was extracted with dichloromethane (3 x 25 mL). The combined organic fractions

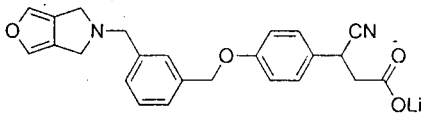
were dried over anhydrous Na_2SO_4 and evaporated on a rotatory evaporator under reduced pressure to afford crude product as pale yellow sticky mass. Ethereal hydrochloride solution was added to the crude product, ether was evaporated off and residue was triturated with ethyl acetate afforded 65 mg of *(S)*-methyl 3-(4-((3-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate hydrochloride intermediate (7). Ester hydrochloride salt intermediate **7** (60 mg, 0.121 mmol) was hydrolyzed using mixture of THF (2 mL) and MeOH (1 mL) was added NaOH (24.19 mg, 0.605 mmol) in water (1 mL) at 25 °C. Reaction mixture was stirred for 12 h at 25 °C. Progress of the reaction was monitored by TLC. After completion of the reaction, volatiles were evaporated off, the residue was treated with ice-water (5 mL), adjusted pH ~4 (1N HCl), extracted with dichloromethane (3 x 25 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvents on a rotatory evaporator under reduced pressure to afford crude product. Crude acid was purified by preparative TLC to afford *(S)*-3-(4-((3-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid **1** (42 mg, 0.094 mmol, 78 % yield)

^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.42 (s, 1H), 7.37–7.24 (m, 6H), 6.94 (d, J = 8.4 Hz, 2H), 6.75 (d, J = 5.2 Hz, 1H), 5.07 (s, 2H), 3.94 (m, 1H), 3.68 (s, 2H), 3.43 (s, 2H), 2.78-2.72 (m, 4H), 2.57-2.55 (m, 2H), 1.77 (d, J = 1.6 Hz, 3H); ESIMS: 446.2 $(M+H)^+$.

The following compounds can be prepared by following the general scheme 1 and the process described in Example 1 above, including their suitable modifications well within the scope of a skilled person.

Example 2

Lithium 3-(4-((3-((4H-furo [3,4-c]pyrrol-5(6H)-yl)methyl)benzyl)oxy)phenyl)-3-cyanopropanoic acid

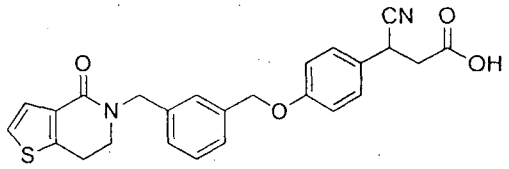


^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.44 (s, 1H), 7.35-7.28 (m, 7H), 6.98 (d, J = 8.8 Hz, 2H), 6.09 (s, 2H), 4.27 (dd, J = 6.4, 8.4 Hz, 1H), 3.86 (s, 2H), 3.57 (s,

4H), 2.53-2.41 (m, 1H), 2.33-2.32 (m, 1H)

Example 3

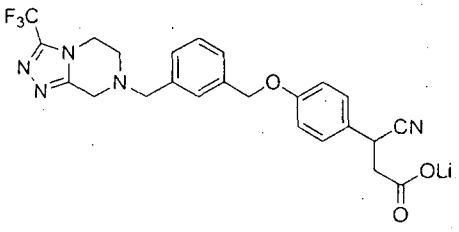
3-cyano-3-(4-((3-((4-oxo-6,7-dihydrothieno[3,2-c]pyridin-5(4H) yl)methyl)benzyl)oxy)phenyl)propanoic acid



^{1}H NMR: ($CDCl_3$, 400MHz):- 7.47 (d, J = 5.2Hz, 1H), 7.37 - 7.23 (m, 6H), 7.11 (d, J = 5.2Hz, 1H), 6.92 (d, J = 8.8Hz, 2H), 5.06 (s, 2H), 4.77 - 4.68 (m, 2H), 4.19 (t, J = 7.6Hz, 1H), 3.55 (t, J = 6.8Hz, 2H), 3.06 - 2.98 (m, 3H), 2.88 - 2.82 (m, 1H)

Example 4

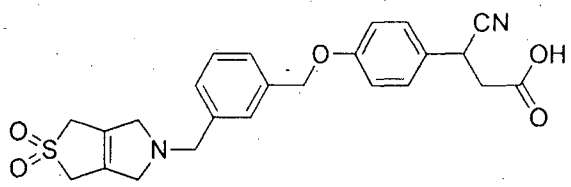
Lithium 3-cyano-3-(4-((3-((3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methyl)benzyl)oxy)phenyl)propanoic acid



^{1}H NMR (CD_3OD, 400 MHz) δ: 7.48 (s, 1H), 7.39-7.36 (m, 3H), 7.31 (dd, = 2, 6.8 Hz, 2H), 6.98 (dd, J = 2.4, 6.8 Hz, 2H), 5.10 (s, 2H), 4.30-4.26 (m, 1H), 4.18 (t, J = 5.2 Hz, 2H), 3.89 (s, 2H), 3.83 (s, 2H), 2.97 (t, J = 5.6 Hz, 2H), 2.74 (dd, J = 8.8, 15.6 Hz, 1H), 2.58 (dd, J = 8.8, 15.6 Hz, 1H).

Example 5

3-cyano-3-(4-((3-((2,2-dioxido-1H-thieno[3,4-c]pyrrol-5(3H,4H,6H)-yl)methyl)benzyl)oxy)phenyl)propanoic acid

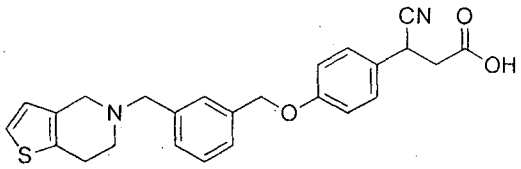


^{1}H NMR (CD_3OD, 400 MHz) δ: 7.66 (d, 1H), 7.60-7.51 (m, 3H), 7.35 (dd, J = 2, 6.8 Hz, 2H), 7.03 (dd, J = 2, 6.4 Hz, 2H), 5.17 (s, 2H), 4.60 (s, 2H), 4.35-4.31 (m,

1H), 4.28 (s, 4H), 3..94 (s, 4H), 2.99 (dd, J = 8.4, 16.8 Hz, 1H), 2.85 (dd, J = 6.4, 16.4 Hz, 1H).

Example 6

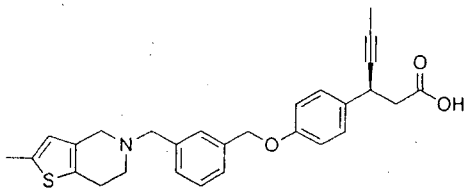
3-cyano-3-(4-((3-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)propanoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.58 (s, 1H), 7.37-7.32 (m, 2H), 7.22-7.16 (m, 4H), 6.88 (dd, J = 2, 6.8 Hz, 2H), 6.71 (d, J = 5.2 Hz, 1H), 5.00 (s, 2H), 4.18-4.14 (m, 1H), 3.99 (s, 2H), 3.88 (s, 2H), 3.19-3.16(m, 2H), 3.03-3.00 (m, 2H), 2.87-2.81 (m, 1H), 2.70-2.64 (m, 1H).

Example 7

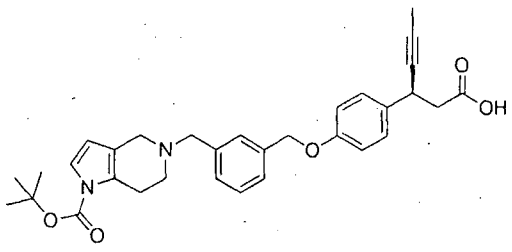
(S)-3-(4-((3-((2-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38-7.25(m, 6H), 6.88 (d, J = 5.2 Hz, 2H), 6.33 (s, 1H), 5.04-4.98 (m, 2H), 4.05-4.00 (m, 1H), 3.80-3.71 (m, 2H), 3.64-3.55 (m, 2H), 2.92-2.61 (m, 6H), 2.39 (s, 3H), 1.82 (d, J = 2.4 Hz, 3H).

Example 8

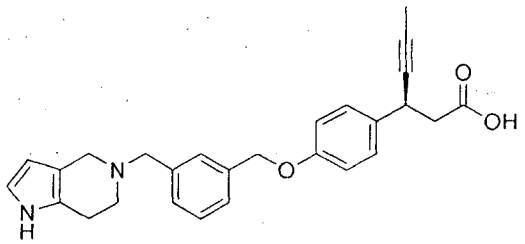
(S)-3-(4-((3-((1-(tert-butoxycarbonyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.47-7.38 (m, 4H), 7.27 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 3.2 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.94 (d, *J* = 3.2 Hz, 2H), 5.05 (s, 2H), 4.08 (s, 2H), 4.05-4.01 (m, 1H), 3.85 ($s_{(br)}$, 2H), 3.30-3.15 (m, 4H), 2.78 (dd, *J* = 8.8, 15.2 Hz, 1H), 2.65 (dd, *J* = 8, 15.2 Hz, 1H), 1.80 (d, *J* = 2.4 Hz, 3H), 1.59 (s, 9H).

Example 9

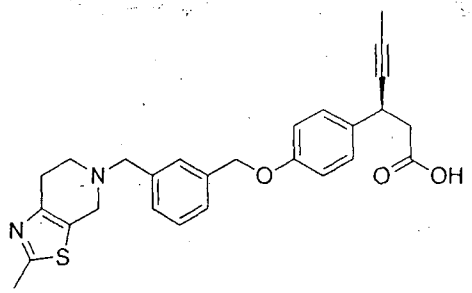
(S)-3-(4-((3-((6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.51 (s, 1H), 7.42-7.33 (m, 4H), 7.25 (d, *J* = 8.9 Hz, 2H), 6.81 (d, *J* = 9 Hz, 2H), 6.63 (t, *J* = 2.4 Hz, 1H), 5.89 (t, *J* = 2.4 Hz, 1H), 5.06 (s, 2H), 4.07-3.99 (m, 3H), 3.87 (s, 2H), 3.08 ($s_{(br)}$, 2H), 2.80-2.74 (m, 3H), 2.61 (m, 1H), 1.80 (d, *J* = 2.4 Hz, 3H)

Example10

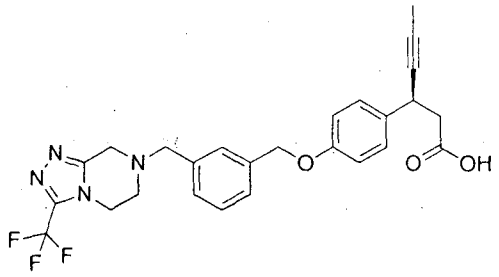
(S)-3-(4-((3-((2-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.41-7.38 (m, 4H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.19-5.08 (m, 2H), 4.04-3.91 (m, 1H), 3.75 ($s_{(br)}$, 4H), 2.87-2.69 (m, 4H), 2.66 (s, 3H), 2.58-2.41 (m, 2H), 1.80 (d, *J* = 2.4 Hz, 3H)

Example 11

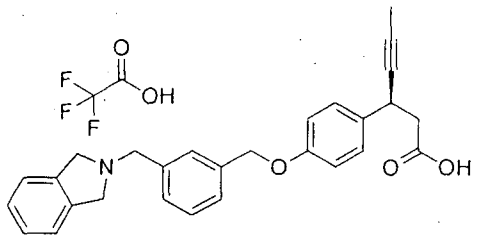
(S)-3-(4-((3-((3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.40-7.26 (m, 6H), 6.86 (d, *J* = 8.8 Hz, 2H), 5.12 (dd, *J* = 12.8, 18.4 Hz, 2H), 4.15-4.12 (m, 2H), 4.04-3.99 (m, 1H), 3.86-3.69 (m, 4H), 3.00-2.85 (m, 2H), 2.82 (dd, *J* = 6.8, 15.2 Hz, 1H), 2.65 (dd, *J* = 6.8, 15.2 Hz, 1H), 1.82 (*J* = 2 Hz, 3H).

Example 12

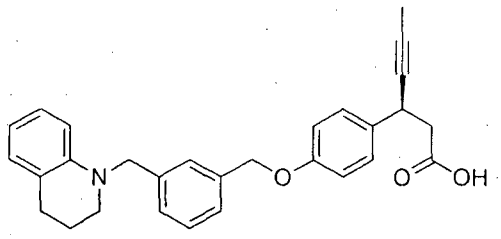
(S)-3-(4-((3-(isoindolin-2-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid trifluoroacetic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.52-7.44 (m, 2H), 7.42-7.34 (m, 4H), 7.31-7.26 (m, 4H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.09 (s, 2H), 4.70(s, 2H), 4.34-4.29 (m, 2H), 4.04-4.00 (m, 1H), 3.32 (s, 2H), 2.85-2.78 (m, 1H), 2.70-2.63 (m, 1H), 1.80 (d, *J* = 2.4 Hz, 3H).

Example 13

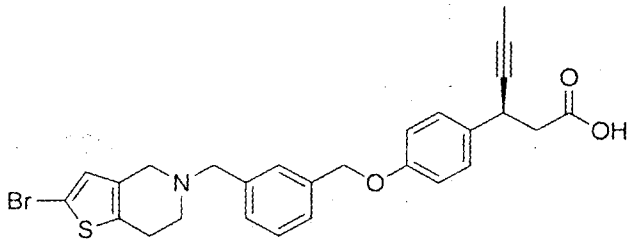
(S)-3-(4-((3-((3,4-dihydroquinolin-1(2H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.32-7.22 (m, 6H), 6.99-6.90 (m, 4H), 6.60-6.57 (m, 1H), 6.50 (d, *J* = 8.4 Hz, 2H), 5.02 (s, 2H), 4.49 (s, 2H), 4.06 ($s_{(br)}$, 1H), 3.36 ($s_{(br)}$, 2H), 3.02-2.78 (m, 4H), 2.02-2.00 (m, 2H), 1.80 (s, 3H).

Example 14

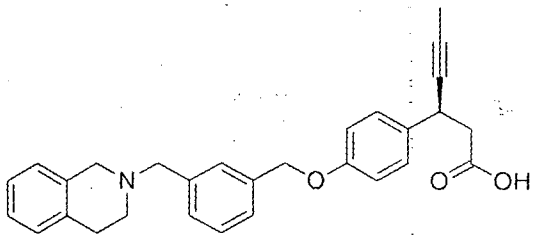
(S)-3-(4-((3-((2-bromo-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.42-7.36 (m, 3H), 7.32-7.25 (m, 3H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.66 (s, 1H), 5.05 (s, 2H), 4.06-4.02 (m, 1H), 3.94-3.92 (m, 2H), 3.68 ($s_{(br)}$, 2H), 3.01 ($s_{(br)}$, 2H), 2.88-2.85 (m, 2H), 2.80-2.74 (m, 1H), 2.69-2.63 (m, 1H), 1.83 (d, *J* = 2.4 Hz, 3H).

Example 15

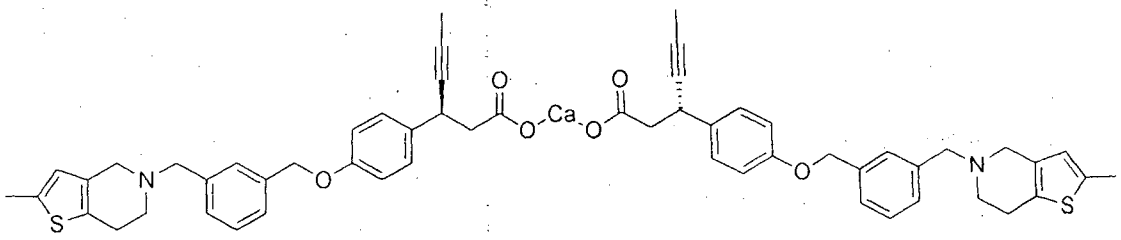
(S)-3-(4-((3-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.47(s, 1H), 7.42-7.27 (m, 5H), 7.22-7.15 (m, 3H), 7.05-7.02 (m, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.10-5.03 (m, 2H), 4.10-4.06 (m, 1H), 2.02-2.00 (m, 2H), 1.80 (s, 3H)., 3.87-3.80 (m, 4H), 2.96-2.86 (m, 4H), 2.86-2.80 (m, 1H), 2.78-2.74 (m, 1H), 1.86 (d, *J* = 2.4 Hz, 3H).

Example 16

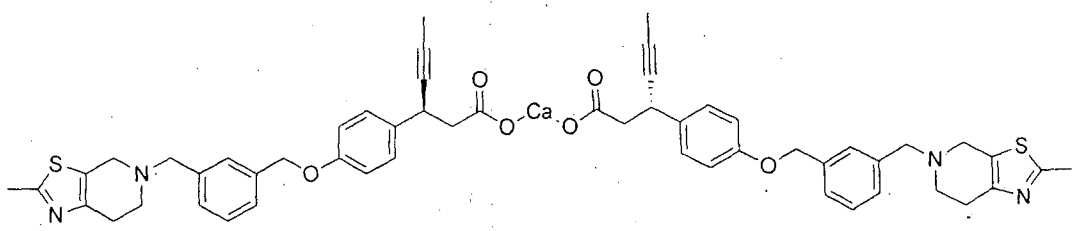
calcium*(S)*-3-(4-((3-((2-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate*(S)*-3-(4-((3-((2-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate



^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.40 (s, 1H), 7.35-7.23 (m, 5H), 6.88 (d, J = 8.4 Hz, 2H), 6.41 (s, 1H), 5.04 (s, 2H), 4.00 ($s_{(br)}$, 1H), 3.64 (s, 2H), 3.32 (s, 2H), 2.68 (s, 4H), 2.40-2.37 (m, 1H), 2.33 (s, 3H), 2.27-2.21 (m, 1H), 1.74 (d, J = 2 Hz, 3H).

Example 17

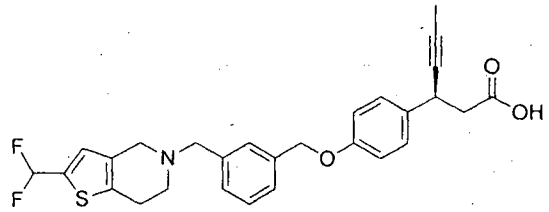
calcium*(S)*-3-(4-((3-((2-methyl-6,7-dihydrothiazolo[4,5-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate*(S)*-3-(4-((3-((2-methyl-6,7-dihydrothiazolo[4,5-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate



^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.41 (s, 1H), 7.34-7.23 (m, 5H), 6.89 (d, J = 8.8 Hz, 2H), 5.01 (s, 2H), 4.05-3.99 (m, 1H), 3.68 (s, 2H), 3.56 (s, 2H), 2.76-2.74 (m, 2H), 2.68 ($s_{(br)}$, 2H), 2.56 (s, 3H), 2.40-2.36 (m, 1H), 2.26-2.22 (m, 1H), 1.73 (d, J = 2.4 Hz, 3H).

Example 18

(S)-3-(4-((3-((2-(Difluoromethyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid

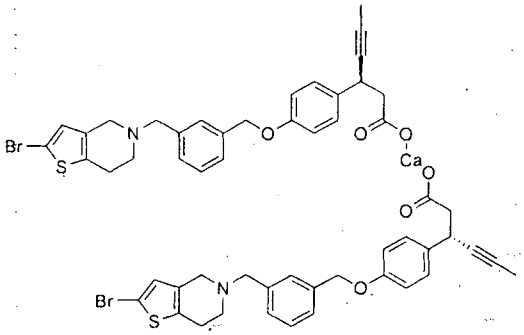


^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.39-7.26 (m, 6H), 6.91-6.59 (m, 4H), 5.03 (s, 2H), 4.12-4.10 (m, 1H), 3.73 (s, 2H), 3.55 (s, 2H), 2.88-2.64 (m, 6H), 1.82 (d, J =

2.4 Hz, 3H).

Example 19

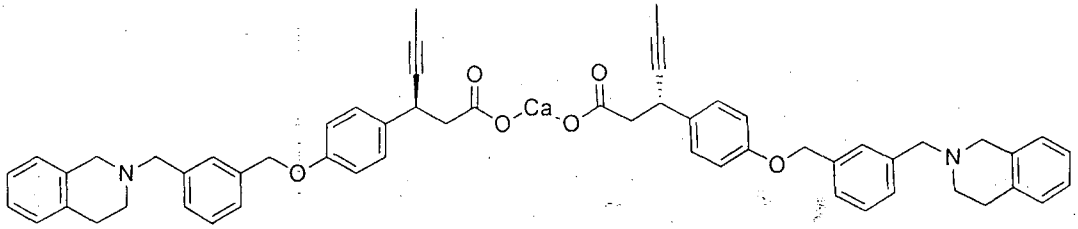
Calcium *(S)*-3-(4-((3-((2-bromo-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate



^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.41 (s, 1H), 7.37-7.24 (m, 5H), 6.93-6.89 (m, 3H), 5.06 (s, 2H), 3.96-3.94 (m, 1H), 3.66 (s, 2H), 3.38 (s, 2H), 2.71 (s, 4H), 2.49-2.32 (m, 2H), 1.76 (d, J = 2.4 Hz, 3H).

Example 20

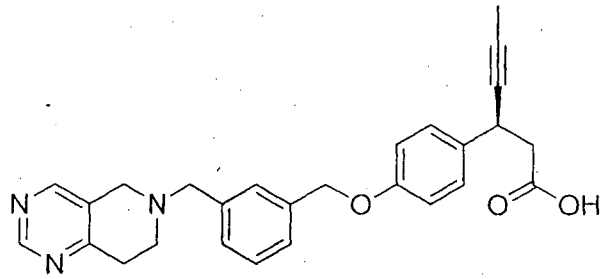
Calcium *(S)*-3-(4-((3-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate



^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.37 (s, 1H), 7.35-7.23 (m, 5H), 7.11-7.07 (m, 3H), 6.98-6.97 (m, 1H), 6.89 (d, J = 8.8 Hz, 2H), 5.05 (s, 2H), 3.99-3.97 (m, 1H), 3.64 (s, 2H), 3.52 (s, 2H), 2.79-2.77 (m, 2H), 2.65-2.64 (m, 2H), 2.42-2.36 (m, 1H), 2.28-2.22 (m, 1H), 1.74 (d, J = 2.4 Hz, 3H).

Example 21

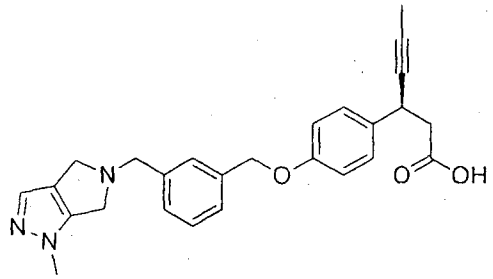
(S)-3-(4-((3-((7,8-Dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.94 (s, 1H), 8.30 (s, 1H), 7.45 (s, 1H), 7.38-7.25 (m, 5H), 6.86 (dd, *J* = 2, 6.8 Hz, 2H), 5.15-5.09 (m, 2H), 4.06-4.03 (m, 1H), 3.78-3.62 (m, 4H), 2.89-2.73 (m, 6H), 1.82 (d, *J* = 2.4 Hz, 3H).

Example 22

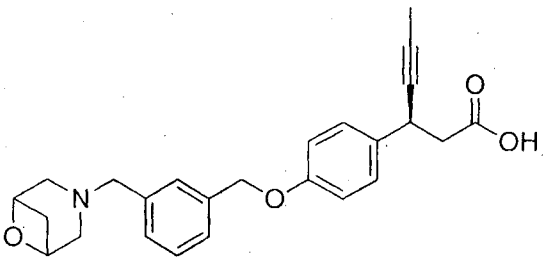
(S)-3-(4-((3-((1-Methylpyrrolo[3,4-c]pyrazol-5(1H,4H,6H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43-7.24 (m, 6H), 7.17(s, 1H), 6.88 (td, *J* = 5.2, 8.4 Hz, 2H), 5.03 (s, 2H), 4.07 (s, 2H), 4.02-3.97 (m, 5H), 3.75 (s, 3H), 2.78-2.72 (m, 1H), 2.66-2.60 (m, 1H), 1.80 (d, *J* = 2.4 Hz, 3H).

Example 23

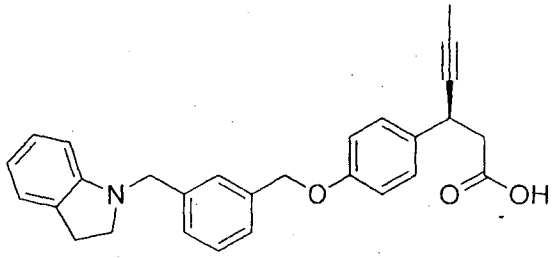
(3S)-3-(4-((3-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ:7.53-7.25 (m, 6H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.09 (s, 2H), 4.54-4.52 (m, 2H), 4.05-3.93 (m, 3H), 3.24-2.94 (m, 4H), 2.81-2.75 (m, 1H), 2.69-2.63 (m, 1H), 2.42 (d, *J* = 8.8 Hz, 2H), 1.83 (d, *J* = 2.4 Hz, 3H).

Example 24

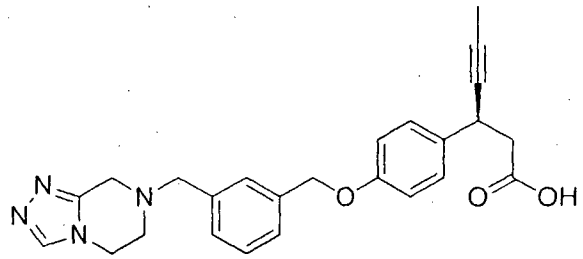
(S)-3-(4-((3-(Indolin-1-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.41 (s, 1H), 7.37-7.25 (m, 5H), 7.10-7.05 (m, 2H), 6.93-6.89 (m, 2H), 6.70-6.66 (m, 1H), 6.51 (d, *J* = 7.6 Hz, 1H), 5.03 (s, 2H), 4.26 (s, 2H), 4.07-4.02 (m, 1H), 3.30 (t, *J* = 8.4 Hz, 2H), 2.96 (t, *J* = 8.4 Hz, 2H), 2.83-2.76 (m, 1H), 2.73-2.67 (m, 1H), 1.83 (d, *J* = 2.4 Hz, 3H).

Example 25

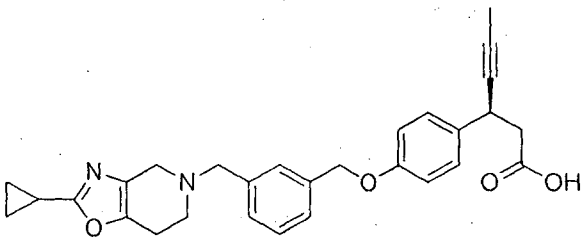
(S)-3-(4-((3-((5,6-Dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR (CD_3OD, 400 MHz) δ: 8.50 (s, 1H), 7.49 (s, 1H), 7.40-7.35 (m, 3H), 7.28 (d, *J* = 6.8 Hz, 2H), 6.93 (d, *J* = 6.8 Hz, 2H), 5.01 (s, 2H), 4.15-4.11 (m, 2H), 4.00-3.97 (m, 1H), 3.87-3.83 (m, 4H), 2.97-2.94 (m, 2H), 2.66-2.62 (m, 2H), 1.81 (d, *J* = 2.4 Hz, 3H).

Example 26

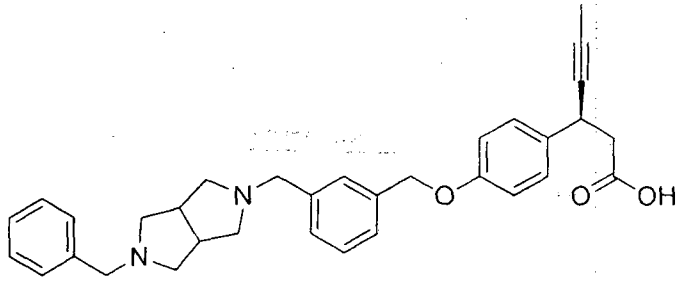
(S)-3-(4-((3-((2-Cyclopropyl-6,7-dihydrooxazolo[4,5-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.52-7.20 (m, 6H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.21-5.12 (m, 2H), 4.00-3.95 (m, 1H), 3.78-3.67 (m, 2H), 3.23-2.59 (m, 8 H), 2.04-1.97 (m, 1H), 1.81 (d, *J* = 2.4 Hz, 3H), 1.00-0.96 (m, 4H).

Example 27

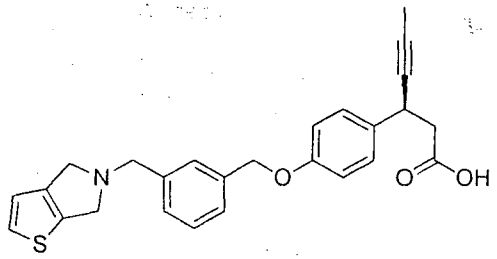
(3S)-3-(4-((3-((5-Benzylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with formic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.45 ($s_{(br)}$, 0.78 H, HCOOH), 7.52-7.15 (m, 9H), 7.16 (d, *J* = 7.2 Hz, 1H), 6.78 (dd, *J* = 2.8, 11.6 Hz, 2H), 5.12 (s, 2H), 4.05-4.00 (m, 1H), 3.93-3.68 (m, 4H), 3.04-3.01 (m, 2H), 2.83-2.78 (m, 3H), 2.68-2.64 (m, 1H), 2.58-2.40 (m, 6H), 1.77 (d, *J* = 2.4 Hz, 3H).

Example 28

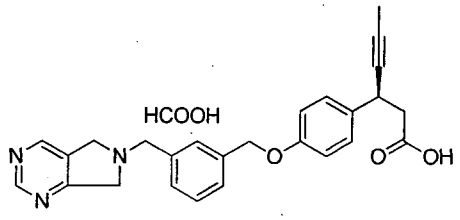
(S)-3-(4-((3-((4H-Thieno[2,3-c]pyrrol-5(6H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43 (s, 1H), 7.39-7.24 (m, 6H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 5.2 Hz, 1H), 5.06-4.99 (m, 2H), 4.17-4.00 (m, 7H), 2.77-2.71 (m, 1H), 2.65-2.59 (m, 1H), 1.80 (d, *J* = 2.4 Hz, 3H).

Example 29

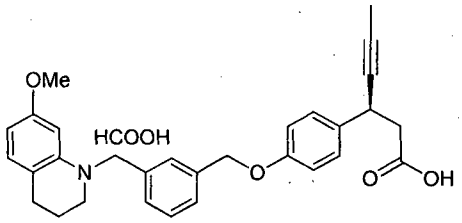
6-(3-((4-((*S*)-1-carboxypent-3-yn-2-yl)phenoxy)methyl)benzyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-6-ium formate



^{1}HNMR($CDCl_3$, 400 MHz) δ: 8.98 (s, 1H), 8.63 (s, 1H), 8.37 (s, 1H), 7.45 (s, 1H), 7.37 – 7.31 (m, 3H), 7.25 (d, *J* = 8.8 Hz ,2H), 6.93 (d, *J* = 8.8Hz , 2H), 5.08 (s, 2H), 3.95 – 3.90 (m, 7H), 2.55- 2.52 (m, 1H), 2.12 (s, 3H).

Example 30

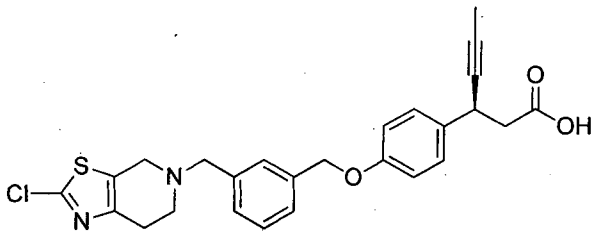
1-(3-((4-((*S*)-1-carboxypent-3-yn-2-yl)phenoxy)methyl)benzyl)-7-methoxy-1,2,3,4-tetrahydroquinolin-1-ium formate



^{1}HNMR($CDCl_3$, 400 MHz) δ 8.21 (s), 0.28 (formate), 7.33 – 7.28 (m, 3H), 7.25 (d, *J* = 8.8 Hz , 2H), 7.19 (d, *J* = 7.2 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.55 (d, *J* = 2.8 Hz, 1H), 6.51 – 6.48 (dd, *J* = 8.8 Hz & 2.8 Hz, 1H), 6.39 (d, *J* = 8.8 Hz, 1H), 5.0 (s, 2H), 4.39 (s, 2H), 3.95 – 3.90 (m, 3H), 3.60 (m, 4H), 3.24 (t, 3H), 2.70 (m, 2H), 2.58 (d, 2H), 2.06 (t, 2H), 1.07 – 1.08 (s, 3H).

Example 31

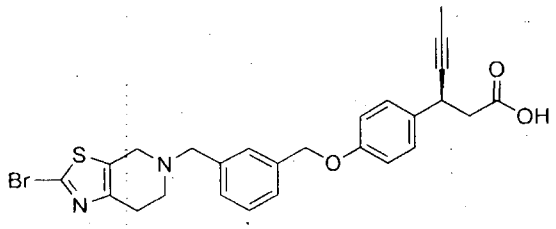
(S)-3-(4-((3-((2-Chloro-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.41-7.30 (m, 3H), 7.35-7.27 (m, 3H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.07 (s, 1H), 4.07-4.02 (m, 1H), 3.82 (s, 2H), 3.72 (s, 2H), 2.98-2.95 (m, 2H), 2.86-2.68 (m, 5H), 1.83 (d, *J* = 2.4 Hz, 3H).

Example 32

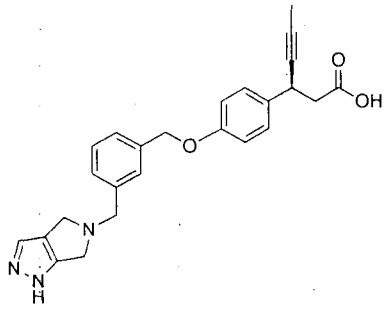
(S)-3-(4-((3-((2-Bromo-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.39-7.35 (m, 3H), 7.29-7.26 (m, 3H), 6.90 (d, *J* = 8.4 Hz, 2H), 5.05 (s, 2H), 4.06-4.01 (m, 1H), 3.79 (s, 2H), 3.70 (s, 2H), 2.92-2.66 (m, 6H), 1.82 (d, *J* = 2.4 Hz, 3H).

Example 33

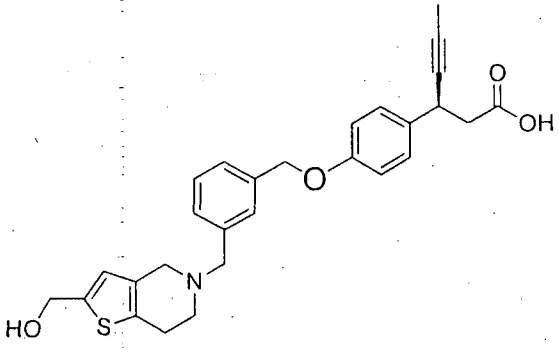
(S)-3-(4-((3-(pyrrolo[3,4-c]pyrazol-5(1H,4H,6H)-ylmethyl)benzyl)oxy)phenyl) hex-4-ynoic acid



^{1}H-NMR ($CDCl_3$, 400 MHz):- δ 7.32-7.53 (m, 3H), 7.19-7.29 (m, 4H), 6.82-6.84 (m, 2H), 5.16 (s, 2H), 3.90-4.06(m, 5H), 3.57 (s, 2H), 2.80-2.85 (m, 1H), 1.81 (s, 3H);

Example 34

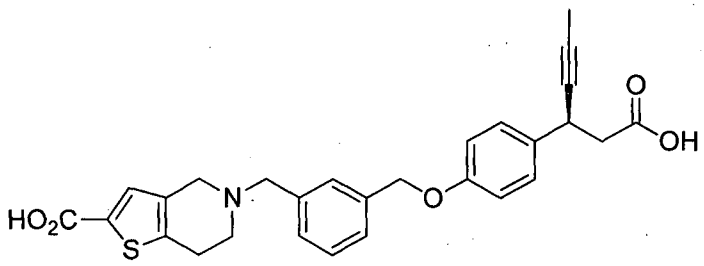
(S)-3-(4-((3-((2-(hydroxymethyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H-NMR (DMSO, 400 MHz):- δ 7.38 (s, 1H), 7.23-7.33 (m, 5H), 6.92 (d, J=8.8 Hz, 2H), 6.56 (s, 1H), 5.35 (s, 2H), 3.91-3.94 (m, 1H), 3.72-3.84 (m, 4H), 3.40-3.50 (m, 2H(merged), 2.86-2.94 (m, 2H), 2.73-2.76 (m, 2H), 2.50-2.58 (m, 2H), 1.76 (s, 3H);

Example 35

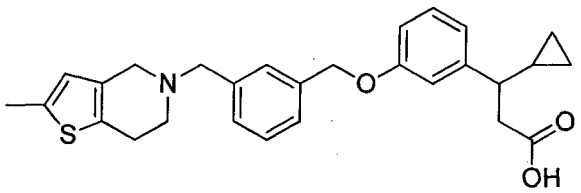
(S)-5-(3-((4-(1-carboxypent-3-yn-2-yl)phenoxy)methyl)benzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid



^{1}H NMR: (DMSO-d_6, 400MHz):- 7.42 (s, 1H), 7.34 - 7.31 (m, 2H), 7.27 - 7.26 (m, 1H), 7.22 (d, J = 8.8Hz, 2H), 6.99 (s, 1H), 6.90 (d, J = 8.8Hz, 2H), 5.09 (s, 2H), 3.95 - 3.91 (m, 1H), 3.65 (s, 2H), 3.29 (s, 2H), 2.74 - 2.71 (m, 4H), 2.63 - 2.52 (m, 2H), 1.76 (s, 3H).

Example 36

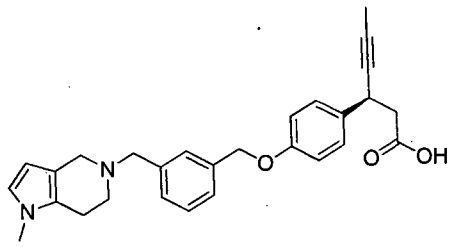
3-cyclopropyl-3-(3-((3-((2-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)propanoic acid



^{1}H NMR: (DMSO-d_6, 400MHz):- 7.46 (s, 1H), 7.37 - 7.31 (m, 3H), 7.14 (t, J = 8Hz, 2H), 6.81 - 6.79 (m, 2H), 6.44 (s, 1H), 5.05 (s, 2H), 3.78 (s, 2H), 3.32 (s, 2H), 2.82 - 2.74 (m, 4H), 2.49 - 2.44 (m, 2H), 2.36 - 2.34 (m, 4H), 1.30 - 1.28 (m, 1H), 0.49 - 0.47 (m, 1H), 0.27 - 0.24 (m, 2H), 0.004 - 0.002 (m, 1H).

Example 37

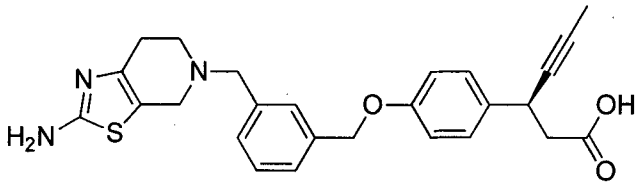
(S)-3-(4-((3-((1-methyl-6,7-dihydro-1H-pyrrolo [3,2-c]pyridin-5(4H)-yl)methyl) benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.53 (s, 1H), 7.47 – 7.32 (d, 3H), 7.24 – 7.12 (m, 2H), 6.85 (d, 2H), 6.51 (d, 1H), 5.58 (d, 1H), 5.0 – 4.95 (d, 2H), 3.9 – 4.1 (m, 1H), 3.87 (d, 1H), 3.80 (d, 1H), 3.48 (s, 3H), 2.9 – 3.1 (m, 3H), 1.08 (m, 3H).

Example 38

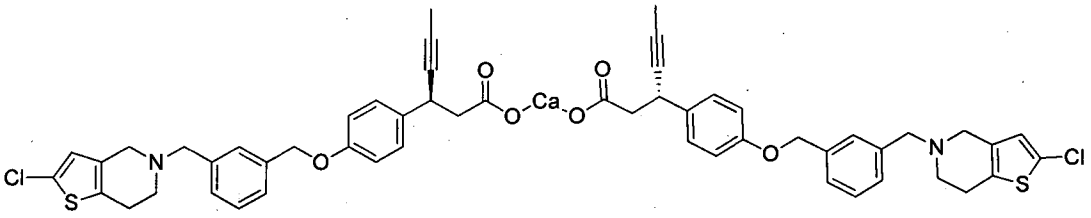
(S)-3-(4-((3-((2-amino-6,7-dihydrothiazolo [5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy) phenyl)hex-4-ynoic acid



^{1}H NMR (DMSO-d_6, 400 MHz) : δ 8.23 (s, 1H), 7.40 (s, 1H), 7.35 (d, 2H), 7.32 – 7.24 (m, 3H), 6.93 (d, *J* = 8.4Hz, 2H), 6.68 (s, 2H), 5.06 (s, 2H), 3.9 – 4.0 (m, 1H), 3.35 (s, 3H), 2.70 – 2.66 (m, 2H), 2.58 (d, 2H), 2.44 (d, 3H).

Example 39

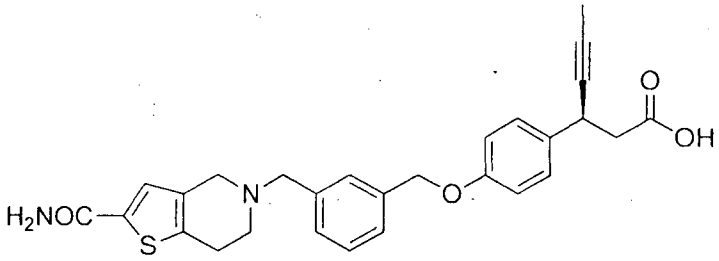
Calcium *(S)*-3-(4-((3-((2-chloro-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.39 (s, 1H), 7.36-7.23 (m, 5H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.78 (s, 1H), 5.04 (s, 2H), 3.99 ($s_{(br)}$, 1H), 3.65 (s, 2H), 3.34 (s, 2H), 2.70 ($s_{(br)}$, 4H), 2.37-2.31 (m, 1H), 2.25-2.19 (m, 1H), 1.73 (d, J = 2.4 Hz, 3H).

Example 40

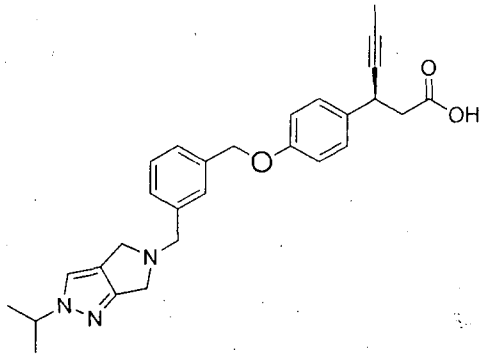
(S)-3-(4-((3-((2-carbamoyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR: (DMSO-d_6, 400MHz):- 12.22 (br s, 1H), 7.76 (br s,1H), 7.42 (s, 1H), 7.37 - 7.25 (m, 7H), 6.94 (d, J = 8.8Hz, 2H), 5.07 (s, 2H), 3.95 - 3.91 (m, 1H), 3.68 (s, 2H), 3.43 (s, 2H), 2.78 - 2.76 (m, 2H), 2.72 - 2.70 (m, 2H), 2.60 - 2.57 (m, 2H), 1.77 (s, 3H).

Example 41

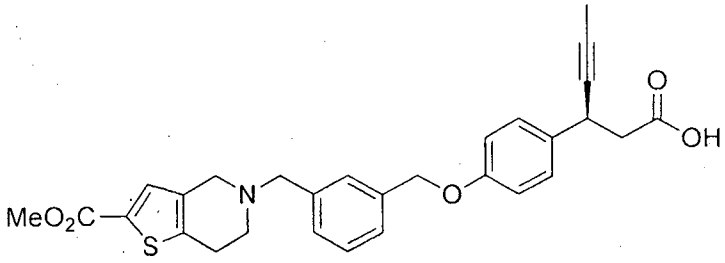
(S)-3-(4-((3-((2-isopropylpyrrolo[3,4-c]pyrazol-5(2H,4H,6H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H-NMR(DMSO, 400 MHz): δ 12.25 (m, 2H), 7.48-7.51 (m, 2H), 7.39 (s, 3H), 7.27 (d, J = 8.8 Hz, 2H), 6.95(d, J = 8.8 Hz, 2H), 5.09 (s, 2H), 4.40-4.47 (m, 1H), 4.10-4.20 (m, 2H), 3.70-3.90 (m, 4H), 2.66-2.66 (m, 2H), 1.77 (s, 3H), 1.36-1.38 (m, 6H);

Example 42

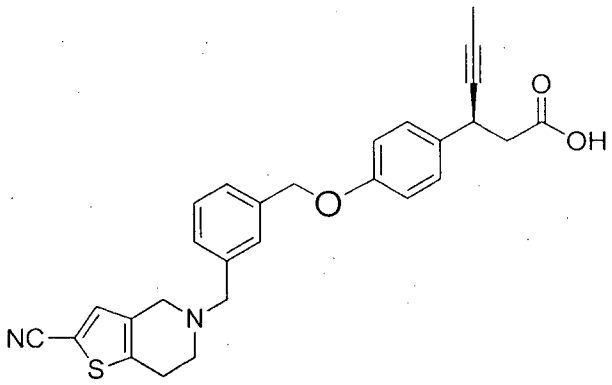
(S)-3-(4-((3-((2-(methoxycarbonyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR: (DMSO-d_6, 400MHz):- 12.22 (br s, 1H), 7.50 (s, 1H), 7.41 (s, 1H), 7.37 - 7.24 (m, 5H), 6.92 (d, J = 8.4Hz, 2H), 5.07 (s, 2H), 3.95 - 3.91 (m, 1H), 3.77 (s, 3H), 3.68 (s, 2H), 3.46 (s, 2H), 2.84 - 2.81 (m, 2H), 2.74 - 2.70 (m, 2H), 2.58 - 2.53 (m, 2H), 1.90 (s, 3H).

Example 43

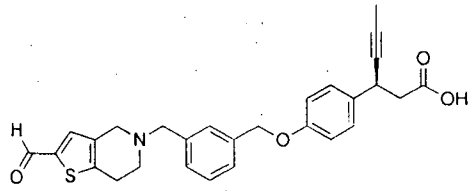
(S)-3-(4-((3-((2-cyano-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H-NMR(DMSO, 400 MHz): δ 8.83 (s, 1H), 7.24-7.41 (m, 6H), 6.92-6.94 (m, 2H), 5.09 (s, 2H),3.91-3.94 (m, 1H), 3.73 (s, 2H), 3.45 (s, 2H), 2.86-2.94 (m, 2H), 2.73-2.76 (m, 2H), 2.50-2.58 (m, 2H), 1.76 (s, 3H);

Example 44

(S)-3-(4-((3-((2-formyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid

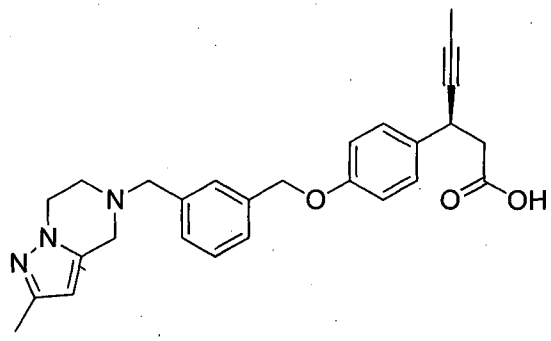


^{1}H NMR: (DMSO-d_6, 400MHz):- 9.79 (s, 1H), 7.70 (s, 1H), 7.42 (s, 1H), 7.36 - 7.31 (m, 3H), 7.26 – 7.24 (d, J = 8 Hz, 2H), 6.94 – 6.92 (d, J = 8 Hz, 2H), 5.07 (s,

2H), 3.93 (br s, 1H), 3.70 (s, 2H), 3.50 (s, 2H), 2.89 (s, 2H), 2.74 (s, 2H), 1.76 (s, 3H), 1.23 (s, 2H).

Example 45

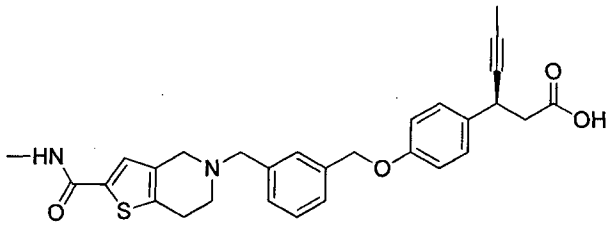
S)-3-(4-((3-((2-methyl-6,7-dihydropyrazolo [1,5-a]pyrazin-5(4H)-yl)methyl)benzyl) oxy)phenyl)hex-4-ynoic acid



^{1}H NMR (DMSO-d_6, 400 MHz) : δ 7.41 (s, 1H), 7.35 (d, J = 6.4 Hz , 2H), 7.30 (m, 1H), 7.25 (d, J = 8.8 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 5.73 (s, 1H), 5.07 (s, 2H), 3.96 – 3.92 (m, 3H), 3.68 (s, 2H), 3.52 (s, 2H), 2.84 (t, 2H), 2.66 (t, 2H), 2.08 (s, 3H), 1.77 (s, 3H)

Example 46

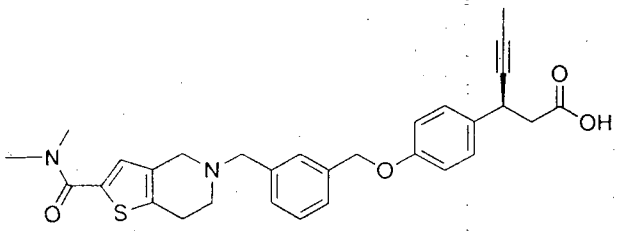
(S)-3-(4-((3-((2-(methylcarbamoyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR: (DMSO-d_6, 400MHz):- 7.42 (s, 1H), 7.35 – 7.24 (m, 6H), 7.1 - 6.93 – 6.91 (m, 2H), 5.07 (s, 2H), 3.9 (m, 1H), 3.68 (s, 2H), 3.41 (s, 2H), 2.71 – 2.70 (m, 2H), 2.67 – 2.66 (m, 6H), 1.76 (s, 3H).

Example 47

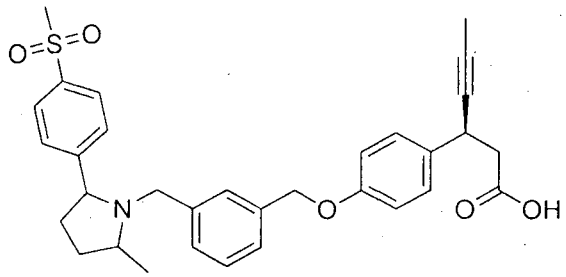
(S)-3-(4-((3-((2-(dimethylcarbamoyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR: (DMSO-d_6, 400MHz):- 7.53 (s, 1H), 7.40 – 7.22 (m, 4H), 7.1 - 6.68 (m, 3H), 5.08 (s, 2H), 4.12 – 4.03 (m, 1H), 3.78 – 3.71 (m, 2H), 3.50 (s, 2H), 3.17 (s, 6H), 2.95 – 2.88 (m, 2H), 2.83 – 2.63 (m, 2H), 1.83 (s, 3H).

Example 48

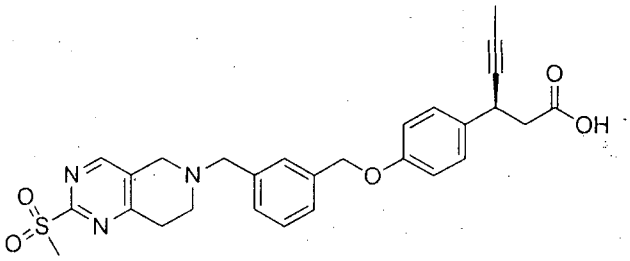
(3S)-3-(4-((3-((2-Methyl-5-(4-(methylsulfonyl)phenyl)pyrrolidin-1-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.93-7.90 (m, 2H), 7.82-7.76 (m, 2H), 7.53-7.16 (m, 7H), 6.92-6.86 (m, 3H), 5.11-5.01 (m, 3H), 4.45-4.30 (m, 1H), 4.07-3.98 (m, 3H), 3.30-3.20 (m, 1H), 3.097-3.090 (m, 3H), 3.03 (s, 1H), 2.87-2.68 (m, 4H), 2.33-1.98 (m, 8H), 1.84-1.82 (m, 5H), 1.62-1.60 (m, 4H)

Example 49

(S)-3-(4-((3-((2-(Methylsulfonyl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid

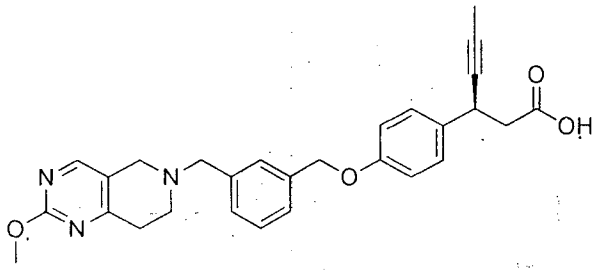


^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.48 (s, 1H), 7.43-7.27 (m, 6H), 6.91 (dd, J = 8.8, 2 Hz, 2H), 5.07 (s, 2H), 4.07-4.03 (m, 1H), 3.80 (s, 2H), 3.72 (s, 2H), 3.32 (s,

3H), 3.15-3.09 (m, 2H), 2.92-2.89 (m, 2H), 2.84-2.78 (m, 1H), 2.74-2.68 (m, 1H), 1.83 (d, *J* = 2.4 Hz, 3H)

Example 50

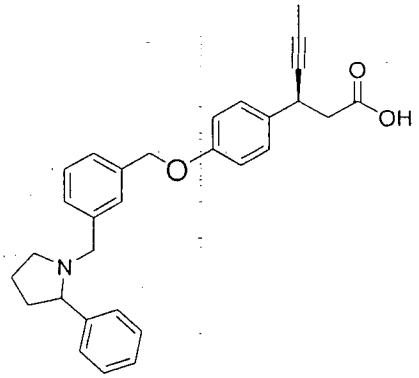
(S)-3-(4-((3-((2-Methoxy-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.09 (s, 1H), 7.53-7.26 (m, 6H), 6.87 (dd, *J* = 6.8, 2 Hz, 2H), 5.17-5.08 (m, 2H), 4.07-4.02 (m, 1H), 3.98 (s, 3H), 3.75 ($s_{(br)}$, 2H), 3.58 ($s_{(br)}$, 2H), 2.88-2.63 (m, 6H), 1.82 (d, *J* = 2.4 Hz, 3H)

Example 51

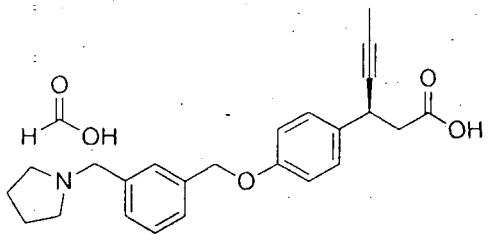
(3S)-3-(4-((3-((2-phenylpyrrolidin-1-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H-NMR($CDCl_3$, 400 MHz): δ 7.43-7.45 (m, 2H), 7.21-7.35 (m, 9H), 6.89-6.91 (d, J = 8 Hz, 2H), 5.0 (s, 2H), 4.03 (m, 1H), 3.81-3.85 (m, 1H), 3.37-3.41 (m, 1H), 3.11-3.17 (m, 3H), 2.74-2.80 (m, 1H), 2.64-2.69 (m, 1H), 3.37-2.14-2.51 (m, 2H), 1.85-1.92 (m, 1H), 1.81 (s, 3H), 1.71-1.75 (m, 2H);

Example 52

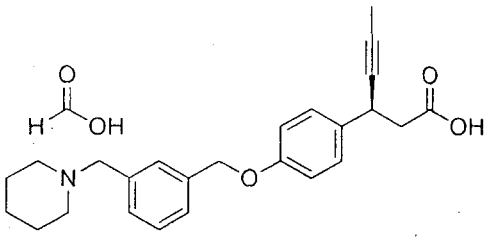
(S)-3-(4-((3-(Pyrrolidin-1-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with formic acid



^{1}H NMR (CD_3OD, 400 MHz) δ: 8.51 (s, 1H, HCOOH), 7.60 (s, 1H), 7.55-7.45 (m, 3H), 7.28 (d, *J* = 8.4 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.14 (s, 2H), 4.34 (s, 2H), 4.02-3.98 (m, 1H), 3.27-3.24 (m, 4H), 2.62-2.50 (m, 2H), 2.08-2.04 (m, 4H), 1.80 (d, *J* = 2.4 Hz, 3H)

Example 53

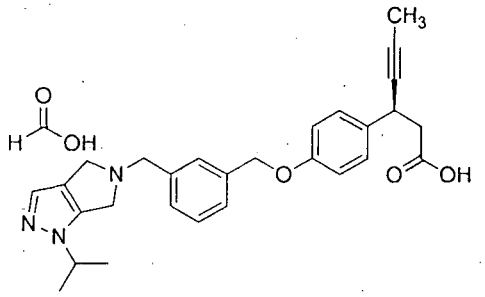
(S)-3-(4-((3-(Piperidin-1-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with formic acid



^{1}H NMR (CD_3OD, 400 MHz) δ: 8.50 (s, 1H, HCOOH), 7.58-7.43 (m, 4H), 7.29 (d, *J* = 8.8, Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.15 (s, 2H), 4.23 (s, 2H), 4.09-4.03 (m, 1H), 3.12-3.08 (m, 4H), 2.63-2.49 (m, 2H), 1.83-1.79 (m, 7H), 1.64-1.61 (m, 2H)

Example 54

(S)-3-(4-((3-((1-isopropylpyrrolo[3,4-c]pyrazol-5(1H,4H,6H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with formic acid

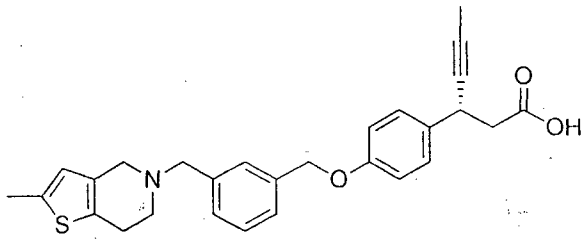


^{1}H NMR (CD_3OD, 400 MHz) δ: 8.41 (s, 1H, HCOOH), 7.54 (s, 1H), 7.43-7.40 (m, 3H), 7.29 (dd, *J* = 7.2, 2 Hz, 2H), 7.21 (s, 1H), 6.93 (dd, *J* = 6.8, 2 Hz, 2H),

5.11 (s, 2H), 4.45-4.41 (m, 1H), 4.14 (s, 2H), 4.07 (s, 2H), 4.02-3.95 (m, 1H), 3.88 (s, 2H), 2.63-2.59 (m, 2H), 1.80 (d, J = 2.4 Hz, 3H), 1.42 (d, J = 6.8 Hz, 6H).

Example 55

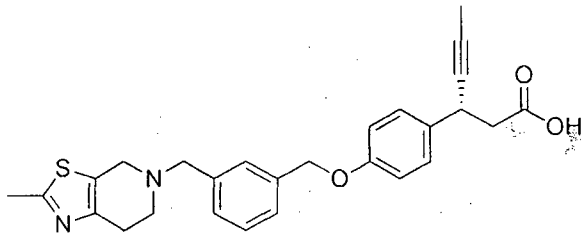
(R)-3-(4-((3-((2-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl) oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.31 (s, 0.36 H, Residual HCOOH), 7.47-7.25 (m, 6H), 6.86 (td, J = 9.6, 2.8 Hz, 2H), 6.34 (s, 1H), 5.04 (s, 2H), 4.07-4.01 (m, 3H), 3.8 ($s_{(br)}$, 2H), 3.20-3.12 (m, 2H), 2.97-2.95 (m, 2H), 2.78-2.73 (m, 1H), 2.66-2.61(m, 1H), 2.41 (s, 3H), 1.80 (d, J = 2.4 Hz, 3H).

Example 56

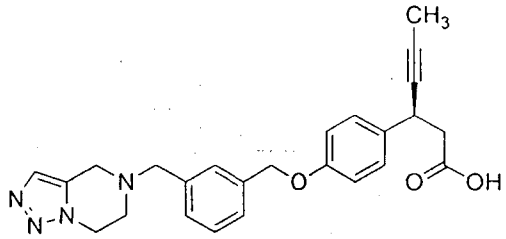
(R)-3-(4-((3-((2-Methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.15 (s, 0.3H, Residual HCOOH), 7.41-7.27 (m, 6H), 6.88 (d, J = 8.4 Hz, 2H), 5.15-5.07 (m, 2H), 4.06-4.02 (m, 1H), 3.90-3.82 (m, 4H), 2.96-2.92 (m, 2H), 2.88-2.64 (m, 7H), 1.82 (d, J = 2.4 Hz, 3H)

Example 57

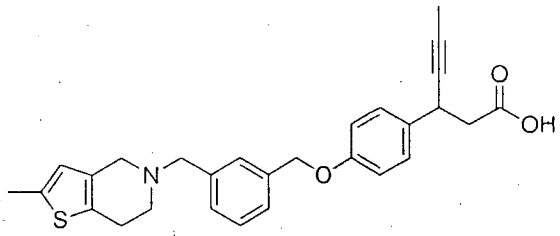
(S)-3-(4-((3-((6,7-Dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR (CD_3OD, 400 MHz) δ: 7.59-7.58 (m, 2H), 7.58-7.43 (m, 3H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.14 (s, 2H), 4.58-4.55 (m, 2H), 4.19 (s, 2H), 4.15 (s, 2H), 4.01-3.97 (m, 1H), 3.44-3.41 (m, 2H), 2.70-2.58 (m, 2H), 1.81 (d, *J* = 2.4 Hz, 3H).

Example 58

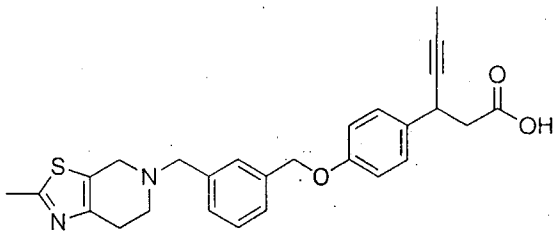
3-(4-((3-((2-Methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl) oxy)phenyl)hex-4-ynoic acid



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.42-4.27 (m, 5H), 6.87 (dd, *J* = 11.2, 3 Hz, 2H), 6.34 (s, 1H), 5.05 (s, 2H), 4.06-4.02 (m, 2H), 3.98 (s, 2H), 3.74 (s, 2H), 3.10-3.04 (m, 2H), 2.92-2.89 (m, 2H), 2.79-2.73 (m, 1H), 2.67-2.61 (m, 1H), 2.41 (s, 3H), 1.81 (d, *J* = 2.4 Hz, 3H).

Example 59

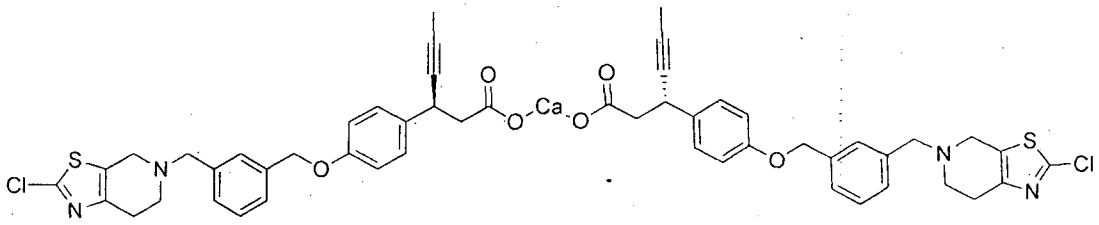
3-(4-((3-((2-Methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid:



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.42-7.35 (m, 4H), 7.29-7.27 (m, 2H), 6.88 (d, J = 8.8 Hz, 2H), 5.14-5.07 (m, 2H), 4.06-4.03 (m, 1H), 3.93-3.85 (m, 4H), 2.99-2.97 (m, 2H), 2.86-2.64 (m, 7H), 1.82 (d, J = 2.4 Hz, 3H

Example 60

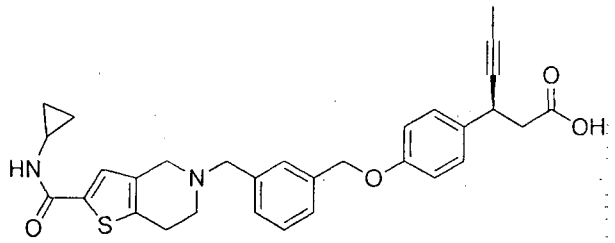
Calcium *(S)*-3-(4-((3-((2-chloro-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate



^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.39 (s, 1H), 7.36-7.23 (M, 5H), 6.88 (d, J = 8.8 Hz, 2H), 5.03 (s, 2H), 4.02-3.99 (m, 1H), 3.69 (s, 2H), 3.39 (s, 2H), 2.80-2.77 (m, 2H), 2.72-2.69 (m, 2H), 2.41-2.36 (m, 1H), 2.27-2.21 (m, 1H), 1.73 (d, J = 2.4 Hz, 3H).

Example 61

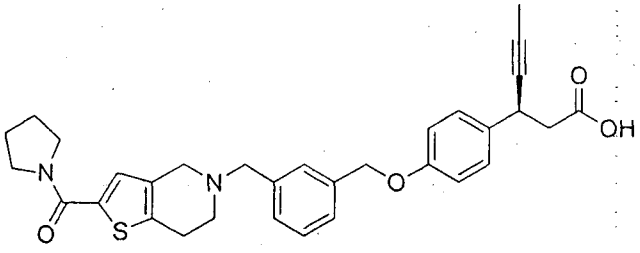
(S)-3-(4-((3-((2-(cyclopropylcarbamoyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR: (DMSO-d_6, 400MHz):- 8.34 (br s, 1H), 7.41 (s, 1H), 7.36 – 7.29 (m, 3H), 7.27 – 7.24 (m, 3H), 6.67 (d, J = 8.4Hz, 2H), 5.07 (s, 2H), 3.95 - 3.91 (m, 1H), 3.67 (s, 2H), 3.42 (s, 2H), 2.77 - 2.66 (m, 5H), 2.57 - 2.51 (m, 2H), 1.76 (s, 3H), 0.67 – 0.62 (m, 2H), 0.53 – 0.49 (m, 2H

Example 62

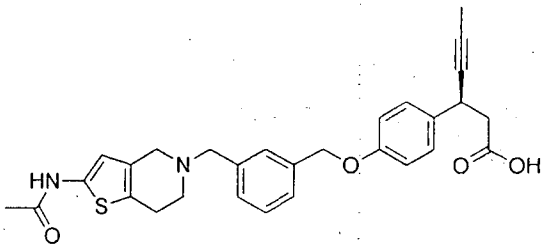
(S)-3-(4-((3-((2-(pyrrolidine-1-carbonyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR: (DMSO-d_6, 400MHz):- 7.42 (s, 1H), 7.37 – 7.26 (m, 3H), 7.25 – 7.13 (m, 3H), 6.93 (d, J = 8.8Hz, 2H), 5.07 (s, 2H), 3.94 - 3.87 (m, 1H), 3.68 (br s, 4H), 3.43 (br s, 4H), 2.80 - 2.73 (m, 4H), 2.59 - 2.50 (m, 2H), 2.91 – 1.81 (m, 4H), 1.76 (s, 3H)

Example 63

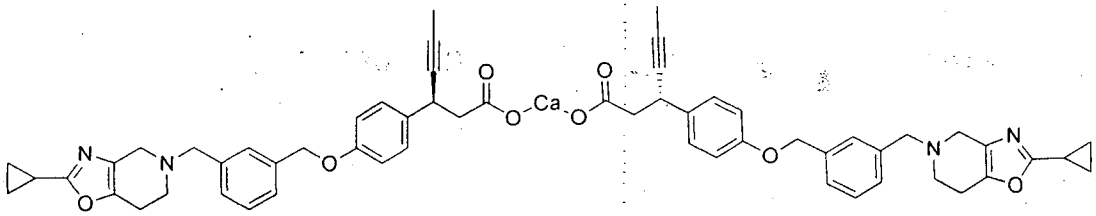
(S)-3-(4-((3-((2-Aacetamido-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid



^{1}H NMR (CD_3OD, 400 MHz) δ: 7.56 (s, 1H), 7.50-7.41 (m, 3H), 7.28 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.35 (s, 1H), 5.12 (s, 2H), 4.15 (s, 2H), 4.01-3.97 (m, 1H), 3.84 (s, 2H), 3.25-3.22 (m, 2H), 2.96-2.93 (m, 2H), 2.66-2.53 (m, 2H), 2.10 (s, 3H), 1.79 (d, J = 2.4 Hz, 3H).

Example 64

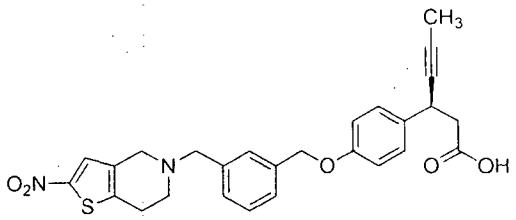
Calcium *(S)*-3-(4-((3-((2-cyclopropyl-6,7-dihydrooxazolo[4,5-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate



^{1}H NMR (DMSO-d_6, 400 MHz) δ:7.38 (s, 1H), 7.34-7.24 (m, 5H), 6.88 (d, J = 8 Hz, 2H), 5.02 (s, 2H), 4.02-4.01 (m, 1H), 3.66 (s, 2H), 3.26 (s, 2H), 2.73-2.71 (m, 2H), 2.58 (s, 2H), 2.41-2.37 (m, 1H), 2.27-2.24 (m, 1H), 2.03-2.00 (m, 1H), 1.72 (s, 3H), 0.98-.093 (m, 2H), 0.86-0.82 (m, 2H).

Example 65

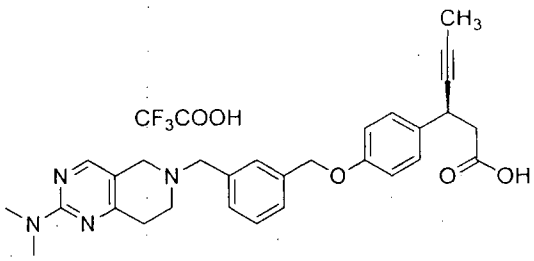
(S)-3-(4-((3-((2-Nitro-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl) oxy)phenyl)hex-4-ynoic acid



^{1}H NMR (CD_3OD, 400 MHz) δ: 7.80 (s, 1H), 7.69 (s, 1H), 7.61-7.52 (m, 3H), 7.30 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 5.17 (s, 2H), 4.54 (s, 2H), 4.30 (s, 2H), 4.01-3.99 (m, 1H), 3.66 ($s_{(br)}$, 2H), 3.31-3.27 (m, 2H), 2.69-2.58 (m, 2H), 1.80 (d, J = 2.4 Hz, 3H)

Example 66

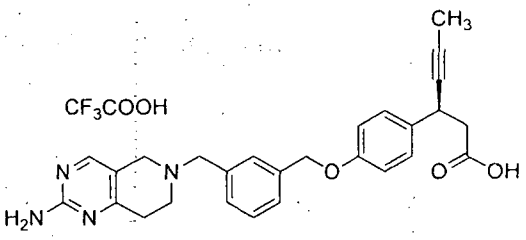
(S)-3-(4-((3-((2-(Dimethylamino)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with 2,2,2-trifluoroacetic acid



^{1}H NMR (CD_3OD, 400 MHz) δ: 8.00 (s, 1H), 7.54 (s, 1H), 7.45-7.42 (m, 3H), 7.28 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 5.13 (s, 2H), 4.01-3.99 (m, 3H), 3.74 (s, 2H), 3.14 (s, 6H), 3.10-3.07 (m, 2H), 2.90-2.87 (m, 2H), 2.64-2.60 (m, 2H), 1.80 (d, J = 2.4 Hz, 3H).

Example 67

(S)-3-(4-((3-((2-Amino-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with 2,2,2-trifluoroacetic acid

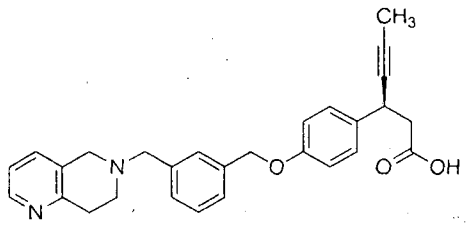


^{1}H NMR (CD_3OD, 400 MHz) δ: 8.10 (s, 1H), 7.67 (s, 1H), 7.62-7.54 (m, 3H),

7.30 (dd, *J* = 6.8, 1.6 Hz, 2H), 6.96 (d, *J* = 6.8, 1.6 Hz, 2H), 5.17 (s, 2H), 4.52 (s, 2H), 4.25 (s, 2H), 4.01-3.99 (m, 1H), 3.63 (s, 2H), 3.09-3.05 (m, 2H), 2.70-2.58 (m, 2H), 1.80 (d, *J* = 2.4 Hz, 3H)

Example 68

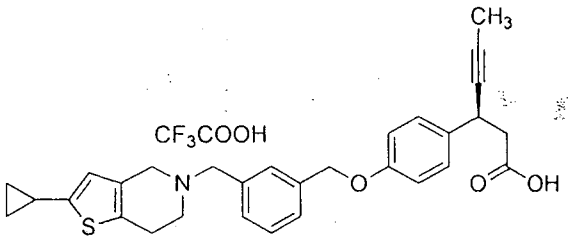
(S)-3-(4-((3-((7,8-Dihydro-1,6-naphthyridin-6(5H)-yl)methyl)benzyl)oxy)phenyl) hex-4-ynoic acid



^{1}H NMR (CD_3OD, 400 MHz) δ: 8.59 (d, *J* = 4 Hz, 1H), 7.87 (d, *J* = 8 Hz, 1H), 7.72 (s, 1H), 7.62-7.51 (m, 4H), 7.30 (dd, *J* = 8.8, 2 Hz, 2H), 6.96 (d, *J* = 8.8, 2 Hz, 2H), 5.17 (s, 2H), 4.57 (s, 2H), 4.49 (s, 2H), 4.01-3.97 (m, 1H), 3.75-3.72 (m, 2H), 3.41-3.38 (m, 2H), 2.69-2.58 (m, 2H), 1.80 (d, *J* = 2.4 Hz, 3H).

Example 69

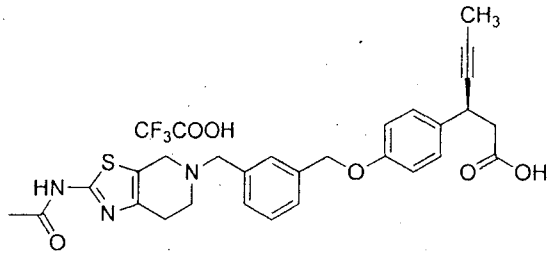
(S)-3-(4-((3-((2-Cyclopropyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with 2,2,2-trifluoroacetic acid



^{1}H NMR (CD_3OD, 400 MHz) δ: 7.66 (s, 1H), 7.60-7.52 (m, 2H), 7.30 (dd, *J* = 6.8, 2 Hz, 2H), 6.90 (dd, *J* = 6.8, 2 Hz, 2H), 6.50 (s, 1H), 5.17 (s, 2H), 4.51 (s, 2H), 4.18 (s, 2H), 4.01-3.97 (m, 1H), 3.12-3.09 (m, 2H), 2.67-2.60 (m, 2H), 1.80 (d, *J* = 2.4 Hz, 3H), 1.00-0.97 (m, 2H), 0.66-0.64 (m, 2H)

Example 70

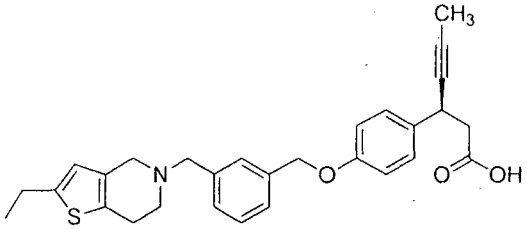
(S)-3-(4-((3-((2-Acetamido-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl) benzyl)oxy)phenyl)hex-4-ynoic acid compound with 2,2,2-trifluoroacetic acid



^{1}H NMR (CD_3OD, 400 MHz) δ: 7.68 (s, 1H), 7.62-7.54 (m, 3H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 5.17 (s, 2H), 4.56 (s, 2H), 4.40 (s, 2H), 4.01-3.97 (m, 1H), 3.67 ($s_{(br)}$, 2H), 3.07-3.04 (m, 2H), 2.69-2.58 (m, 2H), 2.20 (s, 3H), 1.80 (d, *J* = 2.4 Hz, 3H).

Example 71

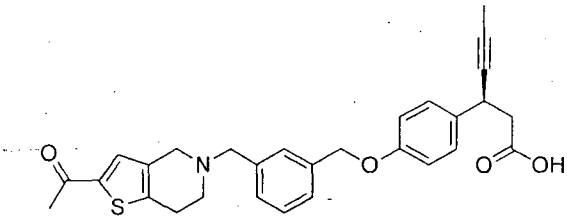
(S)-3-(4-((3-((2-Ethyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl) oxy)phenyl)hex-4-ynoic acid



^{1}H NMR (CD_3OD, 400 MHz) δ: 7.66 (s, 1H), 7.62-7.53 (m, 3H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.53 (s, 1H), 5.17 (s, 2H), 4.51 (s, 2H), 4.20 (s, 2H), 4.01-3.97 (m, 1H), 3.57 ($s_{(br)}$, 2H), 2.81-2.78 (m, 2H), 2.75 (q, *J* = 7.6 Hz, 2H), 2.69-2.57 (m, 2H), 1.80 (d, *J* = 2.4 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H).

Example 72

(S)-3-(4-((3-((2-Acetyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid

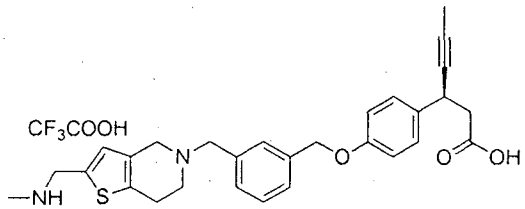


^{1}H NMR (CD_3OD, 400 MHz) δ: 7.56-7.55 (m, 2H), 7.49-7.42 (m, 3H), 7.28 (dd, *J* = 6.8, 2 Hz, 2H), 6.93 (dd, *J* = 6.8, 2 Hz, 2H), 5.12 (s, 2H), 4.09 (s, 2H), 4.01-

3.97 (m, 1H), 3.88 (s, 2H), 3.18-3.14 (m, 2H), 3.07-3.04 (m, 2H), 2.66-2.56 (m, 2H), 2.50 (s, 3H), 1.79 (d, J = 2.4 Hz, 3H)

Example 73

(S)-3-(4-((3-((2-((Methylamino)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with 2,2,2-trifluoroacetic acid



^{1}H NMR (CD_3OD, 400 MHz) δ: 7.67 (s, 1H), 7.62-7.60 (m, 1H), 7.55-7.53 (m, 2H), 7.30 (dd, J = 6.8, 2 Hz, 2H), 7.03 (s, 1H), 6.96 (dd, J = 6.8, 2 Hz, 2H), 5.17 (s, 2H), 4.52 (s, 2H), 4.36 (s, 2H), 4.27 (s, 2H), 4.01-3.98 (m, 1H), 3.62 ($s_{(br)}$, 2H), 3.24-3.21 (m, 2H), 2.71 (s, 3H), 2.69-2.62 (m, 2H), 1.81 (d, J = 2.4 Hz, 3H).

The novel compounds of the present invention can be formulated into suitable pharmaceutically acceptable compositions by combining with suitable excipients by techniques and processes and concentrations as are well known.

The compounds of formula (1 or pharmaceutical compositions containing them are useful as ligands of the GPR 40 receptor suitable for humans and other warm blooded animals, and may be administered either by oral, topical or parenteral administration.

The quantity of active component, that is, the compounds of formula **(I)** according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon several factors such as the particular application method, the potency of the particular compound and the desired concentration.

Biological Activity:

The biological activity of the compounds of the present invention was tested in the following in vitro and in vivo models mentioned here.

Summary of the in vitro screening protocol

To determine the EC_{50} of the compounds on intracellular Ca^{2+} flux using a fluorescent assay (FLIPR)

GPR40 expressing stable cells were seeded at 25,000 numbers /well. 50µL/well of assay buffer (20mM HEPES+ 1X HBSS) was added to the cells and the cells were cultured for 20 min at 37°C. Cells were loaded with 50µL/well of Calcium 5 dye and cultured for 45 min at 37°C.

The cells were challenged with compounds at a top concentration of 1000 nM (1:3 step down dilution – 10 points). Intracellular Calcium flux was assessed by use of Screen Works 3.1 tool and statistical analysis was carried using Graph Pad Prism 4

Many of the compounds of the present invention demonstrated nanomolar potency and significant % stimulation on intracellular Ca^{2+} flux when measured using fluorescent (FLIPR) assay

The compounds exhibited potency in nanomolar range. (Table1)

Table 1: In vitro EC50 values of the GPR 40 agonists of the present invention in FLIPR assay

Compound	EC_{50}(nM)
1	117
7	1.8
16	2.72
17	10.2
19	2.32
22	36.3

Promoter-luciferase assay to measure GPR40 activation

GPR40 activation was measured in HEK293 cells stably transfected with GPR40 cDNA (ChemiBrite cell lines from Millipore, US). These cells were transiently transfected with a pGL2 (Promega Inc.) plasmid having a 5XSRE sequence, cloned 5' of a luciferase gene along with a β-galactosidase plasmid as normalizing control. Briefly, 35000 cells/well were seeded in a 96 well plates. After overnight incubation at 37° C, the cells were washed with PBS and transfected with the 5X-

SRE-Luciferase plasmid and the β-galactosidase plasmid. 6 h post transfection, media was removed and replaced with fresh media with different concentration of drugs and incubated for 16 more hours. The cells were then lysed in 50μL of Glo-Lysis buffer (Promega) for 30 min at room temperature. The cells were then centrifuged and lysates were collected. Luciferase activity was measured by adding 100 μL of luciferase substrate (Promega) in 20μL of lysate and measuring the luminescence in luminometer. The β-galactosidase activity was also measured by adding 20μL of lysates with 20μL of β-galactosidase buffer (Promega) and monitoring the absorbance at 415 nm. Luciferase values were divided by β-galactosidase values to normalize transfection efficiency (Table 2)

Table 2: In vitro EC50 values of the GPR 40 agonists of the present invention in Luciferase assay.

Compound #	EC_{50} (nM)	Compound #	EC_{50} (nM)	Compound #	EC_{50} (nM)
1	7.5	23	5.3	51	3.0
7	1.49	24	0.7	55	56.5
8	11.8	26	4.1	58	3.7
10	16.9	30	4.5	60	5.6
12	5.6	31	9.7	61	12.6
13	0.8	32	4.8	62	3.0
14	0.8	35	204	63	4.4
15	4.6	38	17.8	64	1.2
16	4.6	39	1.7	65	1.6
17	4.7	40	8	68	11.9
18	8.8	43	7.3	69	0.8
19	0.2	44	4.8	71	0.4
20	2.7	46	6	72	2.3
21	2.8	47	9		
22	31.46	50	20.8		

Most of the compounds of the present invention were evaluated against CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 and there was no significant CYP inhibitory effect. The compounds did not show significant hERG binding at 10 μM.

In Vivo efficacy studies:

Primary Screening Protocol for GRP40 agonist test compounds in n-STZ rat model

Wistar rat pups of 1-2 day old injected with Streptozotocin (STZ) at 120 mg/kg dose by intraperitoneal route. All pups allowed grow normally and at the age of 12-14 week they were screen for glucose intolerance by performing the oral glucose tolerance test by tail clip method using glucometer. Animals showing glucose intolerance were selected for evaluation of test compound. Three to seven days of rest period animals were kept on overnight fasting. Next day morning blood glucose levels measured using glucometer and animals were grouped such that their pretreatment glucose levels were not significantly different between groups. Animals were administered with test compound and then then 15-60 min after the compound administration "O" min blood glucose levels were measured and immediately glucose load at 2 g/kg was administered orally. Blood glucose levels were measured at 30, 60 and 120 min after glucose load using by tail clip method using glucometer. Blood was also collected at 10 min after glucose load for measurement of insulin levels. Glucose area under the curve (AUC) was calculated using Graph Pad Prism software and % reduction in AUC-glucose *vs* vehicle treated control was calculated (Table 3).

Table 3: Efficacy of the GPR 40 agonist of the present invention in n-STZ rat model

Compound	**Dose** (per oral)	**% improvement in AUC glucose vs. control**
7	0.1 mg/Kg	30.4
	1 mg/Kg	46.0
	10 mg/Kg	57.0

10	0.1 mg/Kg	21.1
	1 mg/Kg	35.7
	10 mg/Kg	45.0
16	1 mg/Kg	44.6
	10 mg/Kg	59.6
17	1 mg/Kg	37.1
	10 mg/Kg	44.7
60	1 mg/Kg	44
	10 mg/Kg	47
64	1 mg/Kg	46
	10 mg/Kg	47

In the n-STZ rat OGTT model the ED_{50} of compounds **16**, **60** & **64** has been found 0.05 mg/Kg, 0.04 mg/Kg & 0.09 mg/Kg respectively.

Few compounds have exhibited significant pharmacokinetics parameters in rats (Table 4)

Table 4: Pharmacokinetics parameters of compounds **16, 60 & 64**

Parameters	16	60	64
Dose (po) mg/Kg	3	3	3
T_{max} (h)	0.25	1	2
C_{max} (µg/mL)	5.92±2.10	7.77±1.94	8.06±2.19
AUC (0-t)	7.63±1.27	52.52±12.62	82.42±27.63
$T_{1/2}$, po (h)	1.77±0.42	5.45±0.79	4.51±0.61
Mean residence time (h)	2.19±0.31	5.74±0.10	6.59±0.93
iv dose (mg/Kg)	1	1	1
C_0(µg/mL)	5.02±0.37	3.39±0.33	10.16±1.54
AUC (0-t) (µg.h/mL)	3.18±0.40	18.61±2.17	56.14±4.35
Vss (L/Kg)	0.34±0.03	0.33±0.01	0.16±0.01

CL (mL/min./Kg)	5.26±0.65	0.89±0.10	0.27±0.03
$T_{1/2}$, iv (h)	1.45±0.12	5.57±1.46	7.77±1.07
Mean residence time (h)	1.09±0.07	6.28±0.77	10.07±1.36
%F	83	93	45

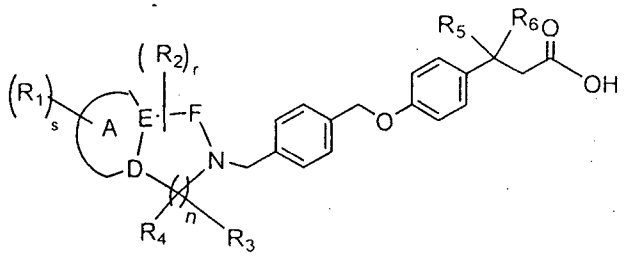
The compounds of formula (I) or pharmaceutical compositions containing them are suitable for humans and other warm blooded animals, and may be administered either by oral, topical or parenteral administration for the treatment of various disease conditions associated with dyslipidemia, obesity etc.

The pharmaceutical composition is provided by employing conventional techniques. Preferably the composition is in unit dosage form containing an effective amount of the active component, that is, the compounds of formula (I) according to this invention.

The quantity of active component, that is, the compounds of formula (I) according to this invention, in the pharmaceutical composition and unit dosage form thereof may be varied or adjusted widely depending upon the particular application method, the potency of the particular compound and the desired concentration. Generally, the quantity of active component will range between 0.5% to 90% by weight of the composition.

We Claim:

1. Compound of the general Formula (I')



Formula (I')

their tautomeric forms, their stereoisomers, their pharmaceutically acceptable salts, and pharmaceutical compositions containing them wherein Each of R_1, R_2, R_3 and R_4 at each occurrence independently represents H, halogen, hydroxyl, CN, NO_2, CHO, COOH, CO, optionally substituted groups selected from, alkyl, alkoxy, thiol, sulphoxide, sulphone, acyl, NH_2 or optionally substituted NHCO-linear or branched $(C_1\text{-}C_6)$alkyl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, hetererocyclylalkyl, heteroaryl, heteroaralkyl or the groups OR, C(O)OR, C(O)R, and SO_2R wherein 'R' at each occurrence independently represents optionally substituted groups selected from H, linear or branched $(C_1\text{-}C_6)$alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, hetrerocyclylalkyl, heteroaryl, heteroaralkyl groups;

'A' is selected from 3-7 member partially saturated, unsaturated or saturated ring which is further having one or more than one heteroatom selected from O, S, or N;

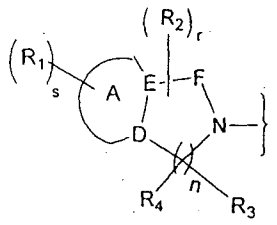
Each of 'E' & 'D' is independently either nitrogen or carbon;

'F' is selected from C, N or O;

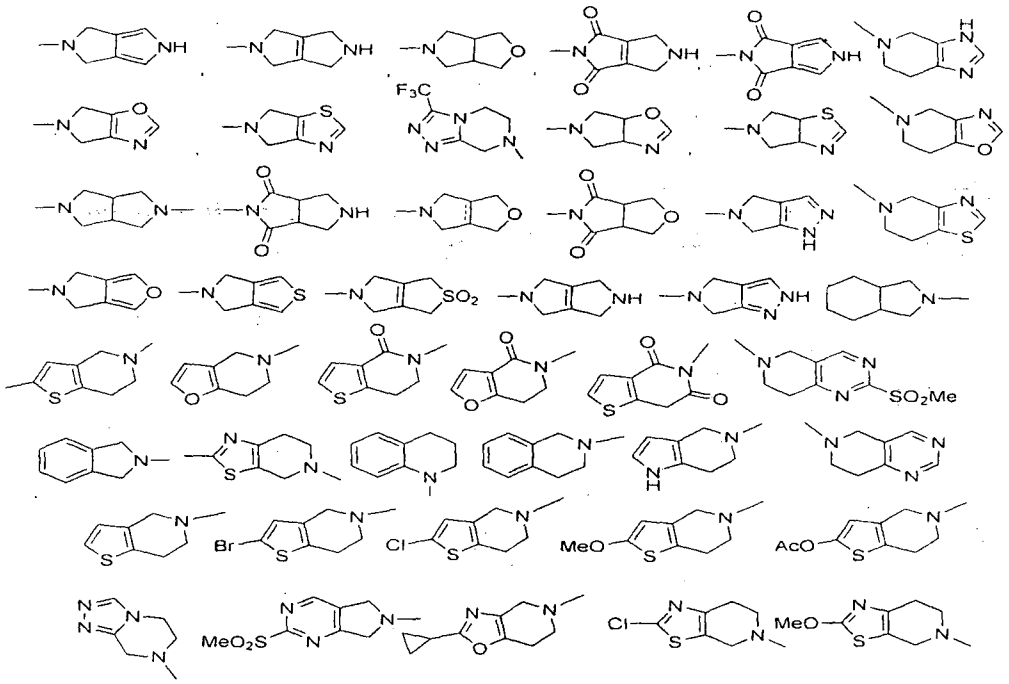
Each of 'n', 'r' and's' independently represents an integer ranging from 0 to 6;

each of R_5 and R_6 is independently selected $(C_2\text{-}C_4)$alkyne, nitrile, or a cycloalkyl; or R_5 and R_6 combine with the carbon atom to which it is attached to form a 3-7 membered cyclic ring which is optionally further have one or more than one heteroatom selected from S, N, or O.

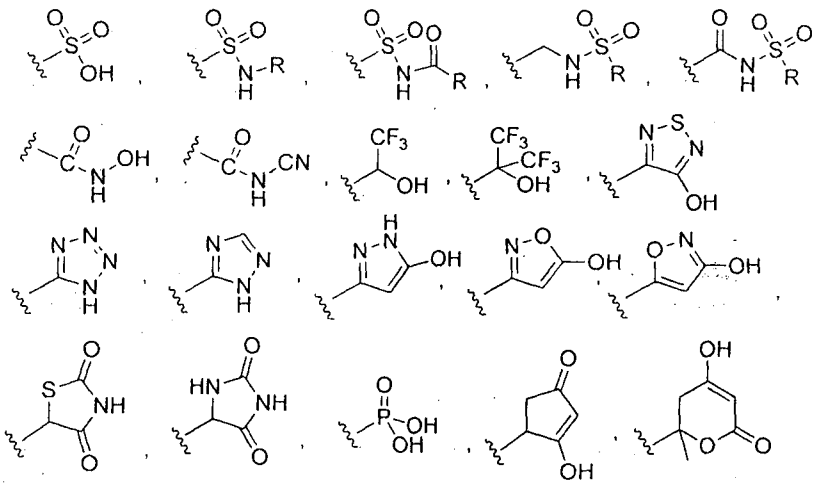
2. The compound as claimed in claim 1 wherein the heterocycles representing



is selected from the following bicyclic rings



3. The compound as claimed in claim 1wherein the COOH is replaced wherever possible with bioisosteric replacements selected from



4. The compound as claimed in claim 1 wherein any of the groups from R_1 to R_6 are substituted with one or many groups, the substituents is independently selected from the groups comprising hydroxyl, oxo, halo, thio, nitro, amino, cyano, formyl, or substituted or unsubstituted groups selected from amidino, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, bicycloalkyl, bicycloalkenyl, alkoxy, alkenoxy, cycloalkoxy, aryl, aryloxy, aralkyl, aralkoxy, heterocylyl, heteroaryl, heterocyclylalkyl, heteroaralkyl, heteroaryloxy, heteroaralkoxy, heterocyclyloxy, heterocyclylalkoxy, heterocyclylalkoxyacyl, acyl, acyloxy, acylamino, monosubstituted or disubstituted amino, arylamino, aralkylamino, carboxylic acid and its derivatives selected from esters and amides, carbonylamino, hydroxyalkyl, aminoalkyl, alkoxyalkyl, aryloxyalkyl, aralkoxyalkyl, alkylthio, thioalkyl, arylthio, alkylsulfonylamino, alkylsulfonyloxy, alkoxycarbonylamino, aryloxycarbonylamino, aralkyloxycarbonylamino, aminocarbonylamino, alkylaminocarbonylamino, alkoxyamino, hydroxyl amino, sulfenyl derivatives, sulfonyl derivatives, sulfonic acid and its derivatives.

5. The compound as claimed in claim 1 wherein the heteroaryl group is selected from pyridyl, thienyl, furyl, pyrrolyl, oxazolyl, thiazolyl, isothiazolyl, imidazolyl, isoxazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzothienyl, indolinyl, indolyl, azaindolyl, azaindolinyl, benzodihydrofuranyl, benzodihydrothienyl, pyrazolopyrimidinyl, pyrazolopyrimidonyl, azaquinazolinyl, azaquinazolinoyl, pyridofuranyl, pyridothienyl, thienopyrimidyl, thienopyrimidonyl, quinolinyl, pyrimidinyl, pyrazolyl, quinazolinyl, quinazolonyl, pyrimidonyl, pyridazinyl, triazinyl, benzoxazinyl, benzoxazinonyl, benzothiazinyl, benzothiazinonyl, benzoxazolyl, benzothiazolyl, benzimidazolyl, benzotriazolyl, phthalazynil, naphthylidinyl, purinyl, carbazolyl, phenothiazinyl, phenoxazinyl groups.

6. The compound as claimed in claim 1 wherein the heterocyclyl group is selected from aziridinyl, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidinyl,

piperazinyl, 2-oxopiperidinyl, 4-oxopiperidinyl, 2-oxopiperazinyl, 3-oxopiperazinyl, morpholinyl, thiomorpholinyl, 2-oxomorpholinyl, azepinyl, diazepinyl, oxapinyl, thiazepinyl, oxazolidinyl, thiazolidinyl, and the like; examples of partially saturated heterocyclic radicals include dihydrothiophene, dihydropyran, dihydrofuran, dihydrothiazole groups.

7. The compound according to claim 1 selected from the group consisting of
(S)-3-(4-((3-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid ;
Lithium 3-(4-((3-((4H-furo[3,4-c]pyrrol-5(6H)-yl)methyl)benzyl)oxy)phenyl)-3-cyanopropanoic acid;
3-cyano-3-(4-((3-((4-oxo-6,7-dihydrothieno[3,2-c]pyridin-5(4H) yl)methyl)benzyl)oxy)phenyl)propanoic acid;
Lithium 3-cyano-3-(4-((3-((3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methyl)benzyl)oxy)phenyl)propanoic acid;
3-cyano-3-(4-((3-((2,2-dioxido-1H-thieno[3,4-c]pyrrol-5(3H,4H,6H)-yl)methyl)benzyl)oxy)phenyl)propanoic acid;
3-cyano-3-(4-((3-((6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)propanoic acid;
(S)-3-(4-((3-((2-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;
(S)-3-(4-((3-((1-(tert-butoxycarbonyl)-6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;
(S)-3-(4-((3-((6,7-dihydro-1H-pyrrolo[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;
(S)-3-(4-((3-((2-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;
(S)-3-(4-((3-((3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;
(S)-3-(4-((3-(isoindolin-2-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((3,4-dihydroquinolin-1(2H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-bromo-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

calcium*(S)*-3-(4-((3-((2-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate*(S)*-3-(4-((3-((2-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate;

calcium*(S)*-3-(4-((3-((2-methyl-6,7-dihydrothiazolo[4,5-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate*(S)*-3-(4-((3-((2-methyl-6,7-dihydrothiazolo[4,5-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate;

(S)-3-(4-((3-((2-(Difluoromethyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

Calcium *(S)*-3-(4-((3-((2-bromo-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate;

Calcium *(S)*-3-(4-((3-((3,4-dihydroisoquinolin-2(1H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate;

(S)-3-(4-((3-((7,8-Dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((1-Methylpyrrolo[3,4-c]pyrazol-5(1H,4H,6H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(3S)-3-(4-((3-(6-Oxa-3-azabicyclo[3.1.1]heptan-3-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-(Indolin-1-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid ;

(S)-3-(4-((3-((5,6-Dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-Cyclopropyl-6,7-dihydrooxazolo[4,5-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(3S)-3-(4-((3-((5-Benzylhexahydropyrrolo[3,4-c]pyrrol-2(1H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with formic acid;

(S)-3-(4-((3-((4H-Thieno[2,3-c]pyrrol-5(6H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

6-(3-((4-((*S*)-1-carboxypent-3-yn-2-yl)phenoxy)methyl)benzyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-6-ium formate;

1-(3-((4-((*S*)-1-carboxypent-3-yn-2-yl)phenoxy)methyl)benzyl)-7-methoxy-1,2,3,4-tetrahydroquinolin-1-ium formate;

(S)-3-(4-((3-((2-Chloro-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-Bromo-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-(pyrrolo[3,4-c]pyrazol-5(1H,4H,6H)-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-(hydroxymethyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-5-(3-((4-(1-carboxypent-3-yn-2-yl)phenoxy)methyl)benzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine-2-carboxylic acid;

3-cyclopropyl-3-(3-((3-((2-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)propanoic acid;

(S)-3-(4-((3-((1-methyl-6,7-dihydro-1H-pyrrolo [3,2-c]pyridin-5(4H)-yl)methyl) benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-amino-6,7-dihydrothiazolo [5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy) phenyl)hex-4-ynoic acid;

Calcium *(S)*-3-(4-((3-((2-chloro-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate;

(S)-3-(4-((3-((2-carbamoyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-isopropylpyrrolo[3,4-c]pyrazol-5(2H,4H,6H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-(methoxycarbonyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-cyano-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-formyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

S)-3-(4-((3-((2-methyl-6,7-dihydropyrazolo [1,5-a]pyrazin-5(4H)-yl)methyl)benzyl) oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-(methylcarbamoyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-(dimethylcarbamoyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(3S)-3-(4-((3-((2-Methyl-5-(4-(methylsulfonyl)phenyl)pyrrolidin-1-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-(Methylsulfonyl)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-Methoxy-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(3S)-3-(4-((3-((2-phenylpyrrolidin-1-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-(Pyrrolidin-1-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with formic acid;

(S)-3-(4-((3-(Piperidin-1-ylmethyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with formic acid;

(S)-3-(4-((3-((1-isopropylpyrrolo[3,4-c]pyrazol-5(1H,4H,6H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with formic acid;

(R)-3-(4-((3-((2-methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(R)-3-(4-((3-((2-Methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((6,7-Dihydro-[1,2,3]triazolo[1,5-a]pyrazin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

3-(4-((3-((2-Methyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

3-(4-((3-((2-Methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

Calcium *(S)*-3-(4-((3-((2-chloro-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate;

(S)-3-(4-((3-((2-(cyclopropylcarbamoyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-(pyrrolidine-1-carbonyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-Aacetamido-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

Calcium *(S)*-3-(4-((3-((2-cyclopropyl-6,7-dihydrooxazolo[4,5-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoate;

(S)-3-(4-((3-((2-Nitro-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-(Dimethylamino)-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with 2,2,2-trifluoroacetic acid;

(S)-3-(4-((3-((2-Amino-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with 2,2,2-trifluoroacetic acid;

(S)-3-(4-((3-((7,8-Dihydro-1,6-naphthyridin-6(5H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-Cyclopropyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with 2,2,2-trifluoroacetic acid;

(S)-3-(4-((3-((2-Acetamido-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with 2,2,2-trifluoroacetic acid;

(S)-3-(4-((3-((2-Ethyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-Acetyl-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid;

(S)-3-(4-((3-((2-((Methylamino)methyl)-6,7-dihydrothieno[3,2-c]pyridin-5(4H)-yl)methyl)benzyl)oxy)phenyl)hex-4-ynoic acid compound with 2,2,2-trifluoroacetic acid;

8. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (**I**) as claimed in any of the preceding claims and optionally one or more pharmaceutically acceptable carriers, diluents or excipients.
9. A method of treating diseases medicated by the GPR40 receptor which comprising administering to a patient in need thereof an effective amount of a compound of Formula (**I**) as claimed in any of the preceding claims or its suitable pharmaceutical composition.
10. A pharmaceutical composition comprising compound of formula (I) along with suitable excipients suitable for the treatment of various disease conditions associated with dyslipidemia, obesity etc.
11. Use of a compound as claimed in any preceding claim in the preparation of a medicament for the prevention or treatment of a condition associated with GPR40 receptor function in a mammal.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2014/000704

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D491/08 A61K31/404 A61K31/407 A61K31/4162 A61K31/4365
A61K31/437 A61K31/439 A61K31/47 A61K31/472 A61K31/4985
A61K31/519 C07D215/06 C07D215/20 C07D217/04 C07C229/14

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

B. FIELDS SEARCHED

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

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 practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 731 505 A1 (TAKEDA PHARMACEUTICAL [JP]) 13 December 2006 (2006-12-13) Examples 26, 45-71, 73-116, 121, 134, 124, 127, 131, 133, 135, 137, 139, 141, 143; claims 1-20	1-11
X	WO 2011/046851 A1 (LILLY CO ELI [US]; HAMDOUCHI CHAFIQ [US]; LINESWALA JAYANA PANKAJ [US]) 21 April 2011 (2011-04-21) Examples 1-39; claims 1-25	1,4,7-11

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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

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"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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 April 2015	07/05/2015

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, Fax: (+31-70) 340-3016	Sotoca Usina, E

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 3 November 2005 (2005-11-03), "enzenepropanoic acid, 4-[[4-[(4-phenyl-1-piperidinyl)methyl]phenyl]methoxy]-", XP002738849, Database accession no. 866586-99-4 the whole document	1,3,4,6
X	DATABASE REGISTRY [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; 3 November 2005 (2005-11-03), "enzenepropanoic acid, 4-[[4-[[4-(3-pyridinylmethyl)-1-piperazinyl]methyl]phenyl]methoxy]-", XP002738850, Database accession no. 866586-89-2 the whole document	1,3,4,6
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2014/000704

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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E	WO 2015/028960 A1 (PIRAMAL ENTPR LTD [IN]) 5 March 2015 (2015-03-05) Examples 32-34, 36, 116, 116a, 117-124, 141-144, 146-150; claims 1-5, 7-17	1,4,8-11

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2014/000704

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(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 105722841 A
(43)申请公布日 2016.06.29

(21)申请号 201480061963.0

(22)申请日 2014.11.03

(30)优先权数据
3577/MUM/2013 2013.11.14 IN

(85)PCT国际申请进入国家阶段日
2016.05.12

(86)PCT国际申请的申请数据
PCT/IN2014/000704 2014.11.03

(87)PCT国际申请的公布数据
WO2015/097713 EN 2015.07.02

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(51)Int.Cl.
C07D 491/08(2006.01)
A61K 31/404(2006.01)
A61K 31/407(2006.01)
A61K 31/4162(2006.01)
A61K 31/4365(2006.01)
A61K 31/437(2006.01)
A61K 31/439(2006.01)
A61K 31/47(2006.01)
A61K 31/472(2006.01)
A61K 31/4985(2006.01)
A61K 31/519(2006.01)
C07D 215/06(2006.01)
C07D 215/20(2006.01)
C07D 217/04(2006.01)
C07C 229/14(2006.01)

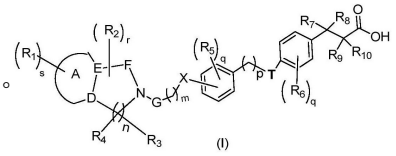
权利要求书7页 说明书51页

(54)发明名称

新型杂环化合物

(57)摘要

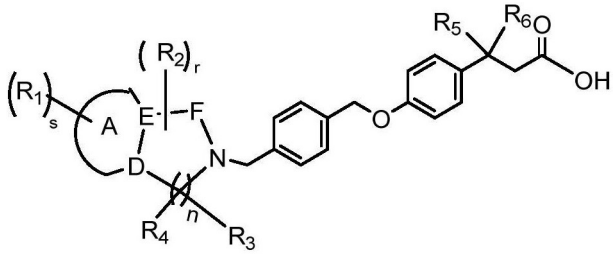
本发明涉及通式(I)的新型GPR 40激动剂、其互变异构形式、其立体异构体、其药用盐、包含它们的药物组合物、用于制备它们的方法、这些化合物在医药中的用途和在它们的制备中所涉及的中间体。



(I)

CN 105722841 A

1.通式(I')化合物



式(I')

其互变异构形式、其立体异构体、其药用盐和包含它们的药物组合物，

其中R_1、R_2、R_3和R_4在每次出现时各自独立地表示H、卤素、羟基、CN、NO_2、CHO、COOH、CO、任选取代的选自以下的基团：烷基、烷氧基、巯基、亚砜基团、砜基团、酰基、NH_2或任选取代的NHCO-直链或支链(C_1-C_6)烷基、芳烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳烷基或基团OR、C(O)OR、C(O)R和SO_2R，其中'R'在每次出现时独立地表示任选取代的选自以下的基团：H、直链或支链(C_1-C_6)烷基、芳基、芳烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳烷基；

'A'选自3-7元部分饱和、不饱和或饱和环，其进一步具有一个或多于一个的选自O、S或N的杂原子；

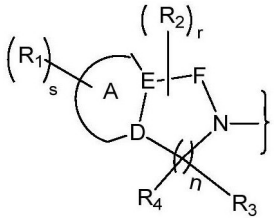
'E'和'D'各自独立地为氮或碳；

'F'选自C、N或O；

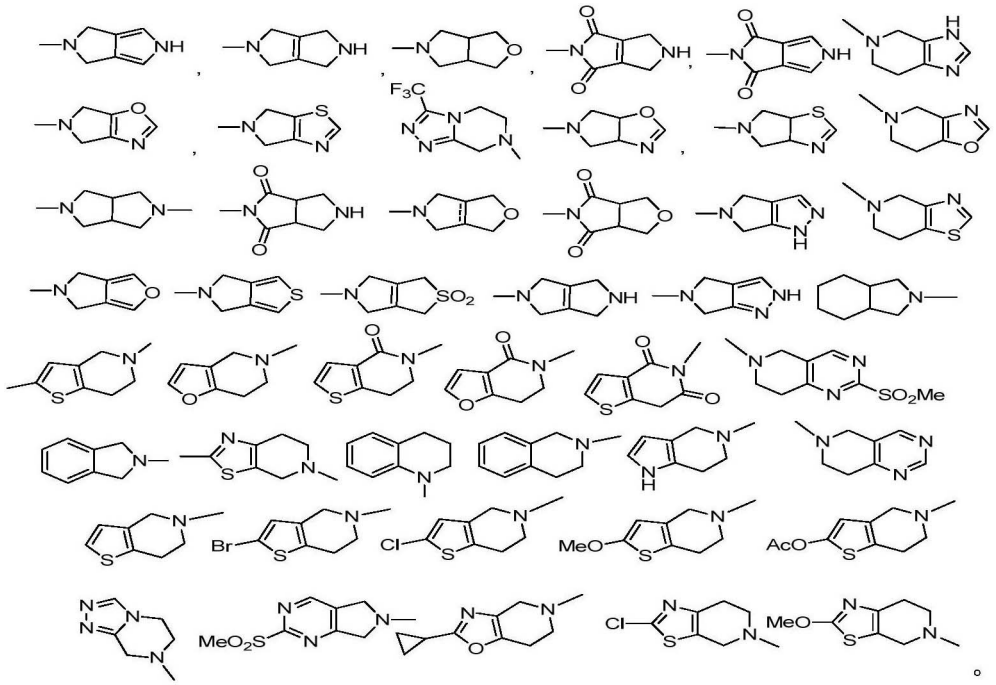
'n'、'r'和's'各自独立地表示0至6的整数；

R_5和R_6各自独立选自(C_2-C_4)炔、腈基团或环烷基；或R_5和R_6与其所连接的碳原子组合形成3-7元环，该环任选地进一步具有一个或多于一个的选自S、N或O的杂原子。

2.权利要求1的化合物，其中下式表示的杂环



选自以下二环：



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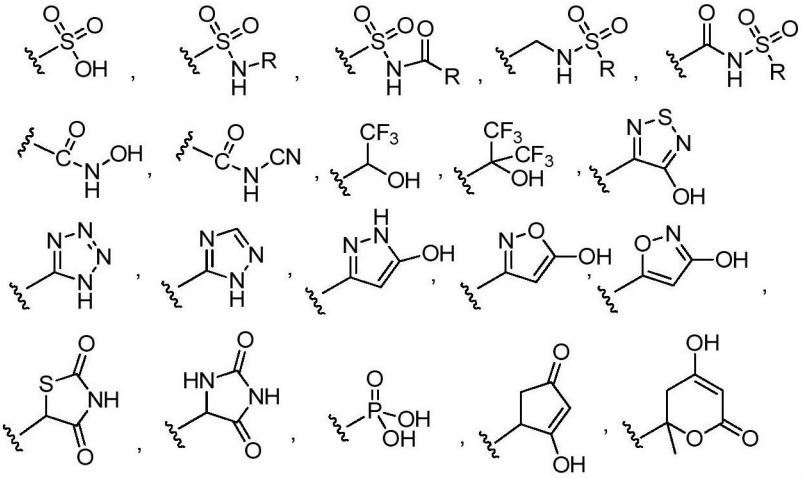
3.权利要求1的化合物，其中所述COOH在任何可能的情况下由选自以下的生物电子等排替代物所替代：



。

4.权利要求1的化合物，其中R_1至R_6的任何基团由一个或多个基团取代，所述取代基独立地选自以下基团：羟基、氧代、卤素、巯基、硝基、氨基、氰基、甲酰基或经取代或未取代的选自以下的基团：脒基、烷基、卤代烷基、烷氧基、卤代烷氧基、烯基、炔基、环烷基、环烯基、二环烷基、二环烯基、烷氧基、烯氧基、环烷氧基、芳基、芳基氧基、芳烷基、芳烷氧基、杂环基、杂芳基、杂环基烷基、杂芳烷基、杂芳基氧基、杂芳烷氧基、杂环基氧基、杂环基烷氧基、杂环基烷氧基酰基、酰基、酰基氧基、酰基氨基、单取代或二取代的氨基、芳基氨基、芳烷基氨基、羧酸基团和其选自酯基和酰胺基团的衍生基团、羰基氨基、羟基烷基、氨基烷基、烷氧基烷基、芳基氧基烷基、芳烷氧基烷基、烷基硫基、巯基烷基、芳基硫基、烷基磺酰基氨基、烷基磺酰基氧基、烷氧基羰基氨基、芳基氧基羰基氨基、芳烷基氧基羰基氨基、氨基羰基氨基、烷基氨基羰基氨基、烷氧基氨基、羟基氨基、亚磺酰基衍生基团、磺酰基衍生基团、磺酸基团和其衍生基团。

5.权利要求1的化合物，其中所述杂芳基选自吡啶基、噻吩基、呋喃基、吡咯基、噁唑基、

噻唑基、异噻唑基、咪唑基、异噁唑基、噁二唑基、噻二唑基、三唑基、四唑基、苯并吡喃基、苯并吡喃酮基、苯并呋喃基、苯并噻吩基、吲哚啉基、吲哚基、氮杂吲哚基、氮杂吲哚啉基、苯并二氢呋喃基、苯并二氢噻吩基、吡唑并嘧啶基、吡唑并嘧啶酮基、氮杂喹唑啉基、氮杂喹唑啉基酮基、吡啶并呋喃基、吡啶并噻吩基、噻吩并嘧啶基、噻吩并嘧啶酮基、喹啉基、嘧啶基、吡唑基、喹唑啉基、喹唑啉酮基、嘧啶酮基、哒嗪基、三嗪基、苯并噁嗪基、苯并噁嗪酮基、苯并噻嗪基、苯并噻嗪酮基、苯并噁唑基、苯并噻唑基、苯并咪唑基、苯并三唑基、酞嗪基、二氮杂萘基、噁呤基、咔唑基、吩噻嗪基、吩噁嗪基。

6.权利要求1的化合物，其中所述杂环基选自氮杂环丙烷基、氮杂环丁烷基、吡咯烷基、咪唑烷基、哌啶基、哌嗪基、2-氧代哌啶基、4-氧代哌啶基、2-氧代哌嗪基、3-氧代哌嗪基、吗啉基、硫吗啉基、2-氧代吗啉基、氮杂䓬基、二氮杂䓬基、氧杂䓬、硫氮杂䓬基、噁唑烷基、噻唑烷基等；所述部分饱和杂环基的实例包括二氢噻吩基、二氢吡喃基、二氢呋喃基、二氢噻唑基。

7.权利要求1的化合物，其选自：

(S)-3-(4-((3-((6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

3-(4-((3-((4H-呋喃并[3,4-c]吡咯-5(6H)-基)甲基)苄基)氧基)苯基)-3-氰基丙酸锂；

3-氰基-3-(4-((3-((4-氧代-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)丙酸；

3-氰基-3-(4-((3-((3-(三氟甲基)-5,6-二氢-[1,2,4]三唑并[4,3-a]吡嗪-7(8H)-基)甲基)苄基)氧基)苯基)丙酸锂；

3-氰基-3-(4-((3-((2,2-二氧化-1H-噻吩并[3,4-c]吡咯-5(3H,4H,6H)-基)甲基)苄基)氧基)苯基)丙酸；

3-氰基-3-(4-((3-((6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)丙酸；

(S)-3-(4-((3-((2-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((1-(叔丁氧基羰基)-6,7-二氢-1H-吡咯并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((6,7-二氢-1H-吡咯并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-甲基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((3-(三氟甲基)-5,6-二氢-[1,2,4]三唑并[4,3-a]吡嗪-7(8H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-(异吲哚啉-2-基甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((3,4-二氢喹啉-1(2H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-溴-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((3,4-二氢异喹啉-2(1H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

二((S)-3-(4-((3-((2-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸)钙；

二((S)-3-(4-((3-((2-甲基-6,7-二氢噻唑并[4,5-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸)钙；

(S)-3-(4-((3-((2-(二氟甲基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-溴-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸钙；

(S)-3-(4-((3-((3,4-二氢异喹啉-2(1H)-基)甲基)苄基)氧基)苯基)己-4-炔酸钙；

(S)-3-(4-((3-((7,8-二氢吡啶并[4,3-d]嘧啶-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((1-甲基吡咯并[3,4-c]吡唑-5(1H,4H,6H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(3S)-3-(4-((3-(6-氧杂-3-氮杂二环[3.1.1]庚-3-基甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-(吲哚啉-1-基甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((5,6-二氢-[1,2,4]三唑并[4,3-a]吡嗪-7(8H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-环丙基-6,7-二氢噁唑并[4,5-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(3S)-3-(4-((3-((5-苄基六氢吡咯并[3,4-c]吡咯-2(1H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,甲酸盐；

(S)-3-(4-((3-((4H-噻吩并[2,3-c]吡咯-5(6H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

6-(3-((4-((S)-1-羧基戊-3-炔-2-基)苯氧基)甲基)苄基)-6,7-二氢-5H-吡咯并[3,4-d]嘧啶-6-鎓甲酸盐；

1-(3-((4-((S)-1-羧基戊-3-炔-2-基)苯氧基)甲基)苄基)-7-甲氧基-1,2,3,4-四氢喹啉-1-鎓甲酸盐；

(S)-3-(4-((3-((2-氯-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-溴-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-(吡咯并[3,4-c]吡唑-5(1H,4H,6H)-基甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-(羟基甲基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-5-(3-((4-(1-羧基戊-3-炔-2-基)苯氧基)甲基)苄基)-4,5,6,7-四氢噻吩并[3,2-c]吡啶-2-羧酸；

3-环丙基-3-(3-((3-((2-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)丙酸；

(S)-3-(4-((3-((1-甲基-6,7-二氢-1H-吡咯并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-氨基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-氯-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸钙；

(S)-3-(4-((3-((2-氨基甲酰基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-异丙基吡咯并[3,4-c]吡唑-5(2H,4H,6H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-(甲氧基羰基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-氰基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-甲酰基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-甲基-6,7-二氢吡唑并[1,5-a]吡嗪-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-(甲基氨基甲酰基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-(二甲基氨基甲酰基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(3S)-3-(4-((3-((2-甲基-5-(4-(甲基磺酰基)苯基)吡咯烷-1-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-(甲基磺酰基)-7,8-二氢吡啶并[4,3-d]嘧啶-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-甲氧基-7,8-二氢吡啶并[4,3-d]嘧啶-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(3S)-3-(4-((3-((2-苯基吡咯烷-1-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-(吡咯烷-1-基甲基)苄基)氧基)苯基)己-4-炔酸,甲酸盐；

(S)-3-(4-((3-(哌啶-1-基甲基)苄基)氧基)苯基)己-4-炔酸,甲酸盐；

(S)-3-(4-((3-((1-异丙基吡咯并[3,4-c]吡唑-5(1H,4H,6H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,甲酸盐；

(R)-3-(4-((3-((2-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(R)-3-(4-((3-((2-甲基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((6,7-二氢-[1,2,3]三唑并[1,5-a]吡嗪-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

3-(4-((3-((2-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

3-(4-((3-((2-甲基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-氯-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸钙；

(S)-3-(4-((3-((2-(环丙基氨基甲酰基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-(吡咯烷-1-羰基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-乙酰氨基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-环丙基-6,7-二氢噁唑并[4,5-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸钙；

(S)-3-(4-((3-((2-硝基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-(二甲基氨基)-7,8-二氢吡啶并[4,3-d]嘧啶-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,2,2,2-三氟乙酸盐；

(S)-3-(4-((3-((2-氨基-7,8-二氢吡啶并[4,3-d]嘧啶-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,2,2,2-三氟乙酸盐；

(S)-3-(4-((3-((7,8-二氢-1,6-二氮杂萘-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-环丙基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,2,2,2-三氟乙酸盐；

(S)-3-(4-((3-((2-乙酰氨基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,2,2,2-三氟乙酸盐；

(S)-3-(4-((3-((2-乙基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-乙酰基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

(S)-3-(4-((3-((2-((甲基氨基)甲基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,2,2,2-三氟乙酸盐。

8.药物组合物,其包含治疗有效量的前述权利要求任一项的式(I')化合物和任选的一种或多种药用载体、稀释剂或赋形剂。

9.治疗经GPR40受体介导的疾病的方法,其包括对有需要的患者给予有效量的前述权利要求任一项的式(I')化合物或其适当的药物组合物。

10.药物组合物,其包含式(I')的化合物以及适当的赋形剂,所述药物组合物适于治疗

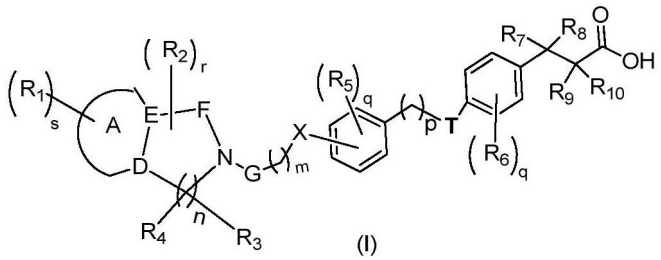
多种与血脂障碍、肥胖症等有关的疾病病症。

11.前述权利要求任一项的化合物在制备用于预防或治疗哺乳动物中与GPR40受体功能有关的病症的药物中的用途。

新型杂环化合物

技术领域

[0001] 本发明涉及通式(I)的新型GPR 40激动剂、其互变异构形式、其立体异构体、其药用盐、包含它们的药物组合物、它们的制备方法、这些化合物在医药中的用途和其制备所涉及的中间体。

[0002] 

(I)

[0003] 本发明涉及G蛋白偶联受体(GPCR)激动剂,其用于治疗肥胖症、糖尿病和相关的代谢病症。

[0004] 通式(I)化合物降低血糖、调节外周饱腹感、降低或调节甘油三酯水平和/或胆固醇水平和/或低密度脂蛋白(LDL)并提高高密度脂蛋白(HDL)血浆水平,因此用于对抗当这种降低(和提高)是有益时的不同医学病症。因此,其可用于治疗和/或预防肥胖症、高脂血症、高胆固醇血症、高血压、动脉粥样硬化疾病事件、血管再狭窄、糖尿病和许多其他相关病症。

[0005] 通式(I)的化合物用于预防或降低发展成动脉粥样硬化的风险,其导致疾病和病症如动脉粥样硬化性心血管疾病、中风、冠状动脉心脏病、脑血管疾病、外周血管疾病和相关病症。

[0006] 这些通式(I)化合物用于治疗和/或预防宽泛地定义为综合征X的代谢性疾病。综合征X的特征包括最初的胰岛素抗性,随后为高胰岛素血症、血脂障碍和葡萄糖耐受不良。葡萄糖不耐受性可导致非胰岛素依赖性糖尿病(NIDDM,II型糖尿病),其特征为高血糖症,其如果不控制可导致糖尿病并发症或由胰岛素抗性所导致的代谢性疾病。不再将糖尿病视为仅与葡萄糖代谢有关,其也影响解剖学和生理学参数,其强度依赖于糖尿病状态的阶段/持续时间和严重性而变化。本发明的化合物还用于预防、停止或减缓上述病症连同所导致的继发症的进展或降低其危险性,所述继发症例如心血管疾病,如动脉硬化、动脉粥样硬化;糖尿病性视网膜病变、糖尿病性神经病变和肾病包括糖尿病性肾病变、肾小球肾炎、肾小球硬化、肾病综合征、高血压性肾硬化和末期肾病,如微白蛋白尿和白蛋白尿,其可为高血糖症或高胰岛素血症的结果。

背景技术

[0007] 糖尿病为全世界超过一亿人口罹患的严重疾病。在美国,有超过一千两百万的糖尿病患者,且每年诊断出600,000新病例。

[0008] 糖尿病是用于一组病症的诊断术语,其特征在于葡萄糖稳态异常,从而导致血糖升高。糖尿病有许多类型,但最常见的两种类型为I型(也称为胰岛素依赖性糖尿病或IDDM)和II型(也称为非胰岛素依赖性糖尿病或NIDDM)。

[0009] 不同型糖尿病的病因并不相同;然而,每个糖尿病患者具有共同的两个特征:由肝脏过度产生葡萄糖且当其变为身体主要燃料时,极少或没有能力将葡萄糖从血液移至细胞内。

[0010] 无糖尿病的人依赖胰岛素(在胰脏中产生的激素),以将葡萄糖由血液移至身体细胞内。然而,具有糖尿病的人不能产生胰岛素或不能有效地使用其所产生的胰岛素;因此,其不能将葡萄糖移至其细胞内。葡萄糖累积在血液中,由此产生称为高血糖症的病症,且随时间可导致严重的健康问题。

[0011] 糖尿病为代谢性、血管性和神经病变性组成相互关联的综合征。代谢性综合征(通常特征为高血糖症)包含因为不存在或显著减少的胰岛素分泌和/或无效的胰岛素作用所致的糖、脂肪和蛋白质代谢的改变。血管综合征由血管异常所组成,其导致心血管、视网膜和肾并发症。外周和自主神经系统的异常也为糖尿病综合征的一部分。

[0012] 约5%至10%的糖尿病患者具有IDDM。这些个体不产生胰岛素,因此必需注射胰岛素以保持其血糖水平正常。IDDM的特征为因为产生胰岛素的胰脏β细胞的破坏导致内源性胰岛素的产生水平低或无法检测,该特征最容易地将IDDM与NIDDM区分。IDDM(曾称之为幼年型糖尿病)相似地影响年轻和较年长的成年人。

[0013] 约90至95%的糖尿病患者为II型(或NIDDM)。NIDDM受试者产生胰岛素,但其体内的细胞为胰岛素抗性:细胞不对激素适当地反应,故葡萄糖累积于其血液中。NIDDM的特征在于内源性胰岛素产生与胰岛素需求之间的相对差异,导致血液葡萄糖水平升高。与IDDM不同的是,NIDDM中总能产生一些内源性胰岛素;许多NIDDM患者具有正常或甚至升高的血液胰岛素水平,然而其他NIDDM患者的胰岛素产生不足(Rotwein,R.et al.N.Engl.J.Med.308,65-71(1983))。大多数经诊断为NIDDM的人年龄为30岁或30岁以上,且所有新病例中有一半为55岁和55岁以上。与白种人和亚洲人相比,NIDDM更常见于美洲原住民、非裔美国人、拉丁美洲人和拉丁裔美国人。此外,其发作可为潜伏的或甚至临床上不明显的,造成诊断的困难。

[0014] NIDDM的主要致病病灶仍难以理解。许多人认为,外周组织的主要胰岛素抗性为起始事件。遗传流行病学研究已支持此观点。类似地,胰岛素分泌异常已被认为是NIDDM的主要缺陷。这两种现象似乎均为促成疾病过程的主要因素(Rimoin,D.L.,et.al.Emery and Rimoin's Principles and Practice of Medical Genetics 3rd Ed.1:1401-1402(1996))。

[0015] 许多NIDDM病人有久坐不动的生活方式且肥胖;他们的体重超过针对其身高和体型所建议的体重的约20%。此外,肥胖症的特征为高胰岛素血症和胰岛素抗性,其为NIDDM、高血压和动脉粥样硬化共同的特性。

[0016] G蛋白偶联受体GPR 40的功能是作为体内长链游离脂肪酸(FFA)的受体,且因而涉及体内众多代谢病症。例如,GPR 40激动剂据称可促进胰岛素分泌,而GPR 40拮抗剂可抑制胰岛素分泌,因此依情况而定,激动剂和拮抗剂可用作一些胰岛素相关病症例如II型糖尿病、肥胖症、胰岛素耐受不良、胰岛素抗性、神经退化性疾病等的治疗剂。

[0017] 越来越多的证据显示,脂肪还可作为用于特定类别受体的细胞外配体,且因此作为"营养传感物"(Nolan CJ et al.J.Clinic.Invest.,2006,116,1802-1812)。游离脂肪酸可调节细胞功能。游离脂肪酸已证实为用于孤儿G蛋白偶联受体(GPCR)的配体且已经提出

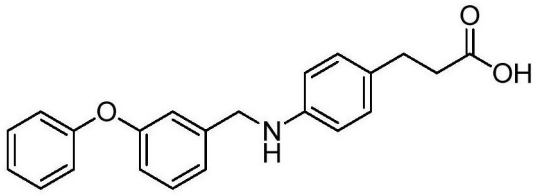
在生理学葡萄糖稳态中发挥重要的作用。

[0018] GPR40、GPR120、GPR41和GPR43示例了越来越多的已显示可通过游离脂肪酸活化的GPCR。GPR40和GPR120通过中至长链游离脂肪酸活化，而GPR 41和GPR 43通过短链脂肪酸活化(Brown AJ et al,2003)。

[0019] GPR 40在胰脏β细胞上高度表达，且增强葡萄糖刺激性胰岛素分泌(Nature,2003,422,173-176,J.Bio.Chem.2003,278,11303-11311,Biochem.Biophys.Res.Commun.2003,301,406-410)。

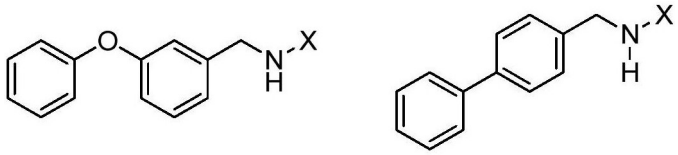
[0020] 报导了游离脂肪酸可从胰脏β细胞通过GPR40调节胰岛素的分泌(Lett.to Nature 2003,422,173-176)。

[0021] GlaxoSmithKline Research and Development,US于Bioorg.Med.Chem.Lett.2006,16,1840-1845中公开了标题为“Synthesis and activity of small molecule GPR40 agonists.”的论文(其是否描述了GW9508?)。另一标题为“Pharmacological regulation of insulin secretion in MIN6 cells through the fatty acid receptor GPR40:Identification of agonist and antagonist small molecules”的论文由GlaxoSmithKline,USA报导于Br.J.Pharmacol.2006,148,619-928(其是否描述了GW9508?)中。

[0022] 

GW 9508

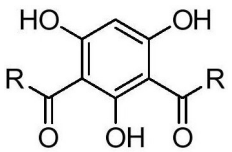
[0023] GPR 40受体的小分子激动剂的固相合成和SAR由Glaxo SmithKline Res.& Dev.USA公开于Bioorg.Med.Chem.Lett.2007,16,1840-1845中，包括具有下列结构的那些。

[0024] 

[0025] Johnson&Johnson Pharmaceutical Research and development公开了“Synthesis and Biological Evaluation of 3-Aryl-3-(4-phenoxy)-propanoic acid as a Novel Series of G-protein-coupled receptor 40 agonists”(J.Med.Chem.2007,16,2807-2817)。

[0026] National Institutes of Health,Bethesda,Maryland公开了“Bidirectional Iterative Approach to the Structural Delineation of the Functional Chemo print in GPR 40 for agonist Recognition”(J.Med.Chem.2007,50,2981-2990)。

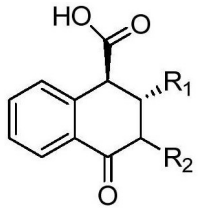
[0027] 作为新一类GPR40(FFAR1)激动剂的下式的二酰基间苯三酚类的发现

[0028] 

[0029] 其已经由Piramal Life Sciences Ltd.于Bioorg.Med.Chem.Lett.2008,18,

6357-6361中公开。

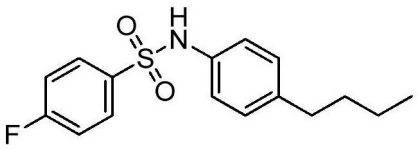
[0030] 下式作为新型G蛋白偶联受体40(GPR40)拮抗剂的1,2,3,4-四氢异喹啉-1-酮的合成和SAR已由Pfizer公开于Bioorg.Med.Chem.Lett.2009,19,2400-2403中。

[0031] 

[0032] Piramal Life Sciences Ltd.于Exp.Opin.Therapeutic Patents 2009,19(2),237-264中公开了“Progress in the discovery and development of small molecule modulators of G-protein coupled receptor 40(GPR40/FFA1/FFAR1),an emerging target for type 2 diabetes”。

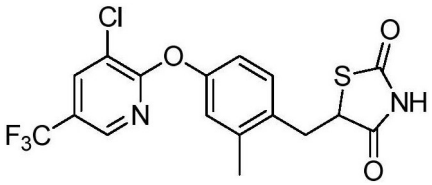
[0033] 有来自Sun Yat.Sen University,Guangzhou的于Zhongguo Bingli Shengli Zazhi 2009,25(7),1376-1380的报导,其提及GPR 40对脂质凋亡的作用。

[0034] 一类新的FFA受体GPR 40拮抗剂公开于Biochem.Biophy.Res.Commun.2009,390,557-563中。

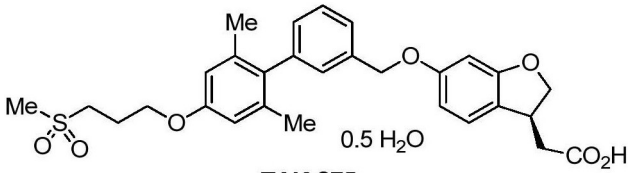
[0035] 

N41(DC260126)

[0036] Merck Res.Laboratories于Bioorg.Med.Chem.Lett.2010,20,1298-1301中公开具有下式的“Discovery of 5-aryloxy-2,4-thiazolidinediones as potent GPR40 agonists”。

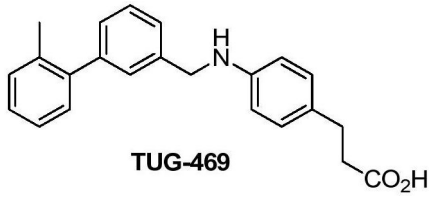
[0037] 

[0038] TAK-875(一种有效的、选择性和口服生物可利用的GPR 40激动剂)由Takeda Pharmaceutical Ltd.报导于ACS Med.Chem.Lett.2010,1(6),290-294中。

[0039] 

TAK-875
EC50= **14 nM**
Ki= 38 nM

[0040] 另一个来自University of Southern Denmark的报导“Structure-Activity of Dihydrocinnamic acids and discovery of potent FFA1(GPR40)agonist TUG-469”于ACS Med.Chem.Lett.2010,1(7),345-349中报导。

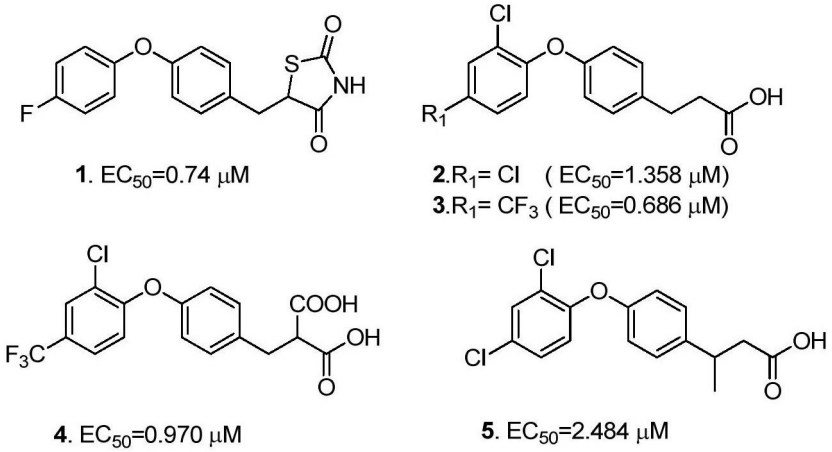
[0041] 

[0042] 游离脂肪酸1受体(FFAR1或GPR40),其在胰脏β细胞上高度表达且扩大葡萄糖刺激性胰岛素分泌,已成为具有吸引力的用于治疗II型糖尿病的靶标(ACS Med.Chem.Lett.2010,1(6),290-294)。

[0043] G蛋白偶联受体(GPR40)的表达和其在人类胰岛中的调节:II型糖尿病和脂肪酸的作用报导于Nutrition Metabolism&Cardiovascular diseases 2010,20(1),22-25中。

[0044] Ranbaxy于Phytother Res.2010,24,1260-63中报导“Identification of Berberine as a novel agonist of fatty acid receptor GPR40”。

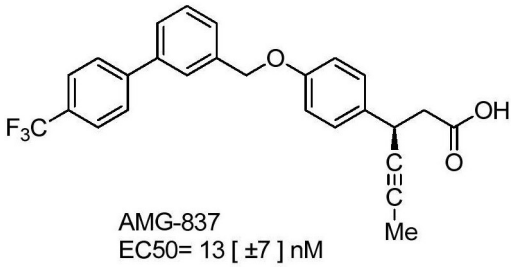
[0045] 下列作为GPR40激动剂的取代的3-(4-芳基氧基芳基)-丙酸由Merck Res.Laboratories报导于Bioorg.Med.Chem.Lett.2011,21,3390-3394中。

[0046] 

[0047] CoMSIA对取代的芳基烷酸类似物作为GPR 40激动剂的研究报导于Chem.Bio.Drug.Des.2011,77,361-372中。

[0048] Takeda于J.Med.Chem.2011,54(5),1365-1378进一步公开了“Design,Synthesis and biological activity of potential and orally available G-protein coupled receptor 40 agonists”。

[0049] Amgen于Bioorg.Med.Chem.Lett.2012,22,1267-1270中揭示了一种有效的口服生物可利用放热GPR 40激动剂AMG-837。

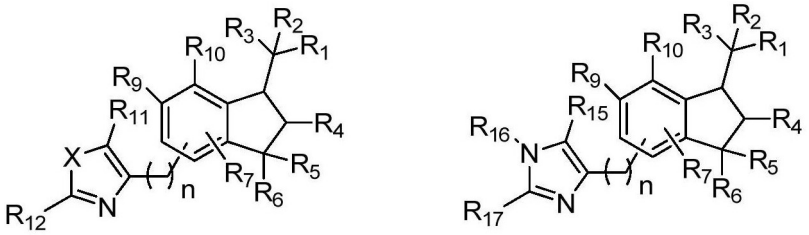
[0050] 

[0051] 作为有效且口服生物可利用的G蛋白偶联受体40激动剂以用于治疗II型糖尿病的含有极性官能团的苯基丙酸衍生物的发现由Takeda报导于J.Med.Chem.2012,55,3756-3776中。

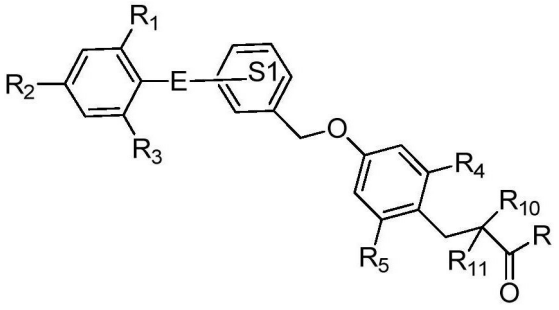
[0052] AM-1638的发现:一种有效和口服生物可利用的GPR40/FFA1完全激动剂报导于ACS Med.Chem.Lett.2012,3(9),726-730中。

[0053] (2,3-二氢-1-苯并呋喃-3-基)乙酸的最优化:非游离脂肪酸样、高度生物可利用的G蛋白偶联受体40/游离酸受体1激动剂作为葡萄糖依赖性促胰岛素剂的发现由Takeda报导于J.Med.Chem.2012,55,3960-3974中。

[0054] Bayer于专利申请WO 2004011446中揭示了具有下式的茚满、二氢苯并呋喃和四氢萘羧酸衍生物和其作为抗糖尿病剂的用途:

[0055] 

[0056] Takeda于专利WO 2005063729中揭示了具有下列通式的3-(4-苄基氧基苯基)丙酸衍生物:

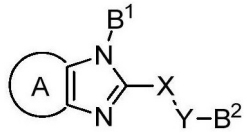
[0057] 

[0058] WO 2005086661 A1(2005年9月22日,Amgen Inc.)揭示了具有下式的用于治疗代谢性疾病的化合物、药物组合物和方法:

[0059] $Q\text{-}L^1\text{-}P\text{-}L^2\text{-}M\text{-}X\text{-}L^3\text{-}A$。

[0060] Akerman等人的US 2006/0004012揭示了用于治疗代谢性疾病的某些化合物、药物组合物和方法,该化合物为GPR 40激动剂。

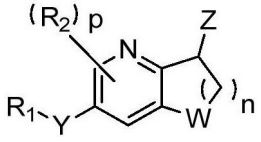
[0061] WO 06/038738A1(2006年4月13日,Takeda Pharmaceutical Ltd.,Japan)揭示了具有下列一般结构的某些受体功能调节剂:

[0062] 

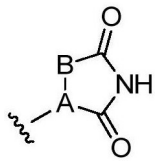
[0063] Merck&Co.于WO2006083781中揭示了抗糖尿病性二环化合物。其中揭示了作为G蛋白偶联受体40(GPR40)激动剂的二环化合物,包括其药用盐和前药,该二环化合物含有与连接5元杂环的环烷基或杂环稠合的苯基或吡啶基环,其可用作治疗化合物,尤其用于治疗II型糖尿病和通常与包括肥胖症和脂质障碍的疾病有关的病症,例如混合型或糖尿病性血脂障碍、高脂血症、高胆固醇血症和高甘油三酯血症。

[0064] Merck&Co.在另一专利申请WO 2006083612中揭示了作为G蛋白偶联受体40(GPR40)激动剂的抗糖尿病性二环化合物,包括其药用盐和前药,其中所述二环化合物含有稠合的吡啶环,其可用作治疗化合物,尤其用于治疗II型糖尿病和通常与包括肥胖症和脂

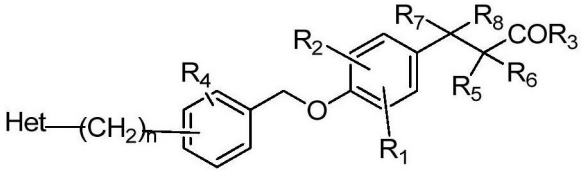
质障碍的疾病有关的病症，例如混合型或糖尿病性血脂障碍、高脂血症、高胆固醇血症和高甘油三酯血症。该专利申请中所揭示的化合物具有下列的一般结构：

[0065] 

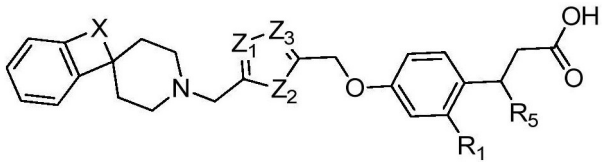
[0066] 其中Z选自$CR_3R_4CO_2R_5$、$-OCR_3R_4CO_2R_5$、$N(R_6)(CR_3R_4CO_2R_5)$、$-SCR_3R_4CO_2R_5$、四唑和杂环II。

[0067] 

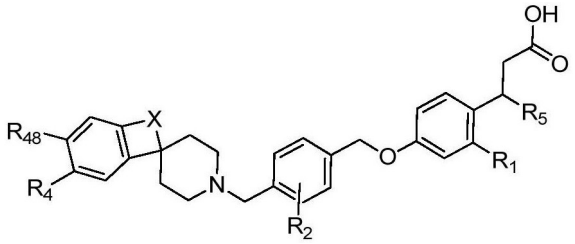
[0068] 稠环化合物已由Yasum等人揭示于专利US 7820837中。US 7517910中提及的下式要求保护具有GPR 40受体功能调节作用的化合物，该化合物可用作用于预防或治疗糖尿病等的胰岛素促分泌剂。

[0069] 

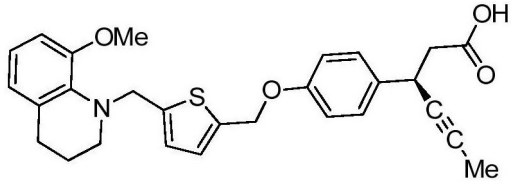
[0070] 新型的螺哌啶化合物已由Eli Lilly&Company在WO 2011066183中提及。

[0071] 

[0072] Eli Lilly还于专利申请US20110092531中揭示了以下螺哌啶。

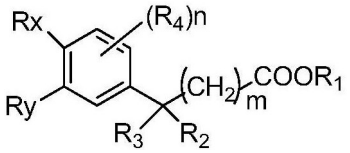
[0073] 

[0074] 可用于治疗糖尿病的新型1,2,3,4-四氢喹啉衍生物已由Eli Lilly&Company描述于专利申请WO 2013025424中。

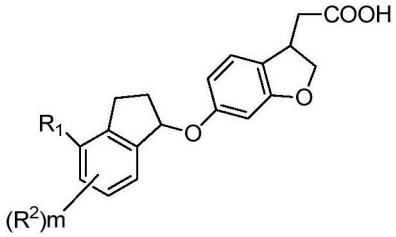
[0075] 

[0076] 标题为“Preparation of β-substituted carboxylic acid derivatives for the treatment of diabetes”的专利申请WO 2013147443已由Daichi Sankyo公开。

[0077] Piramal Enterprises Limited已于专利申请WO 2013/128378公开了具有下列结构的作为GPR激动剂的苯基烷酸衍生物。

[0078] 

[0079] Boehringer Ingelheim已公开了标题为“New indanyloxy dihydrobenzofuranyl acetic acid derivatives and their use as GPR receptor agonists”的专利申请WO 2013/144097和WO 2013/144098,其具有以下定义的结构。

[0080] 

[0081] 用于治疗癌症的新型治疗靶标以及相关疗法和方法由Children’s Medical Center Corporation揭示于专利申请WO 2014145817中。

[0082] WO 2014146604揭示了具有GPR40受体功能调节作用的某些稠环化合物。

[0083] 三环化合物和其用途已由SK Chemicals Co.,Ltd.公开于专利申请WO2014133361中。

[0084] 某些抗糖尿病性二环化合物已揭示于专利申请WO2014130608中。

[0085] Boehringer Ingelheim International于专利申请WO2013164292、WO2014122067、WO2014086712和WO2014082918以及US20140148462、US20140221349和US20140163025中揭示了某些其他茚满基氧基二氢苯并呋喃基乙酸。

[0086] Takeda Pharmaceutical Company Limited已于专利申请EP2743268中揭示了作为GPR40受体调节剂的稠合环状化合物。

[0087] Bristol-Myers Squibb已于专利申请WO2014078611、WO2014078610、WO2014078609和WO2014078608中揭示了二氢吡唑GPR40调节剂。

[0088] LG Life Sciences Limited已于专利WO2014073904中揭示了某些GPR40受体激动剂。Hancke Orozco等人已于专利申请US20140128333中揭示了用于降低肠部葡萄糖吸收并诱导肠降血糖素释放的化合物、组合物和方法。Merck Sharp&Dohme Corp于专利申请US20140045746、WO2014022528中揭示了抗糖尿病性三环化合物且另一申请在专利US20140038970中揭示了某些桥连和稠合抗糖尿病性化合物。

[0089] 可调节G蛋白偶联受体GPR40的新型氟取代化合物已揭示于专利申请US20140058125中。

[0090] Mochida Pharmaceutical Co已于专利US20140057871中揭示了环状酰胺衍生物。Negoro等人已于专利申请US20120035196中揭示了某些羧酸化合物。数个其他专利申请已揭示了各种数目的作为GPR40调节剂的化合物。一些代表性文献提供如下:Chandra Sekhar Gudla等人已于IJCPS,2014,Vol.2(5),852-861中揭示一些新型3-取代3-(芳基氧基芳基)-丙酸。

[0091] WO 2005095338、WO 2006038738、WO 2006083612、WO 2006083781、WO 2007013679、WO 2007136572、WO 2007136573、WO 2007049050、WO 20070123225、WO

2008002931、WO 2008054674、WO 2008054675、WO 200830520、WO 2008130514、WO 2008139987、WO 2009058237、WO 2009048527、WO 2009054423、US 7968552、WO 2009038204、WO 2010045258、WO 2010012650、WO 2010085522、WO 2010085525、WO 2010085528、WO 2010091176、WO 2011044073、WO 2011052756、WO 2011078371、WO 2011069958、WO 2011083752、WO 2012111849、WO 2012108478、WO 2012074126、WO 2012020738、WO 2012004261、WO 2012010413、WO 2012010413、WO 2012011125等。

[0092] 目标在于与胰岛素依赖性I型糖尿病和非胰岛素依赖性II型糖尿病相关的病理生理学的药物具有许多潜在的副作用且并不足以解决高比例的患者的血脂障碍和高甘油三酯血症。治疗通常聚焦在需要使用饮食、运动、降血糖剂和胰岛素的个体患者，但对于新型抗糖尿病药物存在持续的需求，尤其是可以较好耐受并具有较少副作用的那些。

[0093] 同样地，代谢综合征(综合征X，其特征为高血压和其相关病理学包括动脉粥样硬化、血脂症、高脂血症和高胆固醇血症)与胰岛素敏感性的降低有关，当受到挑战时，其可导致异常的血糖水平。心肌缺血和微血管疾病为已确立的与代谢综合征未治疗或控制不良有关的发病。

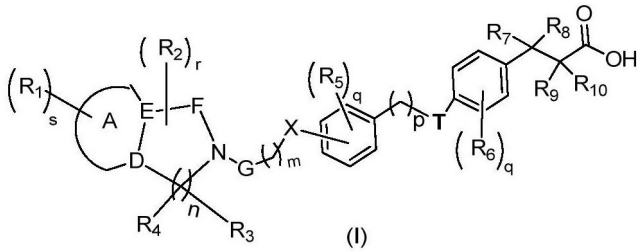
[0094] 对于新型的抗肥胖和抗糖尿病药物存在持续的需求，尤其是可以较好耐受并具有较少副作用的那些。

[0095] 本发明涉及可用于治疗糖尿病的GPR40激动剂。人类的GPR 40表达于胰脏中。如上文讨论，数种GPR 40激动剂已经开发且持续地开发。然而，这些化合物治疗疾病的治疗潜力尚未得到证实，且因此仍需要发展更新型的药物，其具有比目前的治疗方案更佳或具有可比性的效力，具有较少的副作用且需要更低的剂量方案。

[0096] 申请人在本申请公开了用作抗糖尿病、抗肥胖症、降血脂、降脂蛋白血和抗高血糖剂的新型式(I)的化合物，其在治疗和/或预防因高脂血症所致的疾病、分类为综合征X下的疾病和动脉粥样硬化可具有有益的效果，还公开了它们的制备方法。

发明内容

[0097] 本发明的主要目的是提供以通式(I)表示的新型GPR 40激动剂、其互变异构形式、其立体异构体、其药用盐和包含它们的药物组合物或其混合物。

[0098] 

(I)

[0099] 本发明的一个实施方案提供了用于制备以通式(I)表示的化合物、其互变异构形式、其立体异构体、其药用盐的方法。

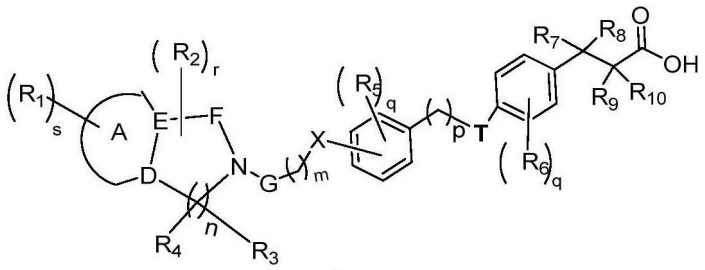
[0100] 本发明的另一实施方案提供了药物组合物，其包含通式(I)的化合物、其互变异构形式、其立体异构体、其药用盐或其与常用于制备这种组合物的适当载体、溶剂、稀释剂和其他介质的混合物。

[0101] 本发明的另一实施方案提供了药物组合物，其包含式(I)的化合物和用于治疗糖

尿病、肥胖症和其他相关病症的第二种适当的治疗剂。

具体实施方式

[0102] 因此，本发明涉及通式(I)的化合物

[0103] 

式(I)

[0104] 其互变异构形式、其立体异构体、其药用盐和包含它们的药物组合物，

[0105] 其中R_1、R_2、R_3、R_4、R_5、R_6在每次出现时各自独立地表示H、卤素、羟基、CN、NO_2、CHO、COOH、CO、任选取代的选自以下的基团：烷基、烷氧基、巯基、亚砜基团、砜基团、酰基、NH_2或任选取代的NHCO-直链或支链(C_1-C_6)烷基、芳烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳烷基或基团OR、C(O)OR、C(O)R和SO_2R，其中'R'在每次出现时独立地表示任选取代的选自以下的基团：H、直链或支链(C_1-C_6)烷基、芳基、芳烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳烷基；在可替换的实施方案中，R_3和R_4可一起形成氧代基团；

[0106] 'A'选自3-7元部分饱和、不饱和或饱和环，其可进一步具有一个或多于一个的选自O、S或N的杂原子；

[0107] 'E'和'D'可各自独立地为氮或碳；'F'可选自C、N或O；'G'可存在或不存在，且当存在时，表示键或选自O、S、NR_a，其中'R_a'表示直链或支链(C_1-C_6)烷基；

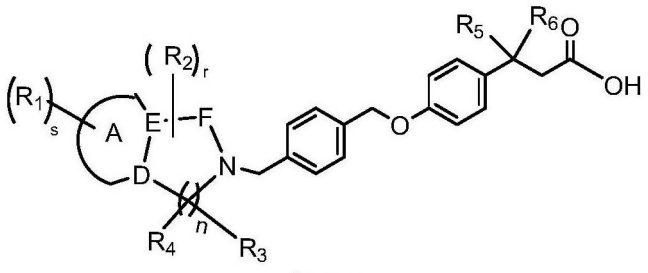
[0108] m＝1-3；'n'、'r'、'p'和's'各自独立地表示0至6的整数；q＝0-4；

[0109] 'X'可存在或不存在，且当存在时，选自CH_2、O、S和NR_a、SO_2NH；其中R_a如上文定义；

[0110] 'T'选自氧、-NH、S、SO、SO_2或NR_a，其中R_a如上文定义；R_7和R_8可各自独立地选自(C_2-C_4)炔、腈或环烷基；可替换地，R_7和R_8可与其连接的碳原子组合形成3-7元环，该环可任选地进一步具有一个或多于一个的选自S、N或O的杂原子；

[0111] R_9和R_{10}可选自氢、烷基、烷氧基和卤素。

[0112] 本发明的优选实施方案涉及通式(I')的化合物

[0113] 

式(I')

[0114] 其互变异构形式、其立体异构体、其药用盐和包含它们的药物组合物，

[0115] 其中R_1、R_2、R_3和R_4在每次出现时各自独立地表示H、卤素、羟基、CN、NO_2、CHO、COOH、

CO、任选取代的选自以下的基团：烷基、烷氧基、巯基、亚砜基团、砜基团、酰基、NH_2或任选取代的NHCO-直链或支链(C_1-C_6)烷基、芳烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳烷基或基团OR、C(O)OR、C(O)R和SO_2R，其中'R'在每次出现时独立地表示任选取代的选自以下的基团：H、直链或支链(C_1-C_6)烷基、芳基、芳烷基、环烷基、环烷基烷基、杂环基、杂环基烷基、杂芳基、杂芳烷基；

[0116] 在可替换的实施方案中，R_3和R_4可一起形成氧代基团；

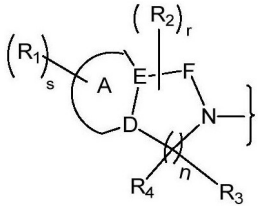
[0117] 'A'选自3-7元部分饱和、不饱和或饱和环，其进一步具有一个或多于一个的选自O、S或N的杂原子；

[0118] 'E'和'D'可各自独立地为氮或碳；'F'可选自C、N或O；

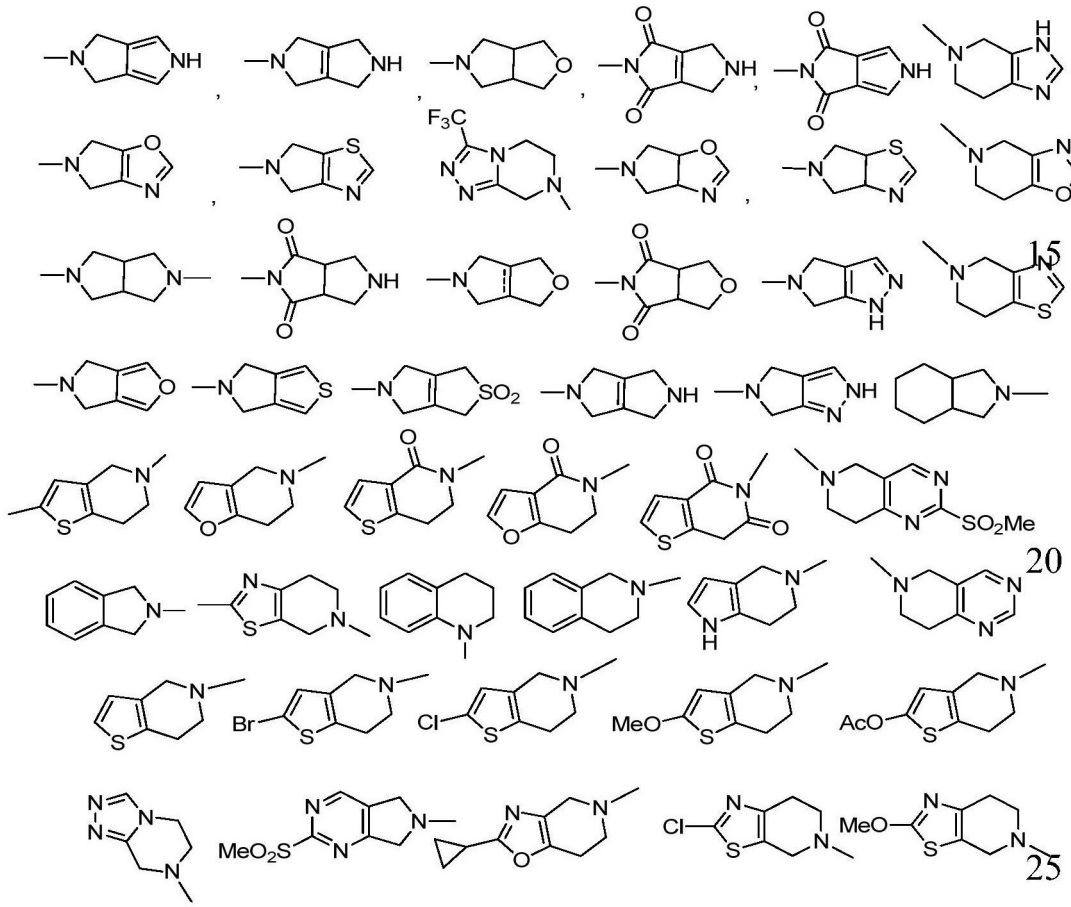
[0119] 'n'、'r'和's'各自独立地表示0至6的整数；

[0120] R_5和R_6可各自独立地选自(C_2-C_4)炔、腈或环烷基；可替换地R_5和R_6可与它们所连接的碳原子组合形成3-7元环，该环可任选地进一步具有一个或多于一个的选自S、N或O的杂原子。

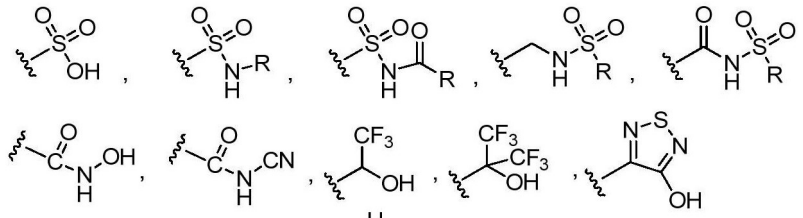
[0121] 下式表示的优选杂环

[0122] 

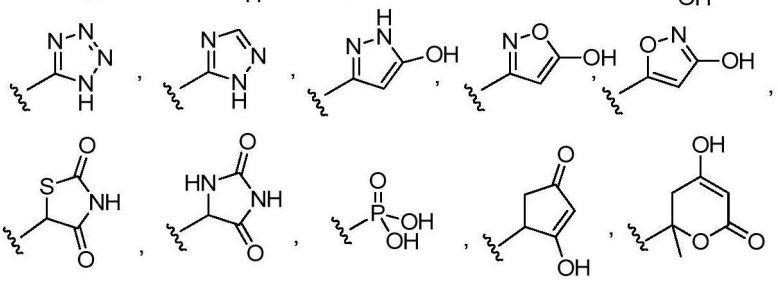
[0123] 可选自如下提及的下列二环

[0124] 

[0125] 取代基-COOH在任何可能的情况下可任选地由诸如以下的生物电子等排替代物替代：



[0126]



[0127] 当R_1至R_{10}的任一基团是由一个或多个基团取代时，这些取代基可独立地选自下列基团：羟基、氧代、卤素、巯基、硝基、氨基、氰基、甲酰基，或取代或未取代的选自以下的基团：脒基、烷基、卤代烷基、烷氧基、卤代烷氧基、烯基、炔基、环烷基、环烯基、二环烷基、二环烯基、烷氧基、烯氧基、环烷氧基、芳基、芳基氧基、芳烷基、芳烷基氧基、杂环基、杂芳基、杂环基烷基、杂芳烷基、杂芳基氧基、杂芳烷氧基、杂环基氧基、杂环基烷氧基、杂环基烷氧基酰基、酰基、酰基氧基、酰基氨基、单取代或二取代的氨基、芳基氨基、芳烷基氨基、羧酸基团和其衍生基团例如酯基和酰胺基团、羰基氨基、羟基烷基、氨基烷基、烷氧基烷基、芳基氧基烷基、芳烷氧基烷基、烷基硫基、巯基烷基、芳基硫基、烷基磺酰基氨基、烷基磺酰基氧基、烷氧基羰基氨基、芳基氧基羰基氨基、芳烷基氧基羰基氨基、氨基羰基氨基、烷基氨基羰基氨基、烷氧基氨基、羟基氨基、亚磺酰基衍生基团、磺酰基衍生基团、磺酸基团和其衍生基团。

[0128] 芳基可为包含一、二或三个环的芳族系统，其中这些环可以依赖方式连接在一起或可稠合；在优选的实施方案中，这些芳基可选自苯基、萘基、四氢萘基、茚满基、联苯基。

[0129] 杂芳基表示5至8元芳族基团，其可为含有一或多个选自O、N或S的杂原子的单一或稠合环；在优选的实施方案中，该基团可选自吡啶基、噻吩基、呋喃基、吡咯基、噁唑基、噻唑基、异噻唑基、咪唑基、异噁唑基、噁二唑基、噻二唑基、三唑基、四唑基、苯并吡喃基、苯并吡喃酮基、苯并呋喃基、苯并噻吩基、吲哚啉基、吲哚基、氮杂吲哚基、氮杂吲哚啉基、苯并二氢呋喃基、苯并二氢噻吩基、吡唑并嘧啶基、吡唑并嘧啶酮基、氮杂喹唑啉基、氮杂喹唑啉羰基、吡啶并呋喃基、吡啶并噻吩基、噻吩并嘧啶基、噻吩并嘧啶酮基、喹啉基、嘧啶基、吡唑基、喹唑啉基、喹唑啉酮基、嘧啶酮基、哒嗪基、三嗪基、苯并噁嗪基、苯并噁嗪酮基、苯并噻嗪基、苯并噻嗪酮基、苯并噁唑基、苯并噻唑基、苯并咪唑基、苯并三唑基、酞嗪基(phthalazynil)、二氮杂萘基、噌吟基、咔唑基、吩噻嗪基、吩噁嗪基。

[0130] 术语"杂环基"表示饱和、部分饱和或不饱和的环状基团，杂原子选自氮、硫或氧；在优选的实施方案中，该基团可选自氮杂环丙烷基、氮杂环丁烷基、吡咯烷基、咪唑烷基、哌啶基、哌嗪基、2-氧代哌啶基、4-氧代哌啶基、2-氧代哌嗪基、3-氧代哌嗪基、吗啉基、硫吗啉基、2-氧代吗啉基、氮杂䓬基、二氮杂䓬基、氧杂䓬、硫氮杂䓬基、噁唑烷基、噻唑烷基等；部分饱和杂环基的实施例包括二氢噻吩基、二氢吡喃基、二氢呋喃基、二氢噻唑基。

[0131] 单独地或与其他基团组合使用的“烷基”指含有一至六个碳的直链或支链基团，选自甲基、乙基、正丙基、异丙基、正丁基、仲丁基、叔丁基、戊基、叔戊基、正戊基、正己基等；

[0132] -单独地或与其他基团组合使用的“烯基”选自含有二至六个碳原子的基团，优选为选自以下的基团：乙烯基、烯丙基、2-丁烯基、3-丁烯基、2-戊烯基、3-戊烯基、4-戊烯基、2-己烯基、3-己烯基、4-己烯基等；“烯基”包括直链和支链的二烯和三烯；

[0133] -单独地或与其他基团组合使用的“炔基”选自含有二至六个碳原子的直链或支链基团，优选为噻吩基、1-丙炔基、2-丙炔基、1-丁炔基、2-丁炔基、3-丁炔基、1-戊炔基、2-戊炔基、3-戊炔基、4-戊炔基、1-己炔基等。术语“炔基”包括二和三炔；

[0134] -单独地或与其他基团组合使用的“环烷基”或“脂环基”选自含有三至六个碳原子的环状基团，优选为环丙基、环丁基、环戊基、环己基等；术语”二环烷基”指稠合在一起的多于一个的环烷基；

[0135] -单独地或与其他基团组合使用的“环烯基”优选地选自环丙烯基、1-环丁烯基、2-环丁烯基、1-环戊烯基、2-环戊烯基、3-环戊烯基、1-环己烯基、2-环己烯基、3-环己烯基等；

[0136] -单独地或与其他基团组合使用的“烷氧基”选自含有上文定义的烷基且该烷基直接连接至氧原子的基团，优选为选自以下的基团：甲氧基、乙氧基、正丙氧基、异丙氧基、正丁氧基、叔丁氧基、异丁氧基、戊基氧基、己基氧基等；

[0137] -单独地或与其他基团组合使用的“环烷氧基”选自含有上文定义的环烷基且该环烷基直接连接至氧原子的基团，优选为选自以下的基团：环丙氧基、环丁氧基、环戊基氧基、环己基氧基、环庚基氧基等；

[0138] -单独地或与其他基团组合使用的“芳基氧基”选自含有上文定义的芳基且该芳基直接连接至氧原子的基团，更佳地为选自以下的基团：苯氧基、萘基氧基、四氢萘基氧基、联苯氧基等；

[0139] -单独地或与其他基团组合使用的“芳烷基”选自含有上文定义的芳基且该芳基直接连接至上文定义的烷基的基团，优选为选自以下的基团：苄基、苯乙基等；

[0140] -单独地或与其他基团组合使用的“芳烷氧基”选自含有上文定义的芳烷基且该芳烷基直接连接至氧原子的基团，优选为选自以下的基团：苄基氧基、苯乙基氧基等；

[0141] -单独地或与其他基团组合使用的“杂芳烷基”选自含有上文定义的杂芳基且该杂芳基直接连接至上文定义的烷基的基团，优选为选自以下的基团：吡啶烷基、噻吩烷基、喹啉烷基等；

[0142] -单独地或与其他基团组合使用的“烯氧基”选自含有上文定义的烯基且该烯基连接至氧原子的基团，优选选自乙烯基氧基、烯丙基氧基、丁烯氧基、戊烯氧基、己烯氧基等；

[0143] -“卤代烷基”选自上文定义的烷基，且由一个或多个卤素适当地取代；例如全卤代烷基，优选为全氟(C_1-C_6)烷基，例如氟甲基、二氟甲基、三氟甲基、氟乙基、二氟乙基、三氟乙基、单或多卤素取代的甲基、乙基、丙基、丁基、戊基或己基；

[0144] -“卤代烷氧基”选自上文定义的适当卤代烷基，该卤代烷基直接连接至氧原子，优选为选自以下的基团：氟甲氧基、氯甲氧基、氟乙氧基、氯乙氧基等；

[0145] -“全卤代烷氧基”选自上文定义的适当全卤代烷基，该全卤代烷基直接连接至氧原子，优选为选自以下的基团：三氟甲氧基、三氟乙氧基等；

[0146] -“杂芳基氧基”、“杂芳烷氧基”、“杂环基氧基”、“杂环基烷氧基”分别选自上文定

义的适当杂芳基、杂芳基烷基、杂环基、杂环基烷基，且连接至氧原子；

[0147] -单独地或与其他基团组合使用的“酰基”选自包含一至八个碳原子的基团，优选选自甲酰基、乙酰基、丙酰基、丁酰基、异丁酰基、戊酰基、己酰基、庚酰基、苯甲酰基等，其可取代；

[0148] -单独地或与其他基团组合使用的“酰基氧基”选自上文定义的适当酰基，该酰基直接连接至氧原子，更优选该基团选自乙酰基氧基、丙酰基氧基、丁酰基氧基、异丁酰基氧基、苯甲酰基氧基等；

[0149] -单独地或与其他基团组合使用的“酰基氨基”选自上文定义的适当酰基，该酰基连接至氨基，更优选地该基团选自CH_3CONH、C_2H_5CONH、C_3H_7CONH、C_4H_9CONH、C_6H_5CONH等，其可经取代；

[0150] -单独地或与其他基团组合使用的“单取代的氨基”表示由一个选自上文定义的(C_1-C_6)烷基、经取代烷基、芳基、经取代芳基或芳基烷基取代的氨基，更优选该基团选自甲基氨基、乙基氨基、正丙基氨基、正丁基氨基、正戊基氨基等；

[0151] -单独地或与其他基团组合使用的“二取代的氨基”表示由两个相同或不同的选自上文定义的(C_1-C_6)烷基、经取代烷基、芳基、经取代芳基或芳基烷基取代的氨基，更优选该基团选自二甲基氨基、甲基乙基氨基、二乙基氨基、苯基甲基氨基等；

[0152] -单独地或与其他基团组合使用的“芳基氨基”表示上文定义的芳基，通过具有自由价键的氨基从氮原子连接，更优选该基团选自苯基氨基、萘基氨基、N-甲基苯氨基等；

[0153] -单独地(-C＝O-)或与其他基团例如上述烷基组合使用的“氧代”或”羰基”例如“烷基羰基”指由上述烷基取代的羰基(-C＝O-)，例如酰基或烷酰基；

[0154] -单独地或与其他基团组合使用的“羧酸”基团指-COOH基团，且包括羧酸的衍生物例如酯基和酰胺基团；

[0155] -单独地或与其他基团组合使用的“酯”基指-COO-基，且包括羧酸衍生物，更优选该酯部分选自烷氧基羰基，例如甲氧基羰基、乙氧基羰基等，其可任选经取代；芳基氧基羰基例如苯氧基羰基、萘基氧基羰基等，其可任选经取代；芳烷氧基羰基例如苄基氧基羰基、苯乙基氧基羰基、萘基甲氧基羰基等，其可任选经取代；杂芳基氧基羰基、杂芳烷氧基羰基，其中杂芳基为上文定义的那些，其可任选经取代；杂环基氧基羰基，其中杂环基为上文定义的那些，其可任选经取代；

[0156] -单独地或与其他基团组合使用的“酰胺”基团表示氨基羰基(H_2N-C＝O)，其中氨基为单或二取代或未取代，更优选地该基团选自甲基酰胺基团、二甲基酰胺基团、乙基酰胺基团、二乙基酰胺基团等；

[0157] -单独地或与其他基团组合使用的“氨基羰基”可选自‘氨基羰基’、‘氨基羰基烷基”、“n-烷基氨基羰基”、“N-芳基氨基羰基”、“N,N-二烷基氨基羰基”、“N-烷基-N-芳基氨基羰基”、“N-烷基-N-羟基氨基羰基”和“N-烷基-N-羟基氨基羰基烷基”，其分别任选地经取代。术语“N-烷基氨基羰基”和“N,N-二烷基氨基羰基”指上文定义的氨基羰基，其已分别地经一个烷基和经两个烷基取代。优选为“低级烷基氨基羰基”，其具有如上所述的低级烷基且该低级烷基连接至氨基羰基。术语“N-芳基氨基羰基”和“N-烷基-N-芳基氨基羰基”指分别由一个芳基、或一个烷基和一个芳基取代的氨基羰基。术语“氨基羰基烷基”包括由氨基羰基取代的烷基；

[0158] -单独地或与其他基团组合使用的“羟基烷基”选自上文定义的烷基，且由一个或多个羟基取代，更优选该基团选自羟基甲基、羟基乙基、羟基丙基、羟基丁基、羟基戊基、羟基己基等；

[0159] -单独地或与其他基团组合使用的“氨基烷基”指上文定义的连接至烷基的氨基(-NH_2)部分，其可经取代，例如单取代和二取代的氨基烷基。本文使用的单独地或与其他基团组合使用的术语“烷基氨基”指上文定义的烷基，该烷基连接至氨基，其可经取代，例如单取代和二取代的烷基氨基；

[0160] -单独地或与其他基团组合使用的“烷氧基烷基”指上文定义的烷氧基，该烷氧基连接至上文定义的烷基，更优选该基团可选自甲氧基甲基、乙氧基甲基、甲氧基乙基、乙氧基乙基等；

[0161] -单独地或与其他基团组合使用的“烷基硫基”指包含上文定义的烷基的直链或支链或环状单价取代基，通过具有自由价键的二价硫原子从硫原子连接，更优选该基团可选自甲基硫基、乙基硫基、丙基硫基、丁基硫基、戊基硫基等，或选自环丙基硫基、环丁基硫基、环戊基硫基、环己基硫基等的环状烷基硫基，其可任选地经取代；

[0162] -单独地或与其他基团组合使用的“硫基烷基”指上文定义的烷基，该烷基连接至式-SR’基，其中R’表示氢、烷基或芳基，例如硫基甲基、甲基硫基甲基、苯基硫基甲基等，其可任选地经取代。

[0163] -单独地或与其他基团组合使用的“烷氧基羰基氨基”选自上文定义的适当的烷氧基羰基，该烷氧基羰基连接至氨基，更优选为甲氧基羰基氨基、乙氧基羰基氨基等；

[0164] -单独地或与其他基团组合使用的“氨基羰基氨基、“烷基氨基羰基氨基”、“二烷基氨基羰基氨基”为羰基氨基(-$CONH_2$)，该羰基氨基分别连接至氨基(NH_2)、烷基氨基或二烷基氨基，其中烷基为上文定义的那些；

[0165] -单独地或与其他基团组合使用的“脒基”表示-C(=NH)-NH_2基；“烷基脒基”表示如上所述的烷基，该烷基连接至脒基；

[0166] -单独地或与其他基团组合使用的“烷氧基氨基”表示上文定义的适当的烷氧基，该烷氧基连接至氨基；

[0167] -单独地或与其他基团组合使用的“羟基氨基”表示-NHOH部分，且可任选地经选自上述的基团取代；

[0168] -单独地或与其他基团组合使用的“亚磺酰基”或“亚磺酰基衍生物”表示二价基团，即-SO-或R_xSO，其中R_x为任选取代的选自上述的烷基、芳基、杂芳基、杂环基；

[0169] -单独地或与其他基团组合、以其他术语例如烷基磺酰基使用的“磺酰基”或“砜基团衍生物”表示二价基团-SO_2-、或R_xSO_2-，其中R_x为上文定义的那些。更优选地，该基团可选自“烷基磺酰基”，其中适当的烷基(选自上文定义的那些)连接至磺酰基，例如甲基磺酰基、乙基磺酰基、丙基磺酰基等，“芳基磺酰基”，其中芳基(上文定义)连接至磺酰基，例如苯基磺酰基等。

[0170] -单独地或与其他基团组合、以其他术语例如烷基磺酰基氧基使用的“磺酰基氧基”表示二价基团-SO_3-、或R_xSO_3-，其中R_x为上文定义的那些。更优选地，该基团可选自“烷基磺酰基”，其中适当的烷基(选自上文定义的那些)连接至磺酰基氧基，例如甲磺酰基氧基、乙磺酰基氧基、丙磺酰基氧基等，“芳基磺酰基”，其中芳基(上文定义)连接至磺酰基，例

如苯磺酰基氧基等。

[0171] 适当的基团和基团上的取代基可选自说明书的任一处所述的那些。

[0172] 特别有效的化合物可选自：

[0173] (S)-3-(4-((3-((6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸(1)；

[0174] 3-(4-((3-((4H-呋喃并[3,4-c]吡咯-5(6H)-基)甲基)苄基)氧基)苯基)-3-氰基丙酸锂；

[0175] 3-氰基-3-(4-((3-((4-氧代-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)丙酸；

[0176] 3-氰基-3-(4-((3-((3-(三氟甲基)-5,6-二氢-[1,2,4]三唑并[4,3-a]吡嗪-7(8H)-基)甲基)苄基)氧基)苯基)丙酸锂；

[0177] 3-氰基-3-(4-((3-((2,2-二氧化-1H-噻吩并[3,4-c]吡咯-5(3H,4H,6H)-基)甲基)苄基)氧基)苯基)丙酸；

[0178] 3-氰基-3-(4-((3-((6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)丙酸；

[0179] (S)-3-(4-((3-((2-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0180] (S)-3-(4-((3-((1-(叔丁氧基羰基)-6,7-二氢-1H-吡咯并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0181] (S)-3-(4-((3-((6,7-二氢-1H-吡咯并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0182] (S)-3-(4-((3-((2-甲基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0183] (S)-3-(4-((3-((3-(三氟甲基)-5,6-二氢-[1,2,4]三唑并[4,3-a]吡嗪-7(8H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0184] (S)-3-(4-((3-(异吲哚啉-2-基甲基)苄基)氧基)苯基)己-4-炔酸；

[0185] (S)-3-(4-((3-((3,4-二氢喹啉-1(2H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0186] (S)-3-(4-((3-((2-溴-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0187] (S)-3-(4-((3-((3,4-二氢异喹啉-2(1H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0188] 二((S)-3-(4-((3-((2-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸)钙；

[0189] 二((S)-3-(4-((3-((2-甲基-6,7-二氢噻唑并[4,5-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸)钙；

[0190] (S)-3-(4-((3-((2-(二氟甲基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0191] (S)-3-(4-((3-((2-溴-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸钙；

[0192] (S)-3-(4-((3-((3,4-二氢异喹啉-2(1H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

钙；

[0193] (S)-3-(4-((3-((7,8-二氢吡啶并[4,3-d]嘧啶-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0194] (S)-3-(4-((3-((1-甲基吡咯并[3,4-c]吡唑-5(1H,4H,6H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0195] (3S)-3-(4-((3-(6-氧杂-3-氮杂二环[3.1.1]庚-3-基甲基)苄基)氧基)苯基)己-4-炔酸；

[0196] (S)-3-(4-((3-(吲哚啉-1-基甲基)苄基)氧基)苯基)己-4-炔酸；

[0197] (S)-3-(4-((3-((5,6-二氢-[1,2,4]三唑并[4,3-a]吡嗪-7(8H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0198] (S)-3-(4-((3-((2-环丙基-6,7-二氢噁唑并[4,5-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0199] (3S)-3-(4-((3-((5-苄基六氢吡咯并[3,4-c]吡咯-2(1H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,甲酸盐；

[0200] (S)-3-(4-((3-((4H-噻吩并[2,3-c]吡咯-5(6H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0201] 6-(3-((4-((S)-1-羧基戊-3-炔-2-基)苯氧基)甲基)苄基)-6,7-二氢-5H-吡咯并[3,4-d]嘧啶-6-鎓甲酸盐；

[0202] 1-(3-((4-((S)-1-羧基戊-3-炔-2-基)苯氧基)甲基)苄基)-7-甲氧基-1,2,3,4-四氢喹啉-1-鎓甲酸盐；

[0203] (S)-3-(4-((3-((2-氯-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0204] (S)-3-(4-((3-((2-溴-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0205] (S)-3-(4-((3-(吡咯并[3,4-c]吡唑-5(1H,4H,6H)-基甲基)苄基)氧基)苯基)己-4-炔酸；

[0206] (S)-3-(4-((3-((2-(羟基甲基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0207] (S)-5-(3-((4-(1-羧基戊-3-炔-2-基)苯氧基)甲基)苄基)-4,5,6,7-四氢噻吩并[3,2-c]吡啶-2-羧酸；

[0208] 3-环丙基-3-(3-((3-((2-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)丙酸；

[0209] (S)-3-(4-((3-((1-甲基-6,7-二氢-1H-吡咯并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0210] (S)-3-(4-((3-((2-氨基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0211] (S)-3-(4-((3-((2-氯-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸钙；

[0212] (S)-3-(4-((3-((2-氨基甲酰基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)

苄基)氧基)苯基)己-4-炔酸；

[0213] (S)-3-(4-((3-((2-异丙基吡咯并[3,4-c]吡唑-5(2H,4H,6H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0214] (S)-3-(4-((3-((2-(甲氧基羰基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0215] (S)-3-(4-((3-((2-氰基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0216] (S)-3-(4-((3-((2-甲酰基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0217] S)-3-(4-((3-((2-甲基-6,7-二氢吡唑并[1,5-a]吡嗪-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0218] (S)-3-(4-((3-((2-(甲基氨基甲酰基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0219] (S)-3-(4-((3-((2-(二甲基氨基甲酰基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0220] (3S)-3-(4-((3-((2-甲基-5-(4-(甲基磺酰基)苯基)吡咯烷-1-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0221] (S)-3-(4-((3-((2-(甲基磺酰基)-7,8-二氢吡啶并[4,3-d]嘧啶-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0222] (S)-3-(4-((3-((2-甲氧基-7,8-二氢吡啶并[4,3-d]嘧啶-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0223] (3S)-3-(4-((3-((2-苯基吡咯烷-1-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0224] (S)-3-(4-((3-(吡咯烷-1-基甲基)苄基)氧基)苯基)己-4-炔酸,甲酸盐；

[0225] (S)-3-(4-((3-(哌啶-1-基甲基)苄基)氧基)苯基)己-4-炔酸,甲酸盐；

[0226] (S)-3-(4-((3-((1-异丙基吡咯并[3,4-c]吡唑-5(1H,4H,6H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,甲酸盐；

[0227] (R)-3-(4-((3-((2-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0228] (R)-3-(4-((3-((2-甲基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0229] (S)-3-(4-((3-((6,7-二氢-[1,2,3]三唑并[1,5-a]吡嗪-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0230] 3-(4-((3-((2-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0231] 3-(4-((3-((2-甲基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0232] (S)-3-(4-((3-((2-氯-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸钙；

[0233] (S)-3-(4-((3-((2-(环丙基氨基甲酰基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-

基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0234] (S)-3-(4-((3-((2-(吡咯烷-1-羰基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0235] (S)-3-(4-((3-((2-乙酰氨基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0236] (S)-3-(4-((3-((2-环丙基-6,7-二氢噁唑并[4,5-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸钙；

[0237] (S)-3-(4-((3-((2-硝基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0238] (S)-3-(4-((3-((2-(二甲基氨基)-7,8-二氢吡啶并[4,3-d]嘧啶-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,2,2,2-三氟乙酸盐；

[0239] (S)-3-(4-((3-((2-氨基-7,8-二氢吡啶并[4,3-d]嘧啶-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸化合物,2,2,2-三氟乙酸盐；

[0240] (S)-3-(4-((3-((7,8-二氢-1,6-二氮杂萘-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0241] (S)-3-(4-((3-((2-环丙基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸化合物,2,2,2-三氟乙酸盐；

[0242] (S)-3-(4-((3-((2-乙酰基氨基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸化合物,2,2,2-三氟乙酸盐；

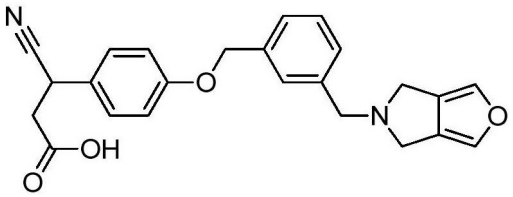
[0243] (S)-3-(4-((3-((2-乙基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

[0244] (S)-3-(4-((3-((2-乙酰基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸；

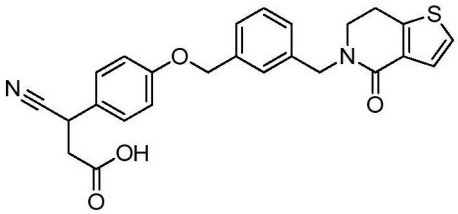
[0245] (S)-3-(4-((3-((2-((甲基氨基)甲基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸化合物,2,2,2-三氟乙酸盐。

[0246] 下列化合物可按照类似于实施例1所述的操作以及本领域技术人员熟知的适当修饰而合成,且视为包含在本发明范围内。

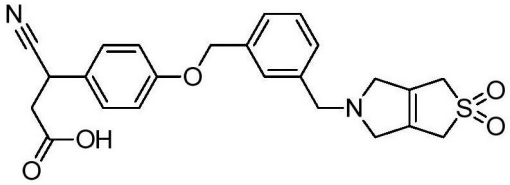
[0247] 3-(4-((3-((4H-呋喃并[3,4-c]吡咯-5(6H)-基)甲基)苄基)氧基)苯基)-3-氰基丙酸

[0248] 

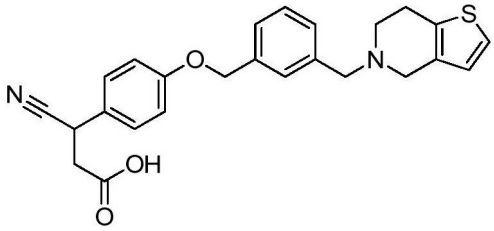
[0249] 3-氰基-3-(4-((3-((4-氧代-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)丙酸

[0250] 

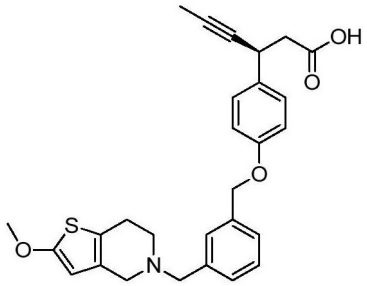
[0251] 3-氰基-3-(4-((3-((2,2-二氧化-1H-噻吩并[3,4-c]吡咯-5(3H,4H,6H)-基)甲基)苄基)氧基)苯基)丙酸

[0252] 

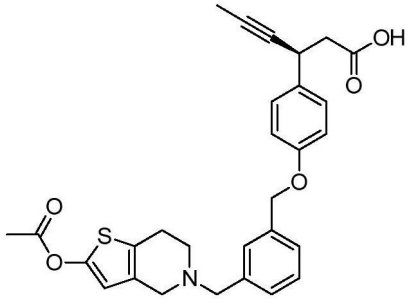
[0253] 3-氰基-3-(4-((3-((6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)丙酸

[0254] 

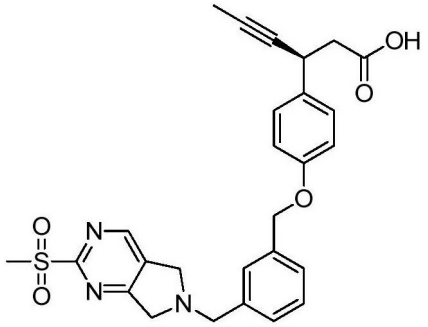
[0255] (S)-3-(4-((3-((2-甲氧基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0256] 

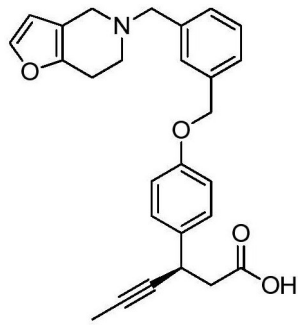
[0257] (S)-3-(4-((3-((2-乙酰氧基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0258] 

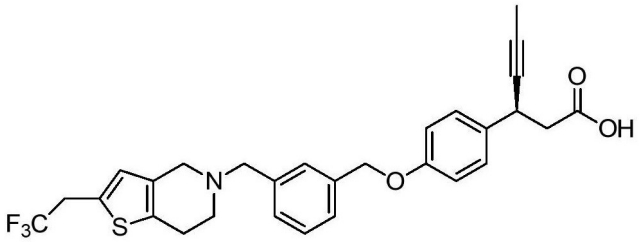
[0259] (S)-3-(4-((3-((2-(甲基磺酰基)-5H-吡咯并[3,4-d]嘧啶-6(7H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0260] 

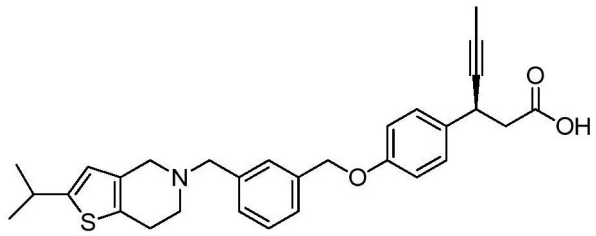
[0261] (S)-3-(4-((3-((6,7-二氢呋喃并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0262] 

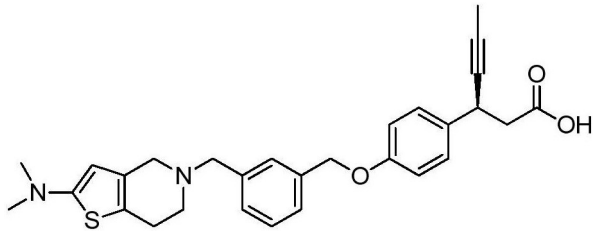
[0263] (S)-3-(4-((3-((2-(2,2,2-三氟乙基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0264] 

[0265] (S)-3-(4-((3-((2-异丙基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

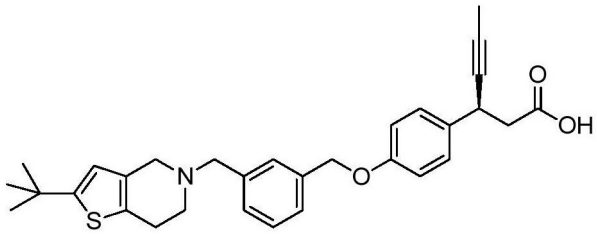
[0266] 

[0267] (S)-3-(4-((3-((2-(二甲基氨基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

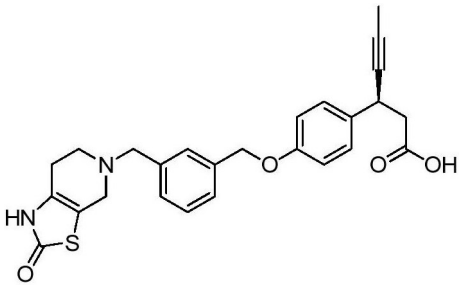
[0268] 

[0269] (S)-3-(4-((3-((2-(叔丁基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄

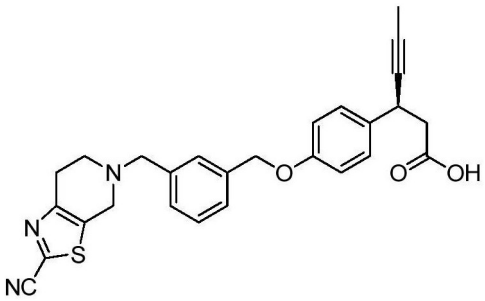
基)氧基)苯基)己-4-炔酸

[0270] 

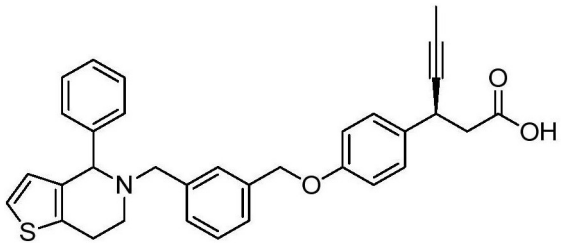
[0271] (S)-3-(4-((3-((2-氧代-1,2,6,7-四氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0272] 

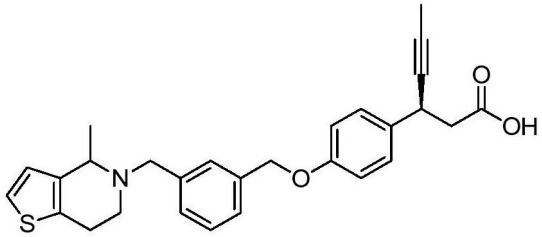
[0273] (S)-3-(4-((3-((2-氰基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0274] 

[0275] (3S)-3-(4-((3-((4-苯基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0276] 

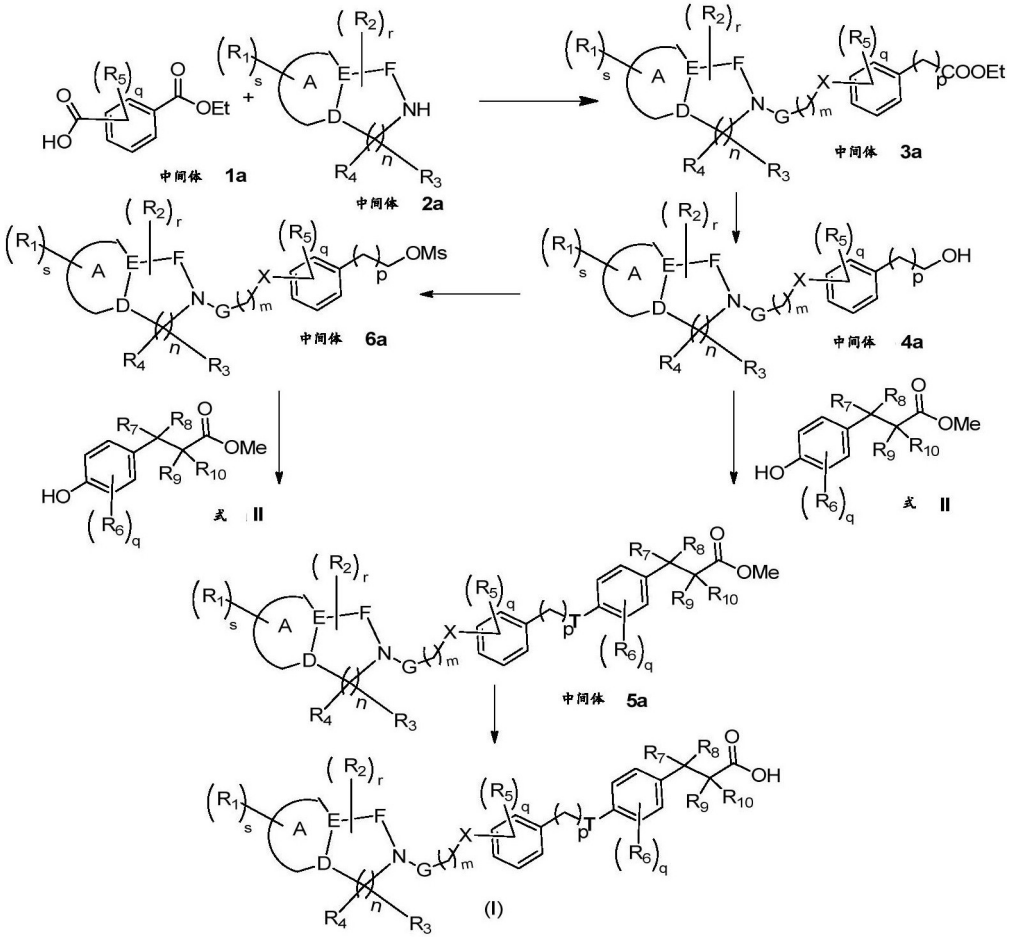
[0277] (3S)-3-(4-((3-((4-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0278] 

[0279] 本发明的新型化合物可使用下列章节中所述的反应和技术连同(适当时)本领域

的技术人员已知的其他适当方法制备。反应在适于所用试剂和材料的溶剂中进行且适用于待达成的转化。本领域的技术人员应当理解，所呈现的合成步骤的性质和顺序可变化以达到使本发明化合物的形成优化的目的，此外某些步骤可进行修饰、改变、添加或删除明显的步骤以优化以及为制备本发明化合物所需。这些明显的变化也应视为本发明的一部分。

[0280] 方案1:通式(I)的化合物可根据下列方案制得

[0281] 

[0282] 式(I)的化合物可根据方案1所描述的反应制得。

[0283] 第一步骤包括使取代的羧酸(中间体1a)与适当取代的杂环(中间体2a)在肽键形成条件下反应以得到中间体3a。中间体3a的酯可使用适当还原剂例如二异丁基氢化铝、氢化锂铝或氢硼化钠等还原以得到中间体4a。中间体4a可进一步与式II化合物在Mitsunobu条件下反应以得到中间体5a。Mitsunobu条件涉及使醇中间体4a与亲核试剂例如酚(式II)使用适当的膦例如三丁基膦、三苯基膦或三乙基膦和偶氮二羰基例如ADDP或偶氮二羧酸酯(DEAD)进行反应。

[0284] 可替换地，中间体4a可使用适当的反应物和条件组合例如甲磺酰氯和三乙胺而转化成具有适当离去基团的化合物例如甲磺酸酯衍生物(中间体6a)。

[0285] 中间体6a可与式II化合物使用二异丙基乙胺或碳酸铯反应以得到中间体5a。

[0286] 中间体5a可使用碱例如氢氧化锂、氢氧化钠或氢氧化钾而水解得到式(I)的羧酸衍生物。

[0287] 任选步骤中，式(I)化合物的药用盐可通过将适当的式(I)的化合物与药用碱或酸在适当溶剂中、于标准条件下反应而形成。任选地，该盐的形成可在酯中间体的水解后同时

发生。

[0288] 这些盐类的形成已在本领域中熟知和了解。

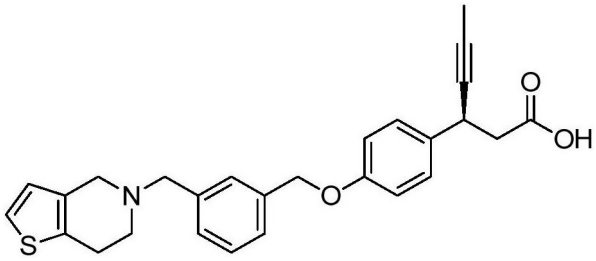
[0289] 本发明化合物可单独地或与一种或多种选自以下的治疗剂组合使用:胰岛素、胰岛素衍生物和模拟剂、胰岛素分泌促进剂、胰岛素增敏剂、双胍剂、α-葡萄糖苷酶抑制剂、促胰岛素磺酰脲受体配体、氯茴苯酸类(meglitinides)、GLP-1、GLP-1类似物、DPP-IV抑制剂、GPR-119活化剂、钠依赖性葡萄糖协同转运蛋白(SGLT2)抑制剂、PPAR调节剂、非-格列酮(non-glitazone)型PPARδ激动剂、HMG-CoA还原酶抑制剂、降胆固醇药、凝乳酶抑制剂、抗血栓和抗血小板剂和其他抗肥胖剂或其药用盐。这些使用将取决于待治疗患者的病症而定且在熟练操作者的实施范围内。

[0290] 按照上述的一般方法,包括本领域技术人员范围内的适当修饰和添加,下列式(1)的化合物制备如下:

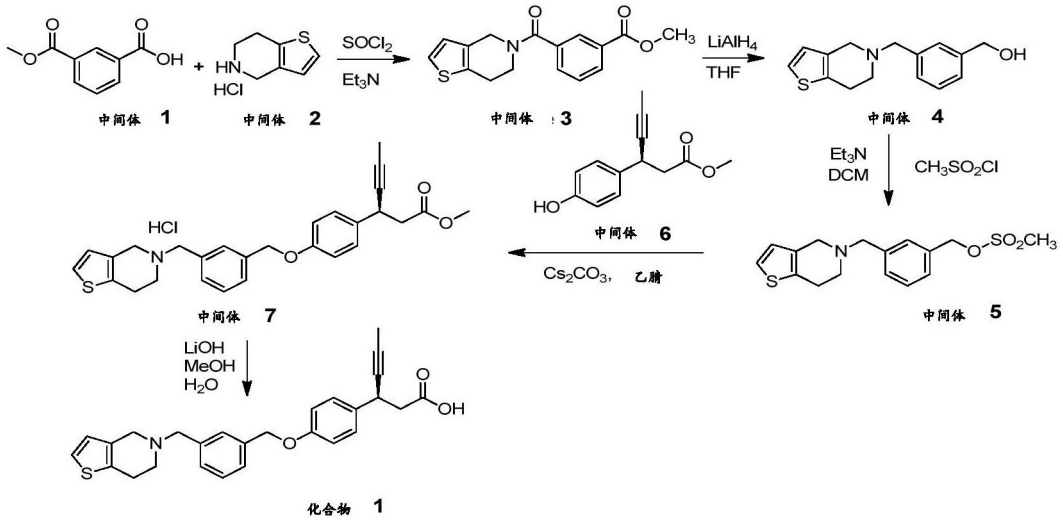
[0291] 实施例中提供的1H NMR光谱数据(见下文)使用400MHz光谱仪(Bruker AVANCE-400)记录且以δ标度报导。除非另外表明,否则用于NMR的溶剂为$CDCl_3$。

[0292] 实施例1

[0293] (S)-3-(4-((3-((6,7-二氢噻吩并[3,2-c]吡啶-5(4H)基)甲基)苄基)氧基)苯基)己-4-炔酸(1)

[0294] 

[0295] 方案2:

[0296] 

[0297] 步骤:

[0298] i.3-(4,5,6,7-四氢噻吩并[3,2-c]吡啶-5-羰基)苯甲酸甲酯(中间体3)

[0299] 将亚硫酰氯(16.21mL,222mmol)分成小份于25℃添加至3-(甲氧基羰基)苯甲酸中间体1(10g,55.5mmol)中,随后加入一滴二甲基甲酰胺。将反应混合物于回流下搅拌3小时。将过量的亚硫酰氯于100℃减压蒸发。将4,5,6,7-四氢噻吩并[3,2-c]吡啶盐酸盐中间体2

(12.19g,69.4mmol)溶于100mL水中,向其中加入氢氧化钠(4.44g,111mmol)的25mL水溶液。将4,5,6,7-四氢噻吩并[3,2-c]吡啶的游离碱于二氯甲烷(75mL)中萃取,在无水碳酸钾干燥。将酰氯溶于无水二氯甲烷(75mL)中,再冷却至0℃。

[0300] 将三乙胺(15.47mL,111mmol)逐滴加至反应混合物中,其后于0℃逐滴加入4,5,6,7-四氢噻吩并[3,2-c]吡啶的二氯甲烷(75mL)溶液。将反应混合物温热至25℃,再搅拌3小时。反应的进展通过TLC监测。将反应混合物倒至冰水(125mL)中,以10%HCl调整至pH约4,再用二氯甲烷(3×100mL)萃取。将合并的有机部分以5%氢氧化钠(100mL)、随后盐水(100mL)洗涤,经无水硫酸钠干燥,再于旋转蒸发器上减压蒸发,得到粗的酰胺中间体3。

[0301] 将粗产物通过快速柱色谱(使用230-400目筛硅胶作为固定相,以及10-50%乙酸乙酯-己烷作为流动相)进行纯化,获得纯的3-(4,5,6,7-四氢噻吩并[3,2-c]吡啶-5-羰基)苯甲酸甲酯(12g,39.8mmol,71.7%产率)。

[0302] ii.(3-((6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苯基)甲醇(中间体4)

[0303] 将$LiAlH_4$(3.02g,80mmol)分成小份于25℃加至3-(4,5,6,7-四氢噻吩并[3,2-c]吡啶-5-羰基)苯甲酸甲酯中间体3(12g,39.8mmol)的无水THF(100mL)溶液中。将反应混合物于回流下搅拌3小时。反应的进展通过TLC通过使用流动相30%乙酸乙酯/己烷监测。将水性硫酸钠悬浮液逐滴加至反应混合物中以淬灭过量的$LiAlH_4$。将乙酸乙酯(150mL)加至反应混合物中,再回流30分钟,再弃去乙酸乙酯,此过程重复三次以确保硫酸锂和氢氧化铝的白色块中无产物。将合并的有机部分经无水硫酸钠干燥,再于旋转蒸发器上减压蒸发,得到淡黄色粘稠块状的粗产物中间体4。

[0304] 将粗的醇中间体4通过快速柱色谱(使用230-400目筛硅胶作为固定相,以及10-50%乙酸乙酯-己烷作为流动相)进行纯化,得到纯的(3-((6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苯基)甲醇中间体4(5.41g,20.86mmol,52.4%产率)。

[0305] iii.(S)-3-(4-((3-((6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸(1)

[0306] 将三乙胺(0.258mL,1.851mmol)、甲磺酰氯(141mg,1.234mmol)先后于0℃加至(3-((6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苯基)甲醇中间体4(0.16g,0.617mmol)的5mL无水四氢呋喃溶液中。将反应混合物于25℃搅拌1小时。反应的进展通过TLC监测。将反应混合物倒至冰水(25mL)中,再以二氯甲烷(3×25mL)萃取。将合并的有机部分经无水硫酸钠干燥,再于旋转蒸发器上减压蒸发,得到淡黄色粘稠块状的甲磺酸3-((6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄酯中间体(5)。

[0307] 将碳酸铯(603mg,1.851mmol)、甲磺酸3-((6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄酯5的2mL乙腈溶液先后于25℃加至(S)-3-(4-羟基苯基)己-4-炔酸甲酯中间体6(162mg,0.740mmol)的乙腈(5.00mL)溶液中。将反应混合物于75℃搅拌3小时。反应的进展通过TLC监测。反应完全后,将挥发物减压蒸出。将反应混合物倒至冰水(25mL)中,再将产物以二氯甲烷(3×25mL)萃取。将合并的有机部分经无水硫酸钠干燥,再于旋转蒸发器上减压蒸发,得到淡黄色粘稠块状的粗产物。将含醚盐酸盐溶液加至粗产物中,将醚蒸出,再将残留物以乙酸乙酯研磨得到65mg(S)-3-(4-((3-((6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸甲酯盐酸盐中间体(7)。将酯盐酸盐中间体7(60mg,0.121mmol)使用THF(2mL)与MeOH(1mL)的混合物水解,于25℃加入氢氧化钠(24.19mg,

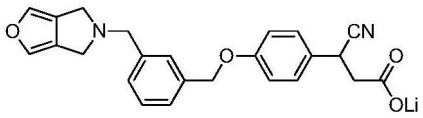
0.605mmol)的水(1mL)溶液。将反应混合物于25℃搅拌12小时。反应的进展通过TLC监测。反应完全后,将挥发物蒸出,将残留物用冰水(5mL)处理,调整pH至约4(1N HCl),以二氯甲烷(3×25mL)萃取,再经无水硫酸钠干燥。将溶剂于旋转蒸发器上减压蒸发,得到粗产物。将粗的酸通过制备性TLC进行纯化,得到(S)-3-(4-((3-((6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)已-4-炔酸1(42毫g,0.094mmol,78%产率)。

[0308] ^{1}H NMR(DMSO-d_6,400MHz)δ7.42(s,1H),7.37-7.24(m,6H),6.94(d,J=8.4Hz,2H),6.75(d,J=5.2Hz,1H),5.07(s,2H),3.94(m,1H),3.68(s,2H),3.43(s,2H),2.78-2.72(m,4H),2.57-2.55(m,2H),1.77(d,J=1.6Hz,3H);ESIMS:446.2$(M+H)^+$。

[0309] 下列化合物可通过按照一般方案1和上述实施例1中所述的方法,包括本领域的技术人员范围内的适当修饰而制得。

[0310] 实施例2

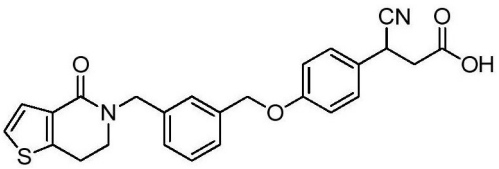
[0311] 3-(4-((3-((4H-呋喃并[3,4-c]吡咯-5(6H)-基)甲基)苄基)氧基)苯基)-3-氰基丙酸锂

[0312] 

[0313] ^{1}H NMR(DMSO-d_6,400MHz)δ:7.44(s,1H),7.35-7.28(m,7H),6.98(d,J=8.8Hz,2H),6.09(s,2H),4.27(dd,J=6.4,8.4Hz,1H),3.86(s,2H),3.57(s,4H),2.53-2.41(m,1H),2.33-2.32(m,1H)

[0314] 实施例3

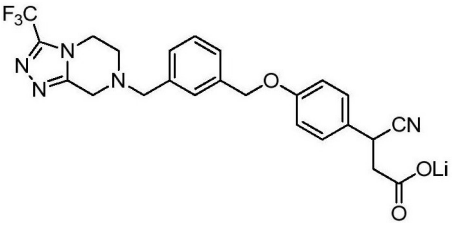
[0315] 3-氰基-3-(4-((3-((4-氧代-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)丙酸

[0316] 

[0317] ^{1}H NMR:($CDCl_3$,400MHz):-7.47(d,J=5.2Hz,1H),7.37-7.23(m,6H),7.11(d,J=5.2Hz,1H),6.92(d,J=8.8Hz,2H),5.06(s,2H),4.77-4.68(m,2H),4.19(t,J=7.6Hz,1H),3.55(t,J=6.8Hz,2H),3.06-2.98(m,3H),2.88-2.82(m,1H)

[0318] 实施例4

[0319] 3-氰基-3-(4-((3-((3-(三氟甲基)-5,6-二氢-[1,2,4]三唑并[4,3-a]吡嗪-7(8H)-基)甲基)苄基)氧基)苯基)丙酸锂

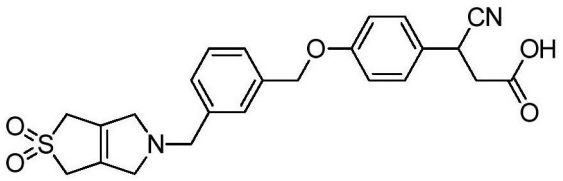
[0320] 

[0321] ^{1}H NMR(CD_3OD,400MHz)δ:7.48(s,1H),7.39-7.36(m,3H),7.31(dd,=2,6.8Hz,2H),6.98(dd,J=2.4,6.8Hz,2H),5.10(s,2H),4.30-4.26(m,1H),4.18(t,J=5.2Hz,2H),3.89(s,2H),3.83(s,2H),2.97(t,J=5.6Hz,2H),2.74(dd,J=8.8,15.6Hz,1H),2.58(dd,J

＝8.8,15.6Hz,1H).

[0322] 实施例5

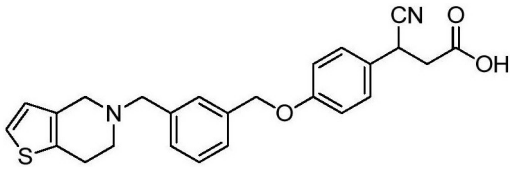
[0323] 3-氰基-3-(4-((3-((2,2-二氧化-1H-噻吩并[3,4-c]吡咯-5(3H,4H,6H)-基)甲基)苄基)氧基)苯基)丙酸

[0324] 

[0325] ^{1}H NMR(CD_3OD,400MHz)δ:7.66(d,1H),7.60-7.51(m,3H),7.35(dd,J＝2,6.8Hz,2H),7.03(dd,J＝2,6.4Hz,2H),5.17(s,2H),4.60(s,2H),4.35-4.31(m,1H),4.28(s,4H),3..94(s,4H),2.99(dd,J＝8.4,16.8Hz,1H),2.85(dd,J＝6.4,16.4Hz,1H).

[0326] 实施例6

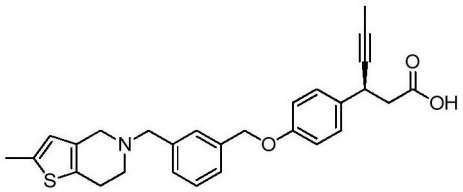
[0327] 3-氰基-3-(4-((3-((6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)丙酸

[0328] 

[0329] ^{1}H NMR($CDCl_3$,400MHz)δ:7.58(s,1H),7.37-7.32(m,2H),7.22-7.16(m,4H),6.88(dd,J＝2,6.8Hz,2H),6.71(d,J＝5.2Hz,1H),5.00(s,2H),4.18-4.14(m,1H),3.99(s,2H),3.88(s,2H),3.19-3.16(m,2H),3.03-3.00(m,2H),2.87-2.81(m,1H),2.70-2.64(m,1H).

[0330] 实施例7

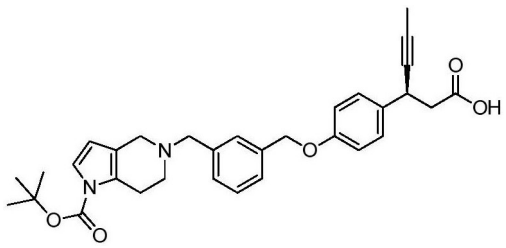
[0331] (S)-3-(4-((3-((2-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0332] 

[0333] ^{1}H NMR($CDCl_3$,400MHz)δ:7.38-7.25(m,6H),6.88(d,J＝5.2Hz,2H),6.33(s,1H),5.04-4.98(m,2H),4.05-4.00(m,1H),3.80-3.71(m,2H),3.64-3.55(m,2H),2.92-2.61(m,6H),2.39(s,3H),1.82(d,J＝2.4Hz,3H).

[0334] 实施例8

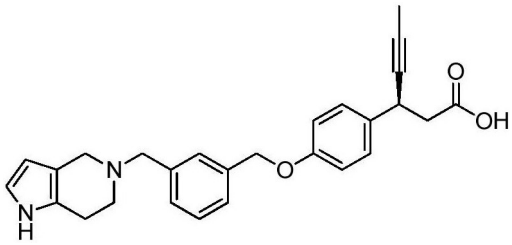
[0335] (S)-3-(4-((3-((1-(叔丁氧基羰基)-6,7-二氢-1H-吡咯并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0336] 

[0337] ^{1}H NMR($CDCl_3$,400MHz)δ:7.47-7.38(m,4H),7.27(d,J=8.8Hz,2H),7.18(d,J=3.2Hz,1H),6.86(d,J=8.8Hz,2H),5.94(d,J=3.2Hz,2H),5.05(s,2H),4.08(s,2H),4.05-4.01(m,1H),3.85($s_{(br)}$,2H),3.30-3.15(m,4H),2.78(dd,J=8.8,15.2Hz,1H),2.65(dd,J=8,15.2Hz,1H),1.80(d,J=2.4Hz,3H),1.59(s,9H).

[0338] 实施例9

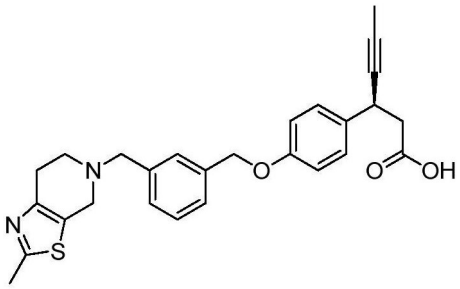
[0339] (S)-3-(4-((3-((6,7-二氢-1H-吡咯并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0340] 

[0341] ^{1}H NMR($CDCl_3$,400MHz)δ:8.51(s,1H),7.42-7.33(m,4H),7.25(d,J=8.9Hz,2H),6.81(d,J=9Hz,2H),6.63(t,J=2.4Hz,1H),5.89(t,J=2.4Hz,1H),5.06(s,2H),4.07-3.99(m,3H),3.87(s,2H),3.08($s_{(br)}$,2H),2.80-2.74(m,3H),2.61(m,1H),1.80(d,J=2.4Hz,3H)

[0342] 实施例10

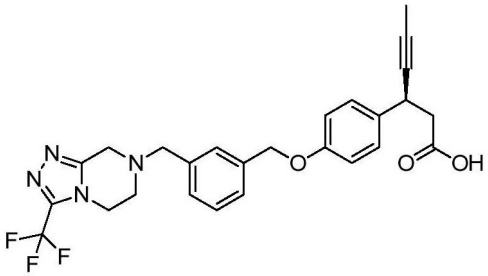
[0343] (S)-3-(4-((3-((2-甲基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0344] 

[0345] ^{1}H NMR($CDCl_3$,400MHz)δ:7.41-7.38(m,4H),7.27(d,J=8.4Hz,2H),6.85(d,J=8.4Hz,2H),5.19-5.08(m,2H),4.04-3.91(m,1H),3.75($s_{(br)}$,4H),2.87-2.69(m,4H),2.66(s,3H),2.58-2.41(m,2H),1.80(d,J=2.4Hz,3H)

[0346] 实施例11

[0347] (S)-3-(4-((3-((3-(三氟甲基)-5,6-二氢-[1,2,4]三唑并[4,3-a]吡嗪-7(8H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

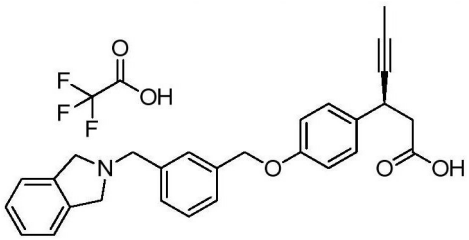
[0348] 

[0349] ^{1}H NMR($CDCl_3$,400MHz)δ:7.40-7.26(m,6H),6.86(d,J=8.8Hz,2H),5.12(dd,J=

12.8,18.4Hz,2H),4.15-4.12(m,2H),4.04-3.99(m,1H),3.86-3.69(m,4H),3.00-2.85(m,2H),2.82(dd,J＝6.8,15.2Hz,1H),2.65(dd,J＝6.8,15.2Hz,1H),1.82(J＝2Hz,3H).

[0350] 实施例12

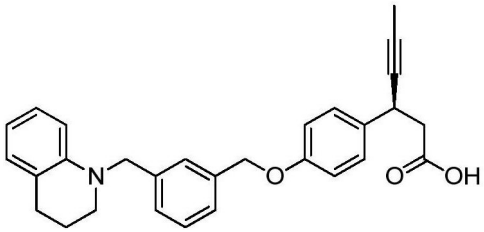
[0351] (S)-3-(4-((3-(异吲哚啉-2-基甲基)苄基)氧基)苯基)己-4-炔酸三氟乙酸盐

[0352] 

[0353] ^{1}H NMR($CDCl_3$,400MHz)δ:7.52-7.44(m,2H),7.42-7.34(m,4H),7.31-7.26(m,4H),6.85(d,J＝8.4Hz,2H),5.09(s,2H),4.70(s,2H),4.34-4.29(m,2H),4.04-4.00(m,1H),3.32(s,2H),2.85-2.78(m,1H),2.70-2.63(m,1H),1.80(d,J＝2.4Hz,3H).

[0354] 实施例13

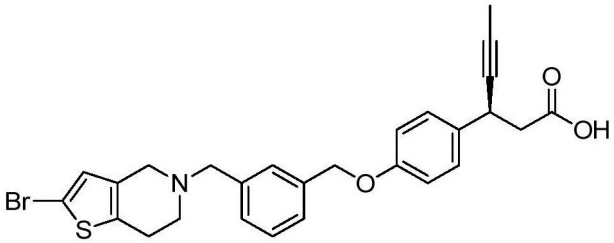
[0355] (S)-3-(4-((3-((3,4-二氢喹啉-1(2H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0356] 

[0357] ^{1}H NMR($CDCl_3$,400MHz)δ:7.32-7.22(m,6H),6.99-6.90(m,4H),6.60-6.57(m,1H),6.50(d,J＝8.4Hz,2H),5.02(s,2H),4.49(s,2H),4.06($s_{(br)}$,1H),3.36($s_{(br)}$,2H),3.02-2.78(m,4H),2.02-2.00(m,2H),1.80(s,3H).

[0358] 实施例14

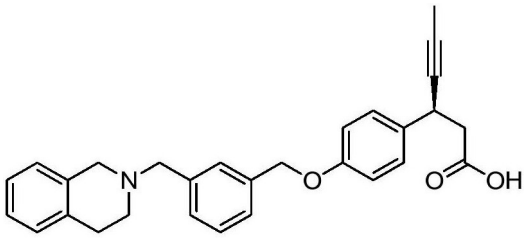
[0359] (S)-3-(4-((3-((2-溴-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0360] 

[0361] ^{1}H NMR($CDCl_3$,400MHz)δ:7.42-7.36(m,3H),7.32-7.25(m,3H),6.90(d,J＝8.4Hz,2H),6.66(s,1H),5.05(s,2H),4.06-4.02(m,1H),3.94-3.92(m,2H),3.68($s_{(br)}$,2H),3.01($s_{(br)}$,2H),2.88-2.85(m,2H),2.80-2.74(m,1H),2.69-2.63(m,1H),1.83(d,J＝2.4Hz,3H).

[0362] 实施例15

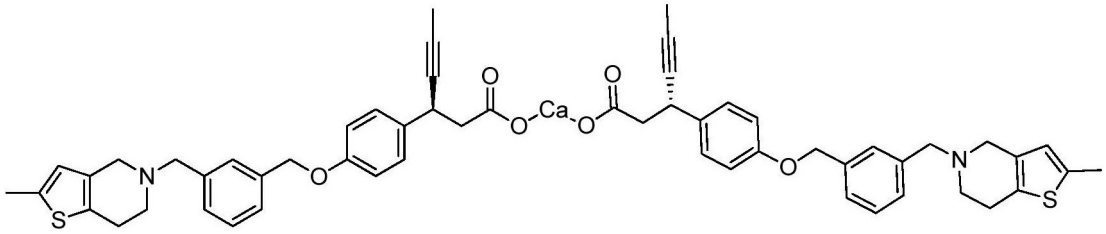
[0363] (S)-3-(4-((3-((3,4-二氢异喹啉-2(1H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0364] 

[0365] ^{1}H NMR($CDCl_3$,400MHz)δ:7.47(s,1H),7.42-7.27(m,5H),7.22-7.15(m,3H),7.05-7.02(m,1H),6.93(d,J＝8.8Hz,2H),5.10-5.03(m,2H),4.10-4.06(m,1H),2.02-2.00(m,2H),1.80(s,3H).,3.87-3.80(m,4H),2.96-2.86(m,4H),2.86-2.80(m,1H),2.78-2.74(m,1H),1.86(d,J＝2.4Hz,3H).

[0366] 实施例16

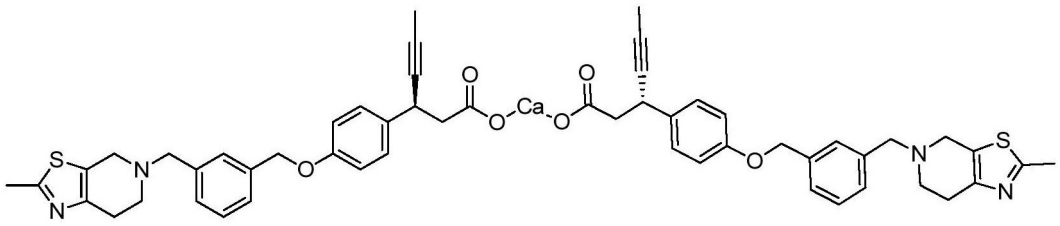
[0367] 二((S)-3-(4-((3-((2-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸)钙

[0368] 

[0369] ^{1}H NMR(DMSO-d_6,400MHz)δ:7.40(s,1H),7.35-7.23(m,5H),6.88(d,J＝8.4Hz,2H),6.41(s,1H),5.04(s,2H),4.00($s_{(br)}$,1H),3.64(s,2H),3.32(s,2H),2.68(s,4H),2.40-2.37(m,1H),2.33(s,3H),2.27-2.21(m,1H),1.74(d,J＝2Hz,3H).

[0370] 实施例17

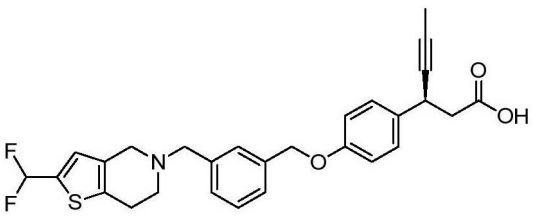
[0371] 二((S)-3-(4-((3-((2-甲基-6,7-二氢噻唑并[4,5-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸)钙

[0372] 

[0373] ^{1}H NMR(DMSO-d_6,400MHz)δ:7.41(s,1H),7.34-7.23(m,5H),6.89(d,J＝8.8Hz,2H),5.01(s,2H),4.05-3.99(m,1H),3.68(s,2H),3.56(s,2H),2.76-2.74(m,2H),2.68($s_{(br)}$,2H),2.56(s,3H),2.40-2.36(m,1H),2.26-2.22(m,1H),1.73(d,J＝2.4Hz,3H).

[0374] 实施例18

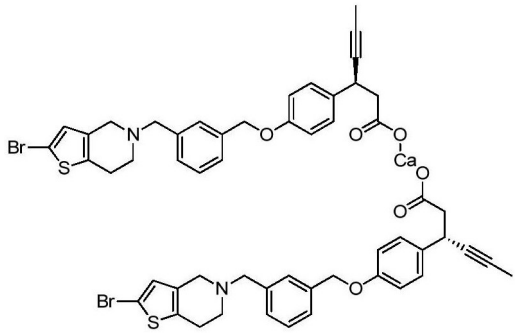
[0375] (S)-3-(4-((3-((2-(二氟甲基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0376] 

[0377] ^{1}H NMR($CDCl_3$,400MHz)δ:7.39-7.26(m,6H),6.91-6.59(m,4H),5.03(s,2H),4.12-4.10(m,1H),3.73(s,2H),3.55(s,2H),2.88-2.64(m,6H),1.82(d,J＝2.4Hz,3H).

[0378] 实施例19

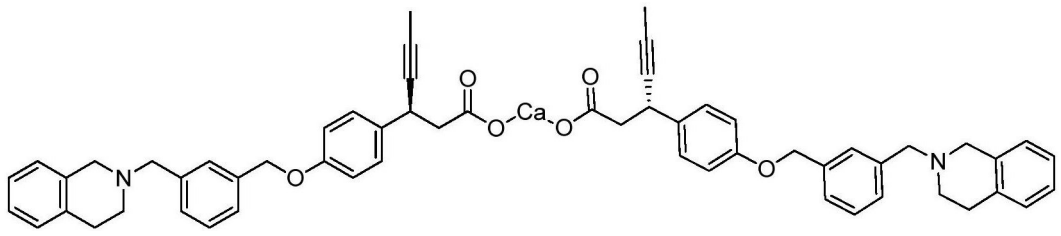
[0379] (S)-3-(4-((3-((2-溴-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸钙

[0380] 

[0381] ^{1}H NMR(DMSO-d_6,400MHz)δ:7.41(s,1H),7.37-7.24(m,5H),6.93-6.89(m,3H),5.06(s,2H),3.96-3.94(m,1H),3.66(s,2H),3.38(s,2H),2.71(s,4H),2.49-2.32(m,2H),1.76(d,J＝2.4Hz,3H).

[0382] 实施例20

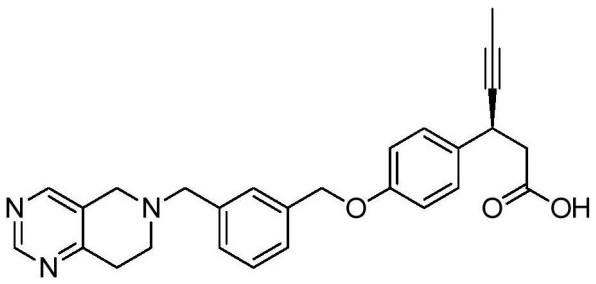
[0383] (S)-3-(4-((3-((3,4-二氢异喹啉-2(1H)-基)甲基)苄基)氧基)苯基)己-4-炔酸钙

[0384] 

[0385] ^{1}H NMR(DMSO-d_6,400MHz)δ:7.37(s,1H),7.35-7.23(m,5H),7.11-7.07(m,3H),6.98-6.97(m,1H),6.89(d,J＝8.8Hz,2H),5.05(s,2H),3.99-3.97(m,1H),3.64(s,2H),3.52(s,2H),2.79-2.77(m,2H),2.65-2.64(m,2H),2.42-2.36(m,1H),2.28-2.22(m,1H),1.74(d,J＝2.4Hz,3H).

[0386] 实施例21

[0387] (S)-3-(4-((3-((7,8-二氢吡啶并[4,3-d]嘧啶-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

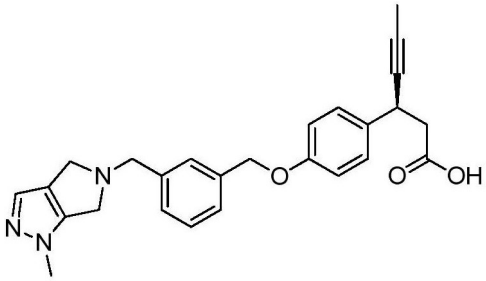
[0388] 

[0389] ^{1}H NMR($CDCl_3$,400MHz)δ:8.94(s,1H),8.30(s,1H),7.45(s,1H),7.38-7.25(m,5H),6.86(dd,J＝2,6.8Hz,2H),5.15-5.09(m,2H),4.06-4.03(m,1H),3.78-3.62(m,4H),

2.89-2.73(m,6H),1.82(d,J＝2.4Hz,3H).

[0390] 实施例22

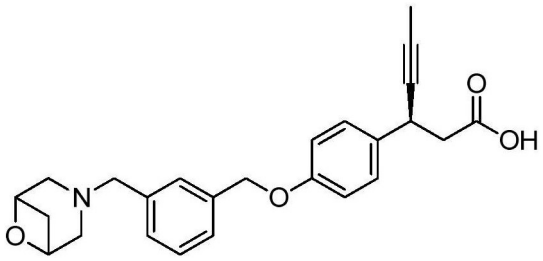
[0391] (S)-3-(4-((3-((1-甲基吡咯并[3,4-c]吡唑-5(1H,4H,6H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0392] 

[0393] ^{1}H NMR($CDCl_3$,400MHz)δ:7.43-7.24(m,6H),7.17(s,1H),6.88(td,J＝5.2,8.4Hz,2H),5.03(s,2H),4.07(s,2H),4.02-3.97(m,5H),3.75(s,3H),2.78-2.72(m,1H),2.66-2.60(m,1H),1.80(d,J＝2.4Hz,3H).

[0394] 实施例23

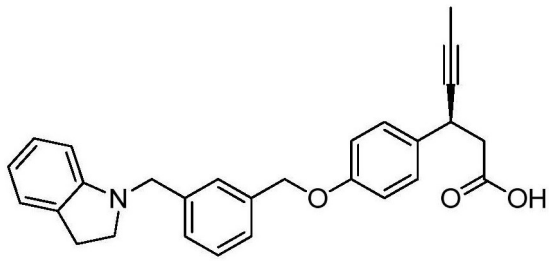
[0395] (3S)-3-(4-((3-(6-氧杂-3-氮杂二环[3.1.1]庚-3-基甲基)苄基)氧基)苯基)己-4-炔酸

[0396] 

[0397] ^{1}H NMR($CDCl_3$,400MHz)δ:7.53-7.25(m,6H),6.89(d,J＝8.4Hz,2H),5.09(s,2H),4.54-4.52(m,2H),4.05-3.93(m,3H),3.24-2.94(m,4H),2.81-2.75(m,1H),2.69-2.63(m,1H),2.42(d,J＝8.8Hz,2H),1.83(d,J＝2.4Hz,3H).

[0398] 实施例24

[0399] (S)-3-(4-((3-(吲哚啉-1-基甲基)苄基)氧基)苯基)己-4-炔酸

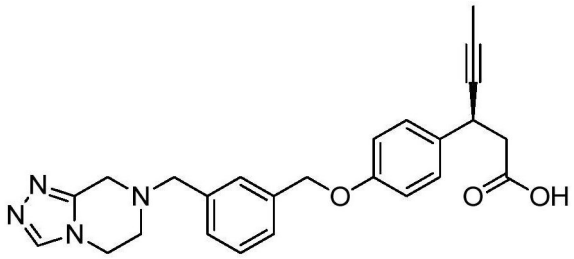
[0400] 

[0401] ^{1}H NMR($CDCl_3$,400MHz)δ:7.41(s,1H),7.37-7.25(m,5H),7.10-7.05(m,2H),6.93-6.89(m,2H),6.70-6.66(m,1H),6.51(d,J＝7.6Hz,1H),5.03(s,2H),4.26(s,2H),4.07-4.02(m,1H),3.30(t,J＝8.4Hz,2H),2.96(t,J＝8.4Hz,2H),2.83-2.76(m,1H),2.73-2.67(m,1H),1.83(d,J＝2.4Hz,3H).

[0402] 实施例25

[0403] (S)-3-(4-((3-((5,6-二氢-[1,2,4]三唑并[4,3-a]吡嗪-7(8H)-基)甲基)苄基)

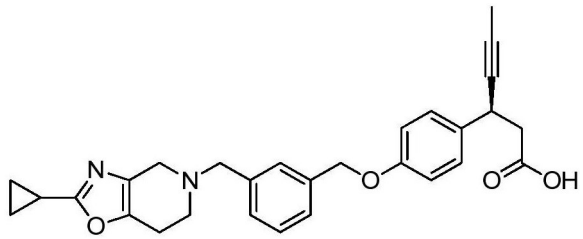
氧基)苯基)己-4-炔酸

[0404] 

[0405] ^{1}H NMR(CD_3OD,400MHz)δ:8.50(s,1H),7.49(s,1H),7.40-7.35(m,3H),7.28(d,J=6.8Hz,2H),6.93(d,J=6.8Hz,2H),5.01(s,2H),4.15-4.11(m,2H),4.00-3.97(m,1H),3.87-3.83(m,4H),2.97-2.94(m,2H),2.66-2.62(m,2H),1.81(d,J=2.4Hz,3H).

[0406] 实施例26

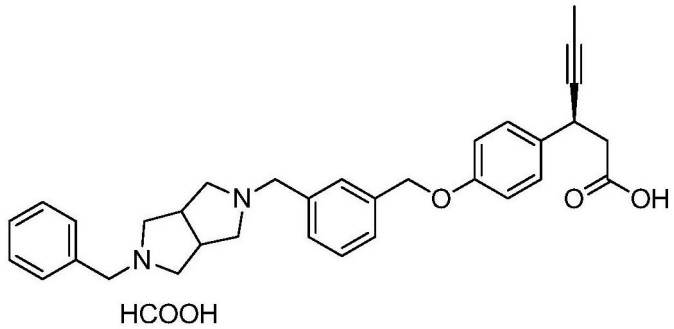
[0407] (S)-3-(4-((3-((2-环丙基-6,7-二氢噁唑并[4,5-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0408] 

[0409] ^{1}H NMR($CDCl_3$,400MHz)δ:7.52-7.20(m,6H),6.81(d,J=8.8Hz,2H),5.21-5.12(m,2H),4.00-3.95(m,1H),3.78-3.67(m,2H),3.23-2.59(m,8H),2.04-1.97(m,1H),1.81(d,J=2.4Hz,3H),1.00-0.96(m,4H).

[0410] 实施例27

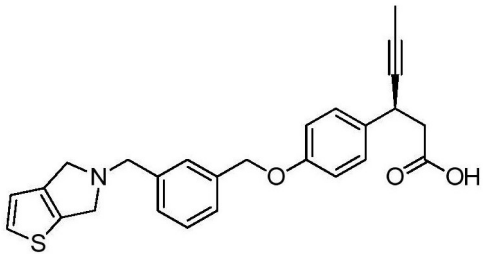
[0411] (3S)-3-(4-((3-((5-苄基六氢吡咯并[3,4-c]吡咯-2(1H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,甲酸盐

[0412] 

[0413] ^{1}H NMR($CDCl_3$,400MHz)δ:8.45($s_{(br)}$,0.78H,HCOOH),7.52-7.15(m,9H),7.16(d,J=7.2Hz,1H),6.78(dd,J=2.8,11.6Hz,2H),5.12(s,2H),4.05-4.00(m,1H),3.93-3.68(m,4H),3.04-3.01(m,2H),2.83-2.78(m,3H),2.68-2.64(m,1H),2.58-2.40(m,6H),1.77(d,J=2.4Hz,3H).

[0414] 实施例28

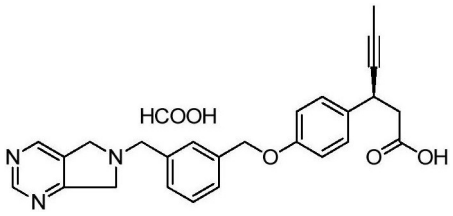
[0415] (S)-3-(4-((3-((4H-噻吩并[2,3-c]吡咯-5(6H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0416] 

[0417] ^{1}H NMR($CDCl_3$,400MHz)δ:7.43(s,1H),7.39-7.24(m,6H),6.86(d,J＝8.4Hz,2H),6.80(d,J＝5.2Hz,1H),5.06-4.99(m,2H),4.17-4.00(m,7H),2.77-2.71(m,1H),2.65-2.59(m,1H),1.80(d,J＝2.4Hz,3H).

[0418] 实施例29

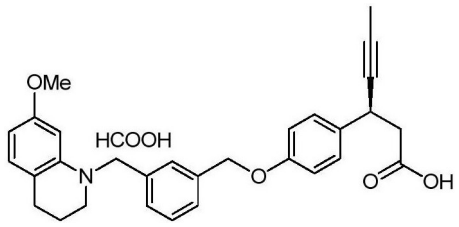
[0419] 6-(3-((4-((S)-1-羧基戊-3-炔-2-基)苯氧基)甲基)苄基)-6,7-二氢-5H-吡咯并[3,4-d]嘧啶-6-鎓甲酸盐

[0420] 

[0421] ^{1}HNMR($CDCl_3$,400MHz)δ:8.98(s,1H),8.63(s,1H),8.37(s,1H),7.45(s,1H),7.37-7.31(m,3H),7.25(d,J＝8.8Hz,2H),6.93(d,J＝8.8Hz,2H),5.08(s,2H),3.95-3.90(m,7H),2.55-2.52(m,1H),2.12(s,3H).

[0422] 实施例30

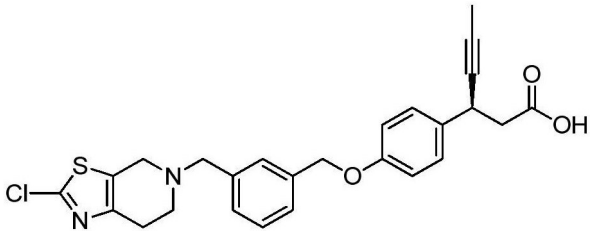
[0423] 1-(3-((4-((S)-1-羧基戊-3-炔-2-基)苯氧基)甲基)苄基)-7-甲氧基-1,2,3,4-四氢喹啉-1-鎓甲酸盐

[0424] 

[0425] ^{1}HNMR($CDCl_3$,400MHz)δ8.21(s),0.28(甲酸盐),7.33-7.28(m,3H),7.25(d,J＝8.8Hz,2H),7.19(d,J＝7.2Hz,1H),6.91(d,J＝8.4Hz,2H),6.55(d,J＝2.8Hz,1H),6.51-6.48(dd,J＝8.8Hz&2.8Hz,1H),6.39(d,J＝8.8Hz,1H),5.0(s,2H),4.39(s,2H),3.95-3.90(m,3H),3.60(m,4H),3.24(t,3H),2.70(m,2H),2.58(d,2H),2.06(t,2H),1.07-1.08(s,3H).

[0426] 实施例31

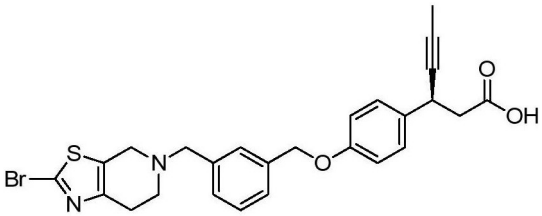
[0427] (S)-3-(4-((3-((2-氯-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0428] 

[0429] ^{1}H NMR($CDCl_3$,400MHz)δ:7.41-7.30(m,3H),7.35-7.27(m,3H),6.90(d,J＝8.4Hz,2H),5.07(s,1H),4.07-4.02(m,1H),3.82(s,2H),3.72(s,2H),2.98-2.95(m,2H),2.86-2.68(m,5H),1.83(d,J＝2.4Hz,3H).

[0430] 实施例32

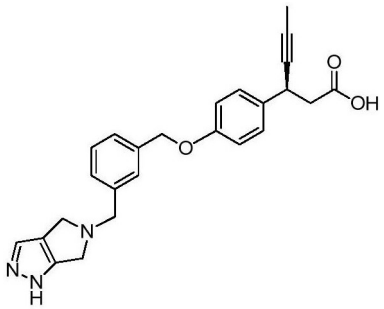
[0431] (S)-3-(4-((3-((2-溴-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0432] 

[0433] ^{1}H NMR($CDCl_3$,400MHz)δ:7.39-7.35(m,3H),7.29-7.26(m,3H),6.90(d,J＝8.4Hz,2H),5.05(s,2H),4.06-4.01(m,1H),3.79(s,2H),3.70(s,2H),2.92-2.66(m,6H),1.82(d,J＝2.4Hz,3H).

[0434] 实施例33

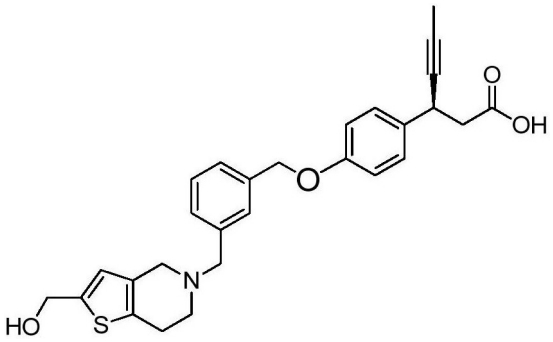
[0435] (S)-3-(4-((3-(吡咯并[3,4-c]吡唑-5(1H,4H,6H)-基甲基)苄基)氧基)苯基)己-4-炔酸

[0436] 

[0437] ^{1}H-NMR($CDCl_3$,400MHz):-δ7.32-7.53(m,3H),7.19-7.29(m,4H),6.82-6.84(m,2H),5.16(s,2H),3.90-4.06(m,5H),3.57(s,2H),2.80-2.85(m,1H),1.81(s,3H);

[0438] 实施例34

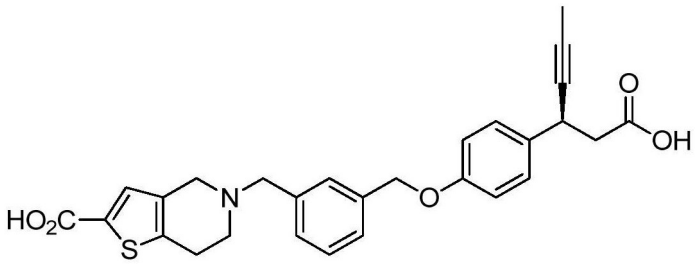
[0439] (S)-3-(4-((3-((2-(羟基甲基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0440] 

[0441] ^{1}H-NMR(DMSO,400MHz):-δ7.38(s,1H),7.23-7.33(m,5H),6.92(d,J＝8.8Hz,2H),6.56(s,1H),5.35(s,2H),3.91-3.94(m,1H),3.72-3.84(m,4H),3.40-3.50(m,2H(合并的),2.86-2.94(m,2H),2.73-2.76(m,2H),2.50-2.58(m,2H),1.76(s,3H);

[0442] 实施例35

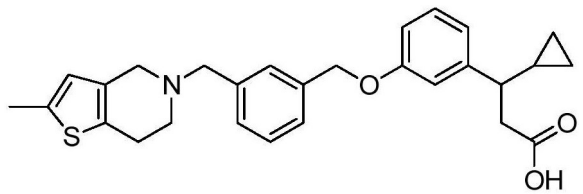
[0443] (S)-5-(3-((4-(1-羧基戊-3-炔-2-基)苯氧基)甲基)苄基)-4,5,6,7-四氢噻吩并[3,2-c]吡啶-2-羧酸

[0444] 

[0445] ^{1}H NMR:(DMSO-d_6,400MHz):-7.42(s,1H),7.34-7.31(m,2H),7.27-7.26(m,1H),7.22(d,J＝8.8Hz,2H),6.99(s,1H),6.90(d,J＝8.8Hz,2H),5.09(s,2H),3.95-3.91(m,1H),3.65(s,2H),3.29(s,2H),2.74-2.71(m,4H),2.63-2.52(m,2H),1.76(s,3H).

[0446] 实施例36

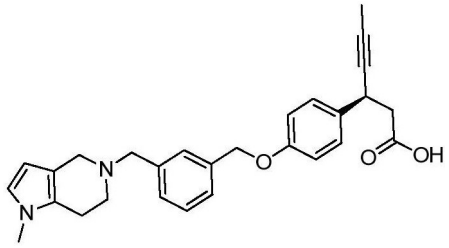
[0447] 3-环丙基-3-(3-((3-((2-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)丙酸

[0448] 

[0449] ^{1}H NMR:(DMSO-d_6,400MHz):-7.46(s,1H),7.37-7.31(m,3H),7.14(t,J＝8Hz,2H),6.81-6.79(m,2H),6.44(s,1H),5.05(s,2H),3.78(s,2H),3.32(s,2H),2.82-2.74(m,4H),2.49-2.44(m,2H),2.36-2.34(m,4H),1.30-1.28(m,1H),0.49-0.47(m,1H),0.27-0.24(m,2H),0.004-0.002(m,1H).

[0450] 实施例37

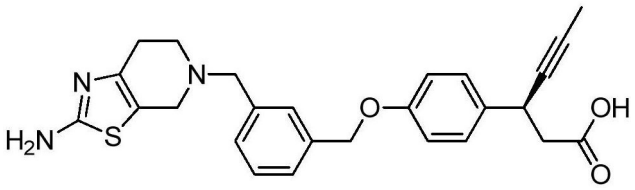
[0451] (S)-3-(4-((3-((1-甲基-6,7-二氢-1H-吡咯并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0452] 

[0453] ^{1}H NMR($CDCl_3$,400MHz):δ7.53(s,1H),7.47-7.32(d,3H),7.24-7.12(m,2H),6.85(d,2H),6.51(d,1H),5.58(d,1H),5.0-4.95(d,2H),3.9-4.1(m,1H),3.87(d,1H),3.80(d,1H),3.48(s,3H),2.9-3.1(m,3H),1.08(m,3H).

[0454] 实施例38

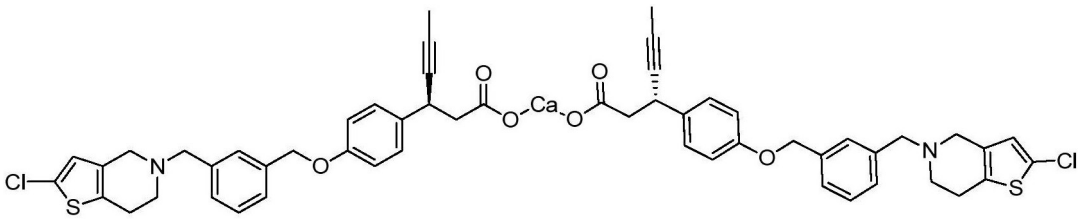
[0455] (S)-3-(4-((3-((2-氨基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0456] 

[0457] ^{1}H NMR(DMSO-d_6,400MHz):δ8.23(s,1H),7.40(s,1H),7.35(d,2H),7.32-7.24(m,3H),6.93(d,J=8.4Hz,2H),6.68(s,2H),5.06(s,2H),3.9-4.0(m,1H),3.35(s,3H),2.70-2.66(m,2H),2.58(d,2H),2.44(d,3H).

[0458] 实施例39

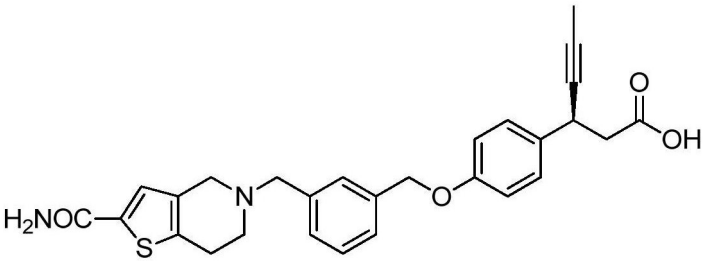
[0459] (S)-3-(4-((3-((2-氯-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸钙

[0460] 

[0461] ^{1}H NMR($CDCl_3$,400MHz)δ:7.39(s,1H),7.36-7.23(m,5H),6.88(d,J=8.8Hz,2H),6.78(s,1H),5.04(s,2H),3.99($s_{(br)}$,1H),3.65(s,2H),3.34(s,2H),2.70($s_{(br)}$,4H),2.37-2.31(m,1H),2.25-2.19(m,1H),1.73(d,J=2.4Hz,3H).

[0462] 实施例40

[0463] (S)-3-(4-((3-((2-氨基甲酰基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

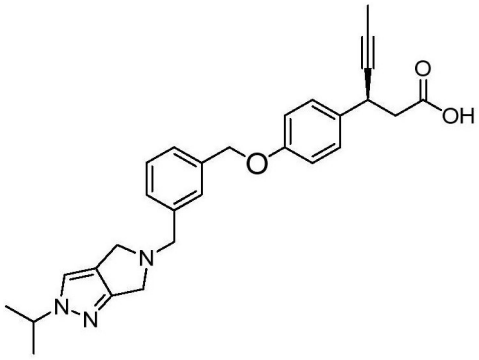
[0464] 

[0465] ^{1}H NMR:(DMSO-d_6,400MHz):-12.22(br s,1H),7.76(br s,1H),7.42(s,1H),7.37-

7.25(m,7H),6.94(d,J＝8.8Hz,2H),5.07(s,2H),3.95-3.91(m,1H),3.68(s,2H),3.43(s,2H),2.78-2.76(m,2H),2.72-2.70(m,2H),2.60-2.57(m,2H),1.77(s,3H).

[0466] 实施例41

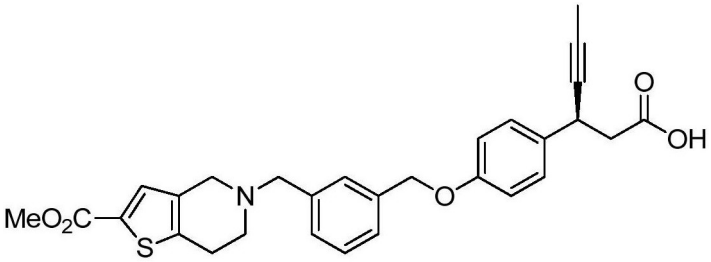
[0467] (S)-3-(4-((3-((2-异丙基吡咯并[3,4-c]吡唑-5(2H,4H,6H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0468] 

[0469] ^{1}H-NMR(DMSO,400MHz):δ12.25(m,2H),7.48-7.51(m,2H),7.39(s,3H),7.27(d,J＝8.8Hz,2H),6.95(d,J＝8.8Hz,2H),5.09(s,2H),4.40-4.47(m,1H),4.10-4.20(m,2H),3.70-3.90(m,4H),2.66-2.66(m,2H),1.77(s,3H),1.36-1.38(m,6H);

[0470] 实施例42

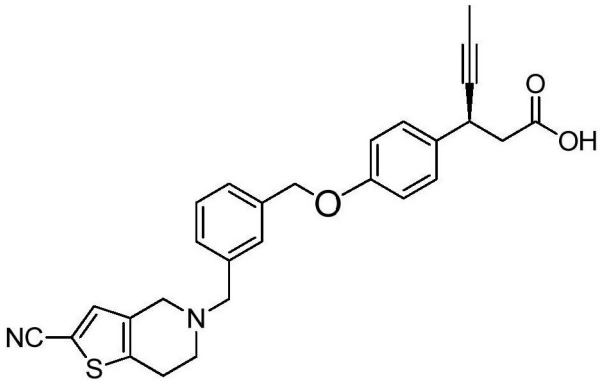
[0471] (S)-3-(4-((3-((2-(甲氧基羰基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0472] 

[0473] ^{1}H NMR:(DMSO-d_6,400MHz):-12.22(br s,1H),7.50(s,1H),7.41(s,1H),7.37-7.24(m,5H),6.92(d,J＝8.4Hz,2H),5.07(s,2H),3.95-3.91(m,1H),3.77(s,3H),3.68(s,2H),3.46(s,2H),2.84-2.81(m,2H),2.74-2.70(m,2H),2.58-2.53(m,2H),1.90(s,3H).

[0474] 实施例43

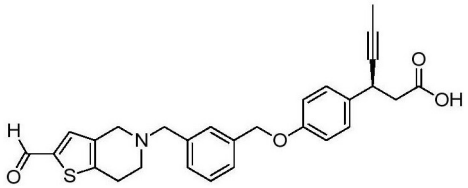
[0475] (S)-3-(4-((3-((2-氰基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0476] 

[0477] ^{1}H-NMR(DMSO,400MHz):δ8.83(s,1H),7.24-7.41(m,6H),6.92-6.94(m,2H),5.09(s,2H),3.91-3.94(m,1H),3.73(s,2H),3.45(s,2H),2.86-2.94(m,2H),2.73-2.76(m,2H),2.50-2.58(m,2H),1.76(s,3H);

[0478] 实施例44

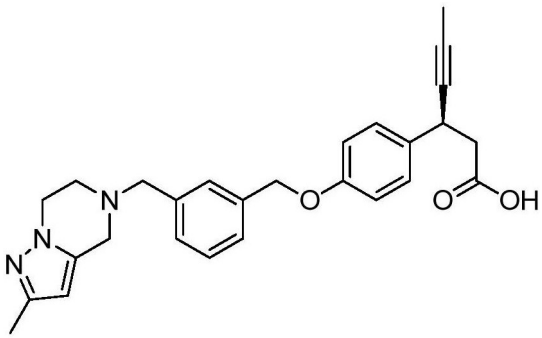
[0479] (S)-3-(4-((3-((2-甲酰基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0480] 

[0481] ^{1}H NMR:(DMSO-d_6,400MHz):-9.79(s,1H),7.70(s,1H),7.42(s,1H),7.36-7.31(m,3H),7.26-7.24(d,J＝8Hz,2H),6.94-6.92(d,J＝8Hz,2H),5.07(s,2H),3.93(br s,1H),3.70(s,2H),3.50(s,2H),2.89(s,2H),2.74(s,2H),1.76(s,3H),1.23(s,2H).

[0482] 实施例45

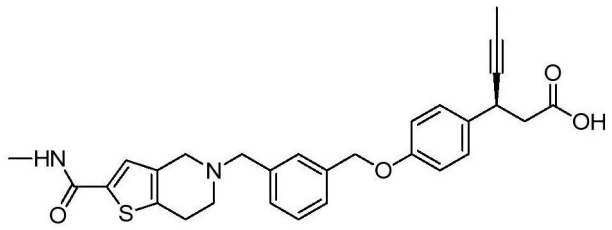
[0483] S)-3-(4-((3-((2-甲基-6,7-二氢吡唑并[1,5-a]吡嗪-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0484] 

[0485] ^{1}H NMR(DMSO-d_6,400MHz):δ7.41(s,1H),7.35(d,J＝6.4Hz,2H),7.30(m,1H),7.25(d,J＝8.8Hz,2H),6.93(d,J＝8.4Hz,2H),5.73(s,1H),5.07(s,2H),3.96-3.92(m,3H),3.68(s,2H),3.52(s,2H),2.84(t,2H),2.66(t,2H),2.08(s,3H),1.77(s,3H)

[0486] 实施例46

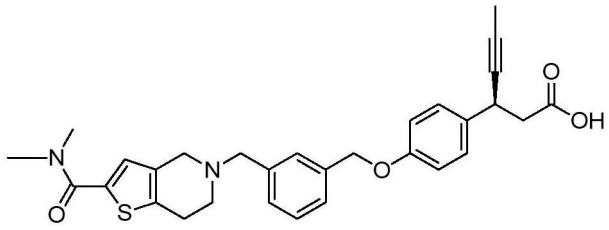
[0487] (S)-3-(4-((3-((2-(甲基氨基甲酰基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0488] 

[0489] ^{1}H NMR:(DMSO-d_6,400MHz):-7.42(s,1H),7.35-7.24(m,6H),7.1-6.93-6.91(m,2H),5.07(s,2H),3.9(m,1H),3.68(s,2H),3.41(s,2H),2.71-2.70(m,2H),2.67-2.66(m,6H),1.76(s,3H).

[0490] 实施例47

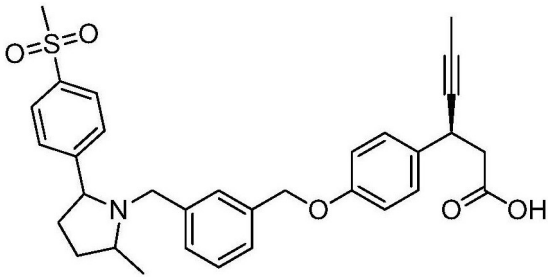
[0491] (S)-3-(4-((3-((2-(二甲基氨基甲酰基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0492] 

[0493] ^{1}H NMR:(DMSO-d_6,400MHz):-7.53(s,1H),7.40-7.22(m,4H),7.1-6.68(m,3H),5.08(s,2H),4.12-4.03(m,1H),3.78-3.71(m,2H),3.50(s,2H),3.17(s,6H),2.95-2.88(m,2H),2.83-2.63(m,2H),1.83(s,3H).

[0494] 实施例48

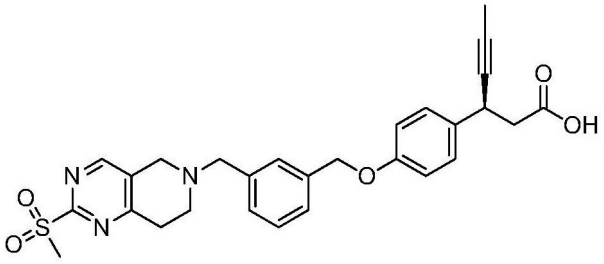
[0495] (3S)-3-(4-((3-((2-甲基-5-(4-(甲基磺酰基)苯基)吡咯烷-1-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0496] 

[0497] ^{1}H NMR($CDCl_3$,400MHz)δ:7.93-7.90(m,2H),7.82-7.76(m,2H),7.53-7.16(m,7H),6.92-6.86(m,3H),5.11-5.01(m,3H),4.45-4.30(m,1H),4.07-3.98(m,3H),3.30-3.20(m,1H),3.097-3.090(m,3H),3.03(s,1H),2.87-2.68(m,4H),2.33-1.98(m,8H),1.84-1.82(m,5H),1.62-1.60(m,4H)

[0498] 实施例49

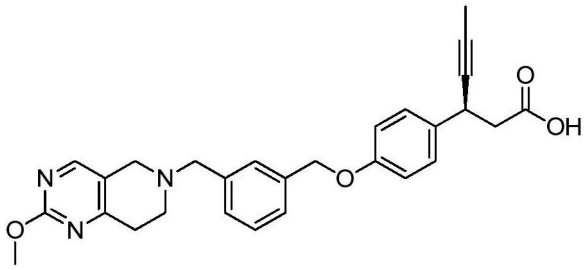
[0499] (S)-3-(4-((3-((2-(甲基磺酰基)-7,8-二氢吡啶并[4,3-d]嘧啶-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0500] 

[0501] ^{1}H NMR($CDCl_3$,400MHz)δ:8.48(s,1H),7.43-7.27(m,6H),6.91(dd,J=8.8,2Hz,2H),5.07(s,2H),4.07-4.03(m,1H),3.80(s,2H),3.72(s,2H),3.32(s,3H),3.15-3.09(m,2H),2.92-2.89(m,2H),2.84-2.78(m,1H),2.74-2.68(m,1H),1.83(d,J=2.4Hz,3H)

[0502] 实施例50

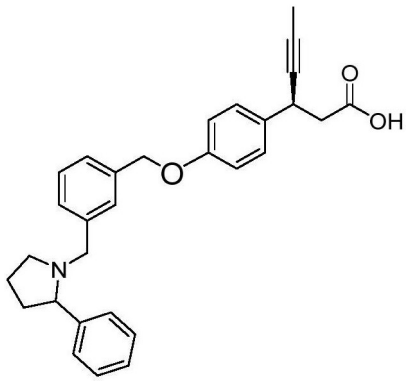
[0503] (S)-3-(4-((3-((2-甲氧基-7,8-二氢吡啶并[4,3-d]嘧啶-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0504] 

[0505] ^{1}H NMR($CDCl_3$,400MHz)δ:8.09(s,1H),7.53-7.26(m,6H),6.87(dd,J＝6.8,2Hz,2H),5.17-5.08(m,2H),4.07-4.02(m,1H),3.98(s,3H),3.75($s_{(br)}$,2H),3.58($s_{(br)}$,2H),2.88-2.63(m,6H),1.82(d,J＝2.4Hz,3H)

[0506] 实施例51

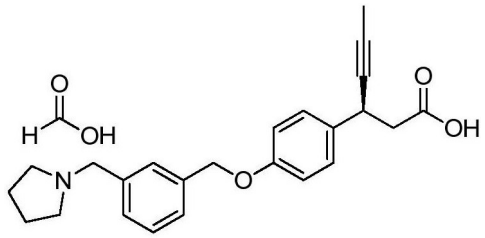
[0507] (3S)-3-(4-((3-((2-苯基吡咯烷-1-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0508] 

[0509] ^{1}H-NMR($CDCl_3$,400MHz):δ7.43-7.45(m,2H),7.21-7.35(m,9H),6.89-6.91(d,J＝8Hz,2H),5.0(s,2H),4.03(m,1H),3.81-3.85(m,1H),3.37-3.41(m,1H),3.11-3.17(m,3H),2.74-2.80(m,1H),2.64-2.69(m,1H),3.37-2.14-2.51(m,2H),1.85-1.92(m,1H),1.81(s,3H),1.71-1.75(m,2H);

[0510] 实施例52

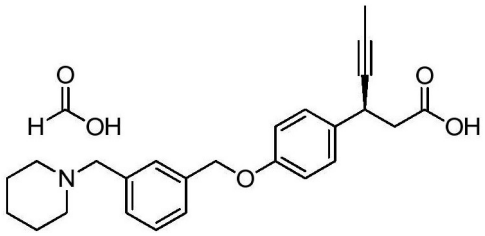
[0511] (S)-3-(4-((3-(吡咯烷-1-基甲基)苄基)氧基)苯基)己-4-炔酸,甲酸盐

[0512] 

[0513] ^{1}H NMR(CD_3OD,400MHz)δ:8.51(s,1H,HCOOH),7.60(s,1H),7.55-7.45(m,3H),7.28(d,J＝8.4Hz,2H),6.91(d,J＝8.8Hz,2H),5.14(s,2H),4.34(s,2H),4.02-3.98(m,1H),3.27-3.24(m,4H),2.62-2.50(m,2H),2.08-2.04(m,4H),1.80(d,J＝2.4Hz,3H)

[0514] 实施例53

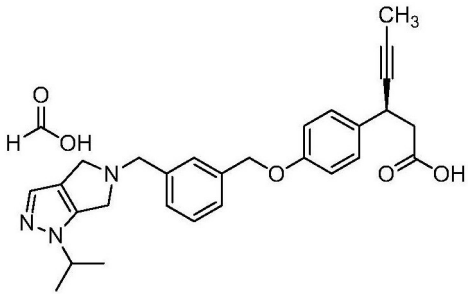
[0515] (S)-3-(4-((3-(哌啶-1-基甲基)苄基)氧基)苯基)己-4-炔酸,甲酸盐

[0516] 

[0517] ^{1}H NMR(CD_3OD,400MHz)δ:8.50(s,1H,HCOOH),7.58-7.43(m,4H),7.29(d,J＝8.8,Hz,2H),6.91(d,J＝8.8Hz,2H),5.15(s,2H),4.23(s,2H),4.09-4.03(m,1H),3.12-3.08(m,4H),2.63-2.49(m,2H),1.83-1.79(m,7H),1.64-1.61(m,2H)

[0518] 实施例54

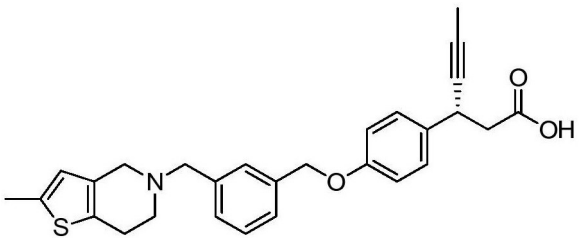
[0519] (S)-3-(4-((3-((1-异丙基吡咯并[3,4-c]吡唑-5(1H,4H,6H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,甲酸盐

[0520] 

[0521] ^{1}H NMR(CD_3OD,400MHz)δ:8.41(s,1H,HCOOH),7.54(s,1H),7.43-7.40(m,3H),7.29(dd,J＝7.2,2Hz,2H),7.21(s,1H),6.93(dd,J＝6.8,2Hz,2H),5.11(s,2H),4.45-4.41(m,1H),4.14(s,2H),4.07(s,2H),4.02-3.95(m,1H),3.88(s,2H),2.63-2.59(m,2H),1.80(d,J＝2.4Hz,3H),1.42(d,J＝6.8Hz,6H).

[0522] 实施例55

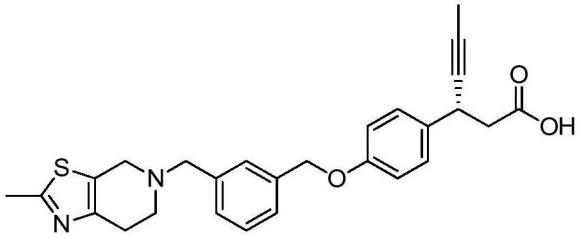
[0523] (R)-3-(4-((3-((2-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0524] 

[0525] ^{1}H NMR($CDCl_3$,400MHz)δ:8.31(s,0.36H,残留的HCOOH),7.47-7.25(m,6H),6.86(td,J＝9.6,2.8Hz,2H),6.34(s,1H),5.04(s,2H),4.07-4.01(m,3H),3.8($s_{(br)}$,2H),3.20-3.12(m,2H),2.97-2.95(m,2H),2.78-2.73(m,1H),2.66-2.61(m,1H),2.41(s,3H),1.80(d,J＝2.4Hz,3H).

[0526] 实施例56

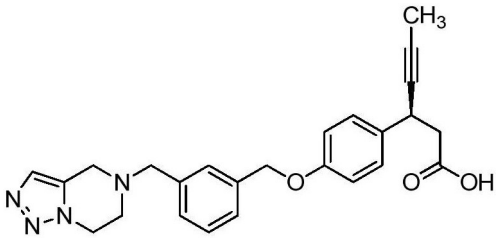
[0527] (R)-3-(4-((3-((2-甲基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0528] 

[0529] ^{1}H NMR($CDCl_3$,400MHz)δ:8.15(s,0.3H,残留的HCOOH),7.41-7.27(m,6H),6.88(d,J＝8.4Hz,2H),5.15-5.07(m,2H),4.06-4.02(m,1H),3.90-3.82(m,4H),2.96-2.92(m,2H),2.88-2.64(m,7H),1.82(d,J＝2.4Hz,3H)

[0530] 实施例57

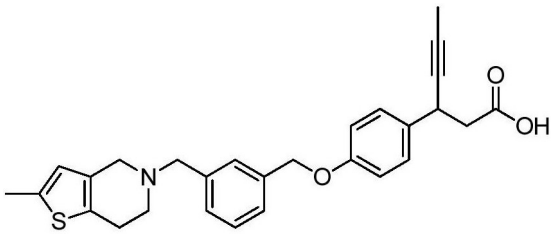
[0531] (S)-3-(4-((3-((6,7-二氢-[1,2,3]三唑并[1,5-a]吡嗪-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0532] 

[0533] ^{1}H NMR(CD_3OD,400MHz)δ:7.59-7.58(m,2H),7.58-7.43(m,3H),7.29(d,J＝8.8Hz,2H),6.93(d,J＝8.8Hz,2H),5.14(s,2H),4.58-4.55(m,2H),4.19(s,2H),4.15(s,2H),4.01-3.97(m,1H),3.44-3.41(m,2H),2.70-2.58(m,2H),1.81(d,J＝2.4Hz,3H).

[0534] 实施例58

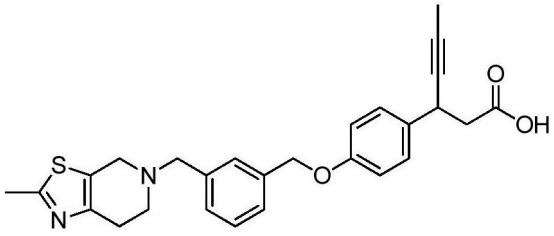
[0535] 3-(4-((3-((2-甲基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0536] 

[0537] ^{1}H NMR($CDCl_3$,400MHz)δ:7.42-4.27(m,5H),6.87(dd,J＝11.2,3Hz,2H),6.34(s,1H),5.05(s,2H),4.06-4.02(m,2H),3.98(s,2H),3.74(s,2H),3.10-3.04(m,2H),2.92-2.89(m,2H),2.79-2.73(m,1H),2.67-2.61(m,1H),2.41(s,3H),1.81(d,J＝2.4Hz,3H).

[0538] 实施例59

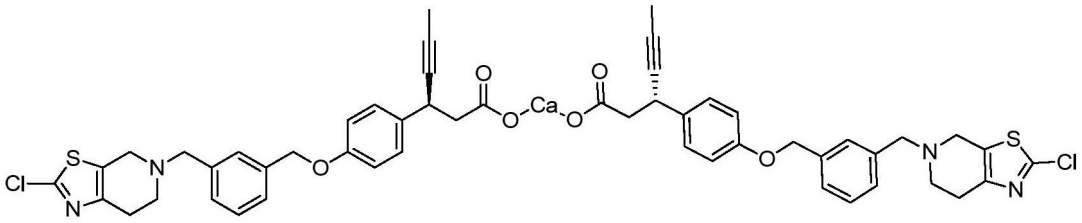
[0539] 3-(4-((3-((2-甲基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸：

[0540] 

[0541] ^{1}H NMR($CDCl_3$,400MHz)δ:7.42-7.35(m,4H),7.29-7.27(m,2H),6.88(d,J＝8.8Hz,2H),5.14-5.07(m,2H),4.06-4.03(m,1H),3.93-3.85(m,4H),2.99-2.97(m,2H),2.86-2.64(m,7H),1.82(d,J＝2.4Hz,3H

[0542] 实施例60

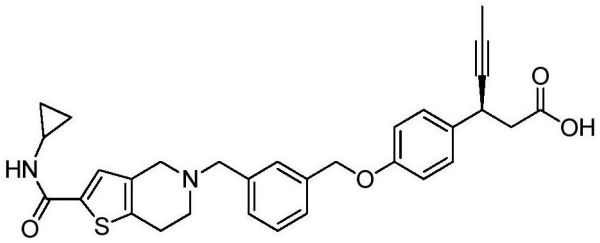
[0543] (S)-3-(4-((3-((2-氯-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸钙

[0544] 

[0545] ^{1}H NMR(DMSO-d_6,400MHz)δ:7.39(s,1H),7.36-7.23(M,5H),6.88(d,J＝8.8Hz,2H),5.03(s,2H),4.02-3.99(m,1H),3.69(s,2H),3.39(s,2H),2.80-2.77(m,2H),2.72-2.69(m,2H),2.41-2.36(m,1H),2.27-2.21(m,1H),1.73(d,J＝2.4Hz,3H).

[0546] 实施例61

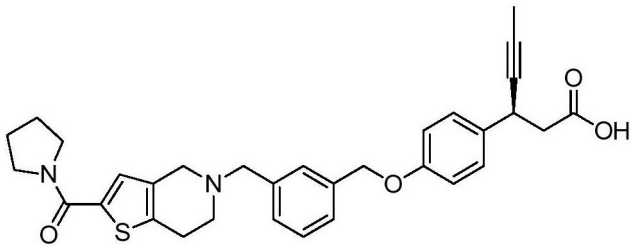
[0547] (S)-3-(4-((3-((2-(环丙基氨基甲酰基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0548] 

[0549] ^{1}H NMR:(DMSO-d_6,400MHz):-8.34(br s,1H),7.41(s,1H),7.36-7.29(m,3H),7.27-7.24(m,3H),6.67(d,J＝8.4Hz,2H),5.07(s,2H),3.95-3.91(m,1H),3.67(s,2H),3.42(s,2H),2.77-2.66(m,5H),2.57-2.51(m,2H),1.76(s,3H),0.67-0.62(m,2H),0.53-0.49(m,2H

[0550] 实施例62

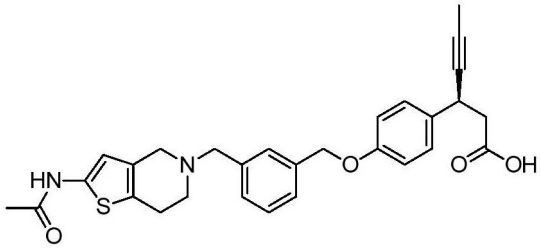
[0551] (S)-3-(4-((3-((2-(吡咯烷-1-羰基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0552] 

[0553] ^{1}H NMR:(DMSO-d_6,400MHz):-7.42(s,1H),7.37-7.26(m,3H),7.25-7.13(m,3H),6.93(d,J＝8.8Hz,2H),5.07(s,2H),3.94-3.87(m,1H),3.68(br s,4H),3.43(br s,4H),2.80-2.73(m,4H),2.59-2.50(m,2H),2.91-1.81(m,4H),1.76(s,3H)

[0554] 实施例63

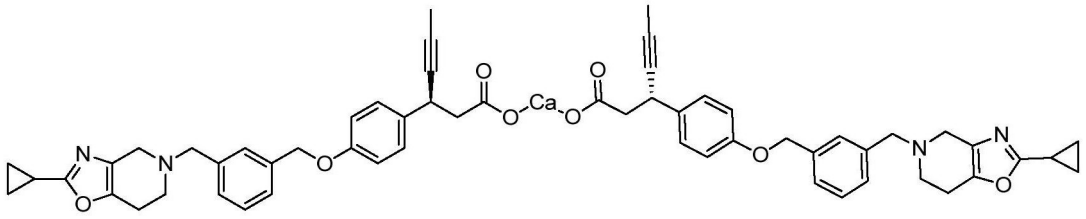
[0555] (S)-3-(4-((3-((2-乙酰氨基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0556] 

[0557] ^{1}H NMR(CD_3OD,400MHz)δ:7.56(s,1H),7.50-7.41(m,3H),7.28(d,J=8.8Hz,2H),6.92(d,J=8.8Hz,2H),6.35(s,1H),5.12(s,2H),4.15(s,2H),4.01-3.97(m,1H),3.84(s,2H),3.25-3.22(m,2H),2.96-2.93(m,2H),2.66-2.53(m,2H),2.10(s,3H),1.79(d,J=2.4Hz,3H).

[0558] 实施例64

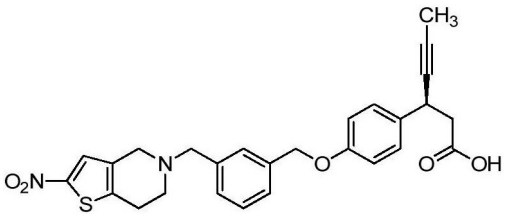
[0559] (S)-3-(4-((3-((2-环丙基-6,7-二氢噁唑并[4,5-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸钙

[0560] 

[0561] ^{1}H NMR(DMSO-d_6,400MHz)δ:7.38(s,1H),7.34-7.24(m,5H),6.88(d,J=8Hz,2H),5.02(s,2H),4.02-4.01(m,1H),3.66(s,2H),3.26(s,2H),2.73-2.71(m,2H),2.58(s,2H),2.41-2.37(m,1H),2.27-2.24(m,1H),2.03-2.00(m,1H),1.72(s,3H),0.98-.093(m,2H),0.86-0.82(m,2H).

[0562] 实施例65

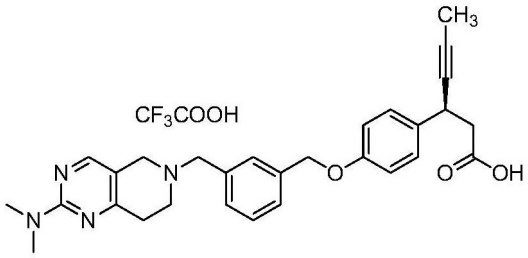
[0563] (S)-3-(4-((3-((2-硝基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0564] 

[0565] ^{1}H NMR(CD_3OD,400MHz)δ:7.80(s,1H),7.69(s,1H),7.61-7.52(m,3H),7.30(d,J=8.4Hz,2H),6.95(d,J=8.4Hz,2H),5.17(s,2H),4.54(s,2H),4.30(s,2H),4.01-3.99(m,1H),3.66($s_{(br)}$,2H),3.31-3.27(m,2H),2.69-2.58(m,2H),1.80(d,J=2.4Hz,3H)

[0566] 实施例66

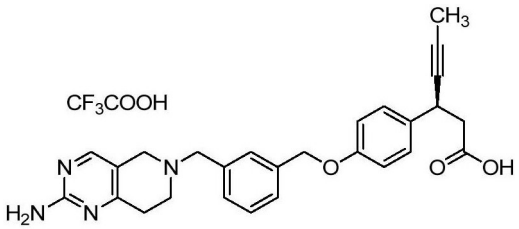
[0567] (S)-3-(4-((3-((2-(二甲基氨基)-7,8-二氢吡啶并[4,3-d]嘧啶-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,2,2,2-三氟乙酸盐

[0568] 

[0569] ^{1}H NMR(CD_3OD,400MHz)δ:8.00(s,1H),7.54(s,1H),7.45-7.42(m,3H),7.28(d,J＝8.4Hz,2H),6.93(d,J＝8.4Hz,2H),5.13(s,2H),4.01-3.99(m,3H),3.74(s,2H),3.14(s,6H),3.10-3.07(m,2H),2.90-2.87(m,2H),2.64-2.60(m,2H),1.80(d,J＝2.4Hz,3H).

[0570] 实施例67

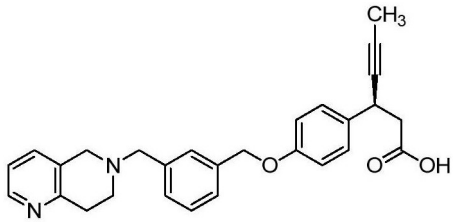
[0571] (S)-3-(4-((3-((2-氨基-7,8-二氢吡啶并[4,3-d]嘧啶-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,2,2,2-三氟乙酸盐

[0572] 

[0573] ^{1}H NMR(CD_3OD,400MHz)δ:8.10(s,1H),7.67(s,1H),7.62-7.54(m,3H),7.30(dd,J＝6.8,1.6Hz,2H),6.96(d,J＝6.8,1.6Hz,2H),5.17(s,2H),4.52(s,2H),4.25(s,2H),4.01-3.99(m,1H),3.63(s,2H),3.09-3.05(m,2H),2.70-2.58(m,2H),1.80(d,J＝2.4Hz,3H)

[0574] 实施例68

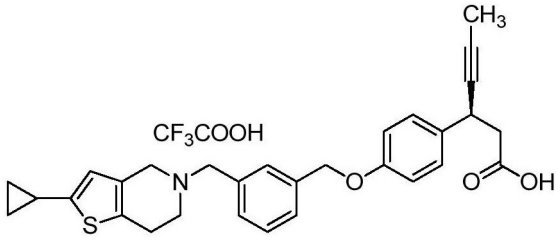
[0575] (S)-3-(4-((3-((7,8-二氢-1,6-二氮杂萘-6(5H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0576] 

[0577] ^{1}H NMR(CD_3OD,400MHz)δ:8.59(d,J＝4Hz,1H),7.87(d,J＝8Hz,1H),7.72(s,1H),7.62-7.51(m,4H),7.30(dd,J＝8.8,2Hz,2H),6.96(d,J＝8.8,2Hz,2H),5.17(s,2H),4.57(s,2H),4.49(s,2H),4.01-3.97(m,1H),3.75-3.72(m,2H),3.41-3.38(m,2H),2.69-2.58(m,2H),1.80(d,J＝2.4Hz,3H).

[0578] 实施例69

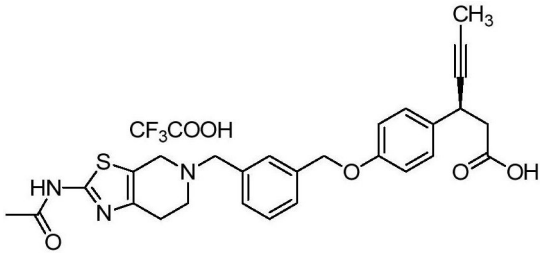
[0579] (S)-3-(4-((3-((2-环丙基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,2,2,2-三氟乙酸盐

[0580] 

[0581] ^{1}H NMR(CD_3OD,400MHz)δ:7.66(s,1H),7.60-7.52(m,2H),7.30(dd,J=6.8,2Hz,2H),6.90(dd,J=6.8,2Hz,2H),6.50(s,1H),5.17(s,2H),4.51(s,2H),4.18(s,2H),4.01-3.97(m,1H),3.12-3.09(m,2H),2.67-2.60(m,2H),1.80(d,J=2.4Hz,3H),1.00-0.97(m,2H),0.66-0.64(m,2H)

[0582] 实施例70

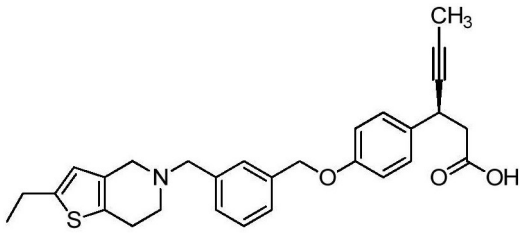
[0583] (S)-3-(4-((3-((2-乙酰基氨基-6,7-二氢噻唑并[5,4-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,2,2,2-三氟乙酸盐

[0584] 

[0585] ^{1}H NMR(CD_3OD,400MHz)δ:7.68(s,1H),7.62-7.54(m,3H),7.30(d,J=8.8Hz,2H),6.95(d,J=8.8Hz,2H),5.17(s,2H),4.56(s,2H),4.40(s,2H),4.01-3.97(m,1H),3.67($s_{(br)}$,2H),3.07-3.04(m,2H),2.69-2.58(m,2H),2.20(s,3H),1.80(d,J=2.4Hz,3H).

[0586] 实施例71

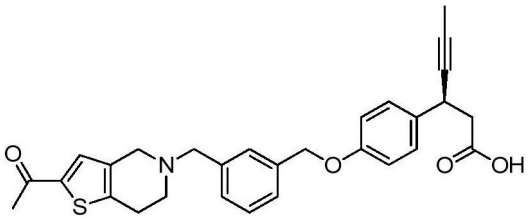
[0587] (S)-3-(4-((3-((2-乙基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0588] 

[0589] ^{1}H NMR(CD_3OD,400MHz)δ:7.66(s,1H),7.62-7.53(m,3H),7.30(d,J=8.8Hz,2H),6.95(d,J=8.8Hz,2H),6.53(s,1H),5.17(s,2H),4.51(s,2H),4.20(s,2H),4.01-3.97(m,1H),3.57($s_{(br)}$,2H),2.81-2.78(m,2H),2.75(q,J=7.6Hz,2H),2.69-2.57(m,2H),1.80(d,J=2.4Hz,3H),1.26(t,J=7.2Hz,3H).

[0590] 实施例72

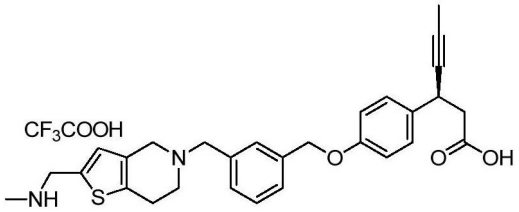
[0591] (S)-3-(4-((3-((2-乙酰基-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸

[0592] 

[0593] ^{1}H NMR(CD_3OD,400MHz)δ:7.56-7.55(m,2H),7.49-7.42(m,3H),7.28(dd,J＝6.8,2Hz,2H),6.93(dd,J＝6.8,2Hz,2H),5.12(s,2H),4.09(s,2H),4.01-3.97(m,1H),3.88(s,2H),3.18-3.14(m,2H),3.07-3.04(m,2H),2.66-2.56(m,2H),2.50(s,3H),1.79(d,J＝2.4Hz,3H)

[0594] 实施例73

[0595] (S)-3-(4-((3-((2-((甲基氨基)甲基)-6,7-二氢噻吩并[3,2-c]吡啶-5(4H)-基)甲基)苄基)氧基)苯基)己-4-炔酸,2,2,2-三氟乙酸盐

[0596] 

[0597] ^{1}H NMR(CD_3OD,400MHz)δ:7.67(s,1H),7.62-7.60(m,1H),7.55-7.53(m,2H),7.30(dd,J＝6.8,2Hz,2H),7.03(s,1H),6.96(dd,J＝6.8,2Hz,2H),5.17(s,2H),4.52(s,2H),4.36(s,2H),4.27(s,2H),4.01-3.98(m,1H),3.62($s_{(br)}$,2H),3.24-3.21(m,2H),2.71(s,3H),2.69-2.62(m,2H),1.81(d,J＝2.4Hz,3H).

[0598] 本发明的新型化合物可通过熟知的技术和方法和浓度通过与适当赋形剂混合而配制成适当的药用组合物。

[0599] 式(1)的化合物或包含它们的药物组合物可作为适用于人和其他温血动物的GPR40受体的配体,且可通过口服、局部或肠胃外给药进行给予。

[0600] 活性组分即根据本发明的式(I)化合物在药物组合物和其单位剂型中的量可取决于数种因素例如具体应用方法、具体化合物的效力和预期的浓度而广泛地变化或调整。

[0601] 生物学活性:

[0602] 本发明化合物的生物学活性以本申请提及的下列体外和体内模型进行测试。

[0603] 体外筛选方案的概要

[0604] 使用荧光测定(FLIPR)确定化合物对细胞内Ca^{2+}流量的EC_{50}。

[0605] 将表达GPR40的稳定细胞以每孔25,000的数目接种。将50μL/孔的测定缓冲液(20mM HEPES+1X HBSS)添加至细胞中,再将细胞于37℃培养20分钟。用50微升/孔的Calcium 5染料装载细胞,再于37℃培养45分钟。

[0606] 将细胞用1000nM的最高浓度(1:3逐步向下稀释-10个点)的化合物激发。细胞内的钙流量通过使用Screen Works 3.1工具评估且统计分析使用Graph Pad Prism 4进行。

[0607] 当使用荧光(FLIPR)测定测量时,多种本发明的化合物证实对细胞内Ca^{2+}流量具有纳摩尔效力和显著的刺激%。

[0608] 化合物显现纳摩尔范围的效力(表1)。

[0609] 表1:本发明的GPR 40激动剂在FLIPR测定中的体外EC_{50}值

[0610]

化合物	EC_{50}(nM)
1	117
7	1.8
16	2.72
17	10.2
19	2.32
22	36.3

[0611] 测量GPR40活化的启动子萤光素酶测定

[0612] GPR40活化在以GPR40 cDNA(来自Millipore,US的ChemiBrite细胞系)稳定转染的HEK293细胞中测量。将这些细胞用具有5XSRE序列的pGL2(Promega Inc.)质粒瞬时转染,克隆萤光素酶基因的5'连同β-半乳糖苷酶质粒作为标准化对照。简言之,将35000个细胞/孔接种于96孔板中。在37℃孵育过夜后,将细胞以PBS洗涤,再以5X-SRE-萤光素酶质粒和β-半乳糖苷酶质粒转染。转染后6小时,移去培养基,再用含不同浓度药物的新鲜培养基替换,并再孵育16小时。随后将细胞于50μL Glo-Lysis缓冲液(Promega)中于室温裂解30分钟。然后将细胞离心,再收集裂解液。萤光素酶的活性通过将100μL萤光素酶底物(Promega)添加至20μL裂解液中,再于发光计中测量发光而测得。β-半乳糖苷酶活性也通过对20μL裂解液添加20μLβ-半乳糖苷酶缓冲液(Promega),再于415nm监测吸光度而测得。将萤光素酶的值除以β-半乳糖苷酶的值以将转染效率标准化(表2)。

[0613] 表2:本发明的GPR 40激动剂在萤光素酶测定中的体外EC_{50}值

[0614]

化合物编号	EC_{50} (nM)	**化合物编号**	EC_{50} (nM)	**化合物编号**	EC_{50} (nM)
1	7.5	23	5.3	51	3.0
7	1.49	24	0.7	55	56.5
8	11.8	26	4.1	58	3.7
10	16.9	30	4.5	60	5.6
12	5.6	31	9.7	61	12.6
13	0.8	32	4.8	62	3.0
14	0.8	35	204	63	4.4
15	4.6	38	17.8	64	1.2
16	4.6	39	1.7	65	1.6
17	4.7	40	8	68	11.9
18	8.8	43	7.3	69	0.8
19	0.2	44	4.8	71	0.4
20	2.7	46	6	72	2.3
21	2.8	47	9		
22	31.46	50	20.8		

[0615] 将大多数本发明化合物针对CYP1A2、CYP2C8、CYP2C9、CYP2C19、CYP2D6和CYP3A4进行评价，结果无显著的CYP抑制效应。化合物在10μM并未显示显著的hERG结合力。

[0616] 体外效力研究：

[0617] GRP40激动剂测试化合物在n-STZ大鼠模型中的初步筛选方案

[0618] 将1-2天大的Wistar大鼠通过腹膜内途径注射120mg/kg剂量的链唑霉素(Streptozotocin,STZ)。允许所有大鼠正常生长，再于12-14周龄通过断尾法使用血糖仪进行口服葡萄糖耐受性测试以筛选其葡萄糖不耐受性。选出显示葡萄糖不耐受性的动物以进行测试化合物的评价。在三至七天的休息期，保持动物禁食过夜。第二天早上使用血糖仪测量血糖水平，并将动物分组使其处理前的葡萄糖水平在组间无显著差异。对动物给予测试化合物，随后在化合物给予的15-60分钟后，测量“0”分的血葡萄糖水平，再立即口服给予2g/kg的葡萄糖负荷。在葡萄糖负荷后的30、60和120分钟使用断尾法使用血糖仪测量血葡萄糖水平。还采集了葡萄糖负荷后10分钟的血液以测量胰岛素水平。葡萄糖的曲线下面积(AUC)使用Graph Pad Prism软件计算，再计算相对于媒介物处理的对照组的AUC-葡萄糖降低%(表3)。

[0619] 表3:本发明的GPR 40激动剂在n-STZ大鼠模型中的效力

[0620]

化合物	剂量 (每口服)	AUC 葡萄糖相对对照的改善%
7	0.1 mg/Kg	30.4
	1 mg/Kg	46.0
	10 mg/Kg	57.0
10	0.1 mg/Kg	21.1
	1 mg/Kg	35.7
	10 mg/Kg	45.0
16	1 mg/Kg	44.6
	10 mg/Kg	59.6
17	1 mg/Kg	37.1
	10 mg/Kg	44.7
60	1 mg/Kg	44
	10 mg/Kg	47
64	1 mg/Kg	46
	10 mg/Kg	47

[0621] 在n-STZ大鼠OGTT模型中，化合物16、60和64的ED_{50}已发现分别为0.05mg/Kg、0.04mg/Kg和0.09mg/Kg。

[0622] 少数化合物在大鼠中已显示显著的药代动力学参数(表4)。

[0623] 表4:化合物16,60&64的药代动力学参数

[0624]

参数	16	60	64
剂量(po) mg/Kg	3	3	3
T_{max} (h)	0.25	1	2
C_{max} (μg/mL)	5.92±2.10	7.77±1.94	8.06±2.19
AUC (0-t)	7.63±1.27	52.52±12.62	82.42±27.63
$T_{1/2}$, po (h)	1.77±0.42	5.45±0.79	4.51±0.61
平均滞留时间(h)	2.19±0.31	5.74±0.10	6.59±0.93
iv 剂量(mg/Kg)	1	1	1
C_0(μg/mL)	5.02±0.37	3.39±0.33	10.16±1.54

[0625]

AUC (0-t) (μg.h/mL)	3.18±0.40	18.61±2.17	56.14±4.35
Vss (L/Kg)	0.34±0.03	0.33±0.01	0.16±0.01
CL (mL/min./Kg)	5.26±0.65	0.89±0.10	0.27±0.03
$T_{1/2}$, iv (h)	1.45±0.12	5.57±1.46	7.77±1.07
平均滞留时间(h)	1.09±0.07	6.28±0.77	10.07±1.36
%F	83	93	45

[0626] 式(I)的化合物或包含它们的药物组合物适用于人类和其他温血动物，且可通过口服、局部或肠胃外给药进行给予以用于治疗与血脂障碍、肥胖症等有关的各种疾病病症。

[0627] 药物组合物通过使用常规技术提供。优选地，组合物为含有有效量的活性组分，即本发明式(I)化合物的单位剂型。

[0628] 活性组分，即本发明的式(I)的化合物在药物组合物和其单位剂型中的量可取决于具体应用方法、具体化合物的效力和预期的浓度而广泛地变化或调整。通常，活性组分的量的范围为0.5％至90％，按组合物的重量计。